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The Environmental Footprint of Anesthesia

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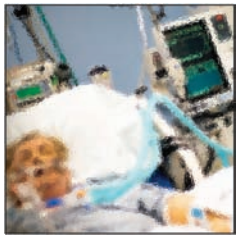
THIS MONTH IN ANESTHESIOLOGY

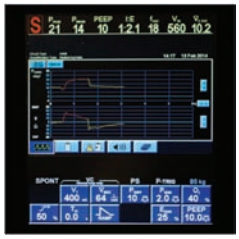
976 Carbon Footprint of General, Regional, and Combined Anesthesia for Total Knee Replacements

Health care produces greenhouse gases both directly (electricity and gas) and indirectly from emissions associated with consumption of goods and services. For anesthesiologists to reduce their workplace carbon footprint, they must understand the sources and amounts of the greenhouse gases produced as they care for patients in the operating room. The carbon footprints in carbon dioxide equivalent emissions associated with general anesthesia (n = 9), spinal anesthesia (n = 10), and combined (general and spinal) anesthesia (n = 10) for total knee replacement surgery in Melbourne, Australia, were similar. Single-use equipment, electricity for the patient air warmer, and pharmaceuticals were major sources of carbon dioxide equivalent emissions across all anesthetics. Sevoflurane was a significant source of the carbon dioxide equivalent emissions of both general anesthesia and combined anesthesia. Washing and sterilizing reusable items contributed substantially to the carbon dioxide equivalent emissions of both spinal and combined anesthesia. Oxygen use was an important contributor to the carbon footprint of spinal anesthesia. *See the accompanying Editorial on* ***page 937****. (Summary: M. J. Avram. Image: "This is the waste of one operation…my operation" by Dutch spacial artist Maria Koijck, created with waste generated during her own surgery; cover photograph by Eva Glasbeek, published with permission from the artist.)*



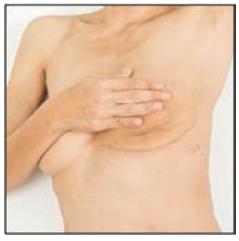
992 Spinal Anesthesia with Targeted Sedation based on Bispectral Index Values Compared with General Anesthesia with Masked Bispectral Index Values to Reduce Delirium: The SHARP Randomized Controlled Trial

The estimated incidence of postoperative delirium after lumbar spine fusion surgery, which is common in older adults, is 10 to 30%. The hypothesis that spinal anesthesia with targeted light sedation based on bispectral index (BIS) values (BIS more than 60 to 70) would reduce the incidence of postoperative delirium compared to general anesthesia with masked BIS values was tested in a randomized controlled superiority trial of 217 older patients undergoing lumbar spine fusion surgery. The median (interquartile range) average BIS value in the spinal anesthesia group was 62 (53 to 70), whereas that in the general anesthesia group was 45 (41 to 50). The overall incidence of delirium, defined as any positive assessment during hospitalization, was 22% (48 of 217). The incidence of delirium in the spinal anesthesia group, 25% (28 of 111), was not different from that of the general anesthesia group, 19% (20 of 106), in the intention-to-treat analysis; the absolute difference (95% CI) was 6.4% (–4.6 to 17.4%) and the relative risk (95% CI) was 1.22 (0.85 to 1.76). *See the accompanying Editorial on* ***page 940****. (Summary: M. J. Avram. Image: J. P. Rathmell.)*



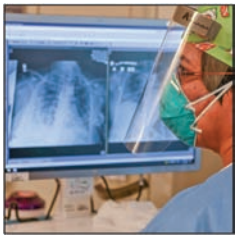
1004 Pressure Support *versus* Spontaneous Ventilation during Anesthetic Emergence—Effect on Postoperative Atelectasis: A Randomized Controlled Trial

Postoperative atelectasis is a common pulmonary complication that increases the risk of hypoxemia and provides the pathophysiologic basis for other postoperative pulmonary complications. Laparoscopic colectomy and robot-assisted laparoscopic prostatectomy are associated with a higher risk of postoperative atelectasis due to the high intra-abdominal pressure and the Trendelenburg position. The hypothesis that pressure support ventilation reduces the incidence of postoperative atelectasis compared to spontaneous respiration with intermittent manual assistance was tested in a randomized, controlled, patient- and evaluator-blinded trial of 97 patients undergoing laparoscopic colectomy or robot-assisted laparoscopic prostatectomy. All patients were evaluated using lung ultrasonography 30 min after their postanesthesia care unit arrival. Anesthesia-induced atelectasis was considered to be clinically significant if more than three of the twelve lung sections evaluated showed any sign of atelectasis. The incidence of postoperative atelectasis diagnosed by lung ultrasonography was 33% (16 of 48) in the pressure support group and 57% (28 of 49) in the control group; the risk ratio (95% CI) was 0.58 (0.35 to 0.91). *See the accompanying Editorial on* ***page 943****. (Summary: M. J. Avram. Image: J. P. Rathmell.)*



1091 Preoperative Paravertebral Block and Chronic Pain after Breast Cancer Surgery: A Double-blind Randomized Trial

Chronic pain after breast cancer surgery is frequent and affects quality of life. The existing evidence on the role of paravertebral block in preventing chronic pain after breast cancer surgery is weak and conflicting. The hypothesis tested in a double-blind, randomized, placebo-controlled study of 352 patients undergoing partial or complete mastectomy with or without lymph node dissection for cancer was that preoperative ultrasound-guided paravertebral block with ropivacaine reduces the incidence of pain greater than or equal to 3 on a 0 to 10 visual analog scale 3 months after surgery. In the intention-to-treat population, 93 of 178 (52%) patients in the paravertebral block group and 83 of 174 (48%) patients in the control group had pain greater than or equal to 3 on the visual analog scale 3 months after surgery. The associated odds ratio (95% CI) was 1.20 (0.79 to 1.82). Similar results were obtained for the secondary outcomes of pain greater than or equal to 3 at 6 and 12 months after surgery. *(Summary: M. J. Avram. Image: Adobe Stock.)*



1076 Treatments Associated with Lower Mortality among Critically Ill COVID-19 Patients: A Retrospective Cohort Study

The mortality rate of critically ill COVID-19 patients admitted to intensive care units declined over time from approximately 50% in the early stage of the pandemic, possibly due to effective treatments. This retrospective cohort study used multivariable analysis to test the hypothesis that certain treatments would be associated with lower mortality in 2,070 patients treated for COVID-19–related complications in the intensive care units of six hospitals affiliated with an academic North American health system from February 2020 to March 2021. Only treatments that were used in at least 5% of patients were included in the analysis. The all-cause in-hospital mortality was 29% (593 of 2,070). The results of the 23 hypotheses tested, corresponding to all treatments included in the multivariable analyses, were corrected for multiple hypothesis testing using the Bonferroni method. Of 23 treatments analyzed, apixaban (used in 20% [408 of 2,072] of patients; hazard ratio [95% CI], 0.42 [0.34 to 0.52]) and aspirin (used in 66% [1,335 of 2,072] of patients; hazard ratio [95% CI], 0.72 [0.54 to 0.96]) were associated with lower mortality. *(Summary: M. J. Avram. Image: J. P. Rathmell.)*

1042 Effect of Global Ventilation to Perfusion Ratio, for Normal Lungs, on Desflurane and Sevoflurane Elimination Kinetics

Understanding the elimination kinetics of inhaled anesthetics is of more practical importance than understanding their uptake kinetics. Normal lungs are assumed to play a major role in the elimination of inhaled anesthetics in the early rapid stages and a negligible role subsequently. The fraction of cardiac output that is completely cleared of anesthetic in one pass is the fractional clearance. A mathematical model of inhaled anesthetic elimination was developed in a *post hoc* analysis of anesthetic partial pressures measured in mixed venous and arterial blood samples after simultaneous administration of desflurane and sevoflurane to seven piglets under normal, low, and high alveolar ventilation to cardiac output ratio ($\dot{V}_A/\dot{Q}$) conditions. After a brief and rapid decline in alveolar anesthetic partial pressure, the fractional clearance of anesthetic became constant, and incomplete clearance from the lungs slowed tissue washout. Slowing of tissue elimination by incomplete lung clearance became more pronounced at low $\dot{V}_A/\dot{Q}$ ratios and was predicted to become more pronounced as blood/gas solubility increases. *See the accompanying Editorial on* ***page 948****.* *(Summary: M. J. Avram. Image: J. P. Rathmell.)*

1122 Prevention of Healthcare-associated Infections in Intensive Care Unit Patients (Clinical Focus Review)

Healthcare-associated infections in higher-income countries affect up to 30% of intensive care unit (ICU) patients who are vulnerable because of not only underlying comorbidities and immunosuppression but also the presence of invasive catheters and devices. They increase morbidity, mortality, and costs. Surgical site infection, central line–associated bloodstream infection, and ventilator-associated events are strongly associated with mortality, whereas catheter-associated urinary tract infection is not consistently associated with it. Contact transmission is the most common route by which healthcare-associated infections are spread in the ICU. This Clinical Focus Review discusses evidence-based strategies for reducing healthcare-associated infections in ICU patients, ranging from hand hygiene and transmission-based precautions to hospital Infection prevention departments with dedicated personnel to perform healthcare-associated infection surveillance and implement control measures. Specific strategies discussed include appropriate perioperative antibiotic prophylaxis to prevent surgical site infection, the use of chlorhexidine as an adjunct for central line–associated blood stream infection prevention, and antimicrobial stewardship to prevent *Clostridioides difficile* infection. *(Summary: M. J. Avram. Image: J. P. Rathmell.)*

1132 Sleep, Pain, and Cognition: Intervenable Targets for Optimal Perioperative Brain Health (Review Article)

Perioperative neurocognitive disorders include postoperative delirium, delayed neurocognitive recovery, and postoperative neurocognitive disorder. Postoperative delirium is an acute, fluctuating disturbance in attention and awareness that is associated with higher risk of long-term cognitive impairment and poor functional outcomes. Delayed neurocognitive recovery and postoperative neurocognitive disorder are characterized by deficits in memory and executive function that are barriers to optimal functional recovery. Three intervenable targets to consider in a multicomponent intervention designed to optimize perioperative brain health are sleep, pain, and cognition. Sleep and circadian disturbances are risk factors for development of neurodegenerative diseases, which are predisposing factors for postoperative delirium. Severe or uncontrolled preoperative or postoperative pain and increased levels of pain from the preoperative to the postoperative period are associated with postoperative delirium. Poor baseline cognition is strongly associated with perioperative neurocognitive disorders. Multicomponent interventions optimizing sleep, pain relief, and cognition can be effective in preventing postoperative delirium, but further work is needed to determine if they can prevent delayed neurocognitive recovery and postoperative neurocognitive disorder. *(Summary: M. J. Avram. Image: From original article.)*

 DOI: 10.10.1097/ALN.0000000000004066

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Volume 135
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◆ Editorial

Special Articles

Respirators provide reliable protection from airborne respiratory pathogens. Reusable elastomeric respirators offer potential advantages compared to disposable filtering facepiece respirators. Development of improved elastomeric respirators should be an international public health priority.

Ellison C. Pierce, Jr., M.D., and a team of innovative leaders led the creation of novel American Society of Anesthesiologists committees, the founding of the Anesthesia Patient Safety Foundation, and the evolution of the anesthesia patient safety movement.

Perioperative Medicine

CLINICAL SCIENCE

The carbon footprint in carbon dioxide equivalent emissions associated with general anesthesia (n = 9), spinal anesthesia (n = 10), and combined (general and spinal) anesthesia (n = 10) for total knee replacement surgery in Melbourne, Australia, were similar. Single-use equipment, electricity for the patient air warmer, and pharmaceuticals were major sources of carbon dioxide equivalent emissions across all anesthetics. Sevoflurane was a significant source of the carbon dioxide equivalent emissions of both general anesthesia and combined anesthesia. Washing and sterilizing reusable items contributed substantially to the carbon dioxide equivalent emissions of both spinal and combined anesthesia. Oxygen use was an important contributor to the carbon footprint of spinal anesthesia.

◇ *Refers to This Month in ANESTHESIOLOGY*
◆ *Refers to Editorial*
This article has an Audio Podcast
See Supplemental Digital Content
CME Article
This article has a Video Abstract
Readers' Toolbox
This article has a Visual Abstract
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ON THE COVER: Health care itself contributes to climate change. Anesthesia is a "carbon hotspot," yet few data exist to compare anesthetic choices. In this issue of ANESTHESIOLOGY, McGain *et al*. examined the carbon dioxide equivalent emissions associated with general anesthesia, spinal anesthesia, and combined (general and spinal anesthesia) during a total knee replacement. In an accompanying editorial, Struys and Eckelman discuss how practicing anesthesiologists can lower the environmental footprint of anesthesia. Cover Design: A. Johnson, Vivo Visuals Studio. Cover Image: "This is the waste of one operation… my operation" by Dutch spacial artist Maria Koijck, created with waste generated during her own surgery. Cover Photograph: Eva Glasbeek, published with permission from the artist.

- McGain *et al.*: Carbon Footprint of General, Regional, and Combined Anesthesia for Total Knee Replacements, p. 976
- Struys and Eckelman: Environmental Footprint of Anesthesia: More than Inhaled Anesthetics! p. 937

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BASIC SCIENCE

Critical Care Medicine

CLINICAL SCIENCE

Respiratory drive and effort and dynamic lung compliance were evaluated in 25 nonintubated patients with extrapulmonary sepsis or septic shock using arterial blood gases, esophageal pressure monitoring, and electrical impedance tomography at baseline with low-flow nasal oxygen therapy, during high-flow nasal cannula support and again with low-flow nasal oxygen therapy. Patient comfort was evaluated using a 10-point visual analog scale at each step. High-flow nasal oxygen therapy significantly reduced elevated respiratory drive and effort. There was no correlation between patient perceived comfort and measures of drive and effort. The impact of the findings from this physiologic study on patient outcome remain to be determined.

In a retrospective cohort consisting of 2,070 critically ill COVID-19 patients treated in six hospitals, multivariable regression analysis showed lower in-hospital mortality associated with apixaban, aspirin, or enoxaparin treatment. Propensity score–matching analyses demonstrated lower mortality for patients receiving apixaban (27% [96 of 360] *vs.* 37% [133 of 360]), aspirin (26% [121 of 473] *vs.* 30% [140 of 473]), or enoxaparin (25% [87 of 347] *vs.* 34% [117 of 347]) compared to matched controls.

Pain Medicine

CLINICAL SCIENCE

More than 350 study participants undergoing mastectomy were randomized to either paravertebral blocks with ropivacaine or saline injections. Both groups received multimodal analgesia. Although paravertebral block using ropivacaine had a small analgesic effect in the immediate postoperative period, no differences in pain 3, 6, and 12 months after surgery were detected.

Data from the PAIN OUT registry involving more than 11,000 patients undergoing spinal surgery, joint replacement, and laparoscopic cholecystectomy were used in a retrospective cohort analysis. Pain reported postoperative day 1 declined slightly with age. Severe postoperative pain was prevalent regardless of age or surgical type.

Education

IMAGES IN ANESTHESIOLOGY

CLINICAL FOCUS REVIEW

Healthcare-associated infections contribute to morbidity, mortality, and increased cost in intensive care unit patients. Understanding evidence-based prevention strategies can help to optimize patient outcomes.

REVIEW ARTICLE

Multicomponent interventions are effective in preventing postoperative delirium, and work is ongoing to determine whether they can be effective in preventing other postoperative neurocognitive disorders. Interventions optimizing sleep, pain, and cognition are essential components for clinicians to include in strategies to maximize the recovery of body and mind of vulnerable patients.

MIND TO MIND

Correspondence

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This Month's ANESTHESIOLOGY Journal-based CME Article

Read the article by O'Gara *et al.* entitled "Sleep, Pain, and Cognition: Modifiable Targets for Optimal Perioperative Brain Health" on page 1132.

Learning Objectives

After successfully completing this activity, the learner will be able to recognize the three main modifiable factors of perioperative cognitive disorder that anesthesiologists can impact, describe the most appropriate sedation regimen found to help avoid delirium in postoperative intensive care unit patients, and identify the most appropriate analgesia regimen to avoid delirium in postoperative patients.

Disclosures

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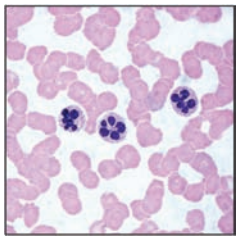
Martin J. London, M.D., Editor

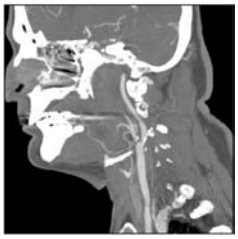
Key Papers from the Most Recent Literature Relevant to Anesthesiologists



An ACE inhibitor reduces bactericidal activity of human neutrophils in vitro and impairs mouse neutrophil activity in vivo. Sci Transl Med 2021; 13:eabj2138. PMID: 34321319.

Angiotensin-converting enzyme (ACE) inhibitors represent a valuable class of drugs used to treat hypertension, diabetic kidney disease, and heart failure. Recent evidence suggests that ACE inhibitors can negatively affect neutrophil function. In a translational study using *in vitro* cellular experiments and *in vivo* mouse models, loss of ACE activity either by ACE inhibition (ramipril) or gene deletion (knockout model) reduced the capacity of murine neutrophils to produce an oxidative burst and thus eliminate bacteria such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, or *Klebsiella pneumoniae*. In contrast, the angiotensin receptor blocker losartan had no adverse effect. *In vivo*, ACE inhibitor administration increased susceptibility to infection in a murine model of endocarditis in a manner similar to an ACE knockout strain alone (ACE knockout 100% infected, wild type treated with ramipril 90% infected, wild type untreated 40% infected). It also reduced the probability of survival (all ACE knockout mice dead after 3 days *vs.* only 40% of wild-type mice). In seven healthy human volunteers, neutrophils collected after short-term ramipril treatment (5 mg daily for 1 week) showed reduced antibacterial activity compared with neutrophils from volunteers without ramipril exposure or after a 7-day drug washout. *(Article Selection: Michael Zaugg, M.D., M.B.A., F.R.C.P.C. Image: Adobe Stock.)*

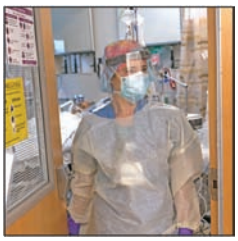
Take home message: These translational studies suggest a potentially detrimental and as yet unrecognized effect on the immune response to bacterial infections by an otherwise highly beneficial angiotensin-converting enzyme inhibitor.



Second asymptomatic carotid surgery trial (ACST-2): A randomised comparison of carotid artery stenting versus carotid endarterectomy. Lancet 2021; 398:1065–73. PMID: 34469763.

The relative clinical benefit and safety of prophylactic carotid endarterectomy *versus* carotid arterial stenting in preventing stroke in patients with asymptomatic severe (70 to 99%) carotid stenosis is unclear. Asymptomatic patients (N = 3,625) with severe unilateral or bilateral carotid stenosis recruited from 130 centers in 33 countries were randomly allocated to receive either carotid endarterectomy or stenting and followed annually for a mean of 5 yr. Overall, 1% had a disabling stroke or death and 2% a nondisabling stroke periprocedurally (30 days). There were no significant differences between the groups, except that slightly more patients having a stenting procedure had nondisabling procedural strokes (2.7% *vs.* 1.6%, $P = 0.03$). There was no difference in subsequent strokes over the 5-yr follow-up: 5.3% after stenting *versus* 4.5% after endarterectomy (rate ratio = 1.16; 95% CI, 0.86 to 1.57; $P = 0.33$). Combining rate ratios for any nonprocedural stroke in all previous published trials (this trial doubled the number of available subjects), the rate ratio between stenting and endarterectomy was similar in both symptomatic and asymptomatic patients (overall rate ratio = 1.11; 95% CI, 0.91 to 1.32; $P = 0.21$). *(Article Selection: Jamie Sleigh, Ph.D. Image: J. P. Rathmell.)*

Take home message: Carotid endarterectomy or stenting have similar periprocedural stoke risks and effect on stroke prevention at 5 yr in patients with asymptomatic severe carotid stenosis.



Therapeutic anticoagulation with heparin in critically ill patients with COVID-19. N Engl J Med 2021; 385:777–89. PMID: 34351722.

COVID-19 is known to be associated with lethal thrombotic complications. Although prophylactic and therapeutic anticoagulation have been recommended, the optimal strategy remains controversial. This pragmatic international, adaptive, multiplatform (three trials with independent data and safety monitoring boards reporting from 393 sites in 10 countries), randomized, controlled trial aimed to determine whether an initial strategy of therapeutic anticoagulation with unfractionated or low-molecular–weight heparin improved in-hospital survival and reduced the duration support in critically ill patients with COVID-19. The primary outcome was organ support–free days (cardiovascular or respiratory) up to day 21 for survivors on an ordinal scale (death in hospital by day 90 assigned –1). A total of 1,098 patients were assigned to either standard of care (n = 564) or therapeutic anticoagulation (n = 534). The percentage of patients who survived to hospital discharge was similar in the two groups (63% and 65%, respectively; adjusted odds ratio, 0.84; 95% credible interval, 0.64 to 1.11). The median value for organ support-free days was 1 (interquartile range, –1 to 16) among the patients receiving therapeutic anticoagulation and was 4 (interquartile range, –1 to 16) among the patients receiving standard of care anticoagulation (adjusted proportional odds ratio, 0.83; 95% credible interval, 0.67 to 1.03). *(Article Selection: David Faraoni, M.D., Ph.D. Image: J. P. Rathmell.)*

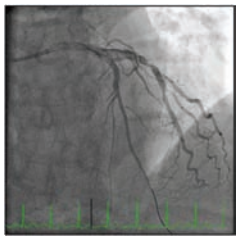
Take home message: In critically ill patients with COVID-19, therapeutic anticoagulation was not associated with better survival rates or reduced days of intensive care support when compared to standard of care thromboprophylaxis.

DOI: 10.1097/ALN.0000000000004069

Therapeutic anticoagulation with heparin in noncritically ill patients with COVID-19. N Engl J Med 2021; 385:790–802. PMID: 34351721.

The role of prophylactic anticoagulation in noncritically ill patients with COVID-19 is uncertain. This open-label, adaptive, multiplatform (three trials with independent data and safety monitoring boards reporting from 121 sites in 9 countries), controlled trial randomized noncritically ill COVID-19 patients (absence of critical care–level organ support at enrollment) to receive either therapeutic anticoagulation with heparin or usual care thromboprophylaxis. The primary outcome was organ support–free days, evaluated on an ordinal scale that combined in-hospital death (assigned a value of −1) and the number of days free of cardiovascular or respiratory organ support up to day 21. A total of 1,181 patients were enrolled in the group receiving therapeutic anticoagulation and 1,050 were enrolled in the usual care group. Prespecified criteria for superiority were set. Among 2,219 patients in the final analysis, the probability that therapeutic anticoagulation led to greater support–free days when compared to usual care was 98.6% (adjusted odds ratio, 1.27; 95% credible interval, 1.03 to 1.58). The adjusted absolute between–group difference in survival until hospital discharge without organ support favoring therapeutic anticoagulation was 4.0 percentage points (95% credible interval, 0.5 to 7.2). Major bleeding occurred more commonly in those on therapeutic anticoagulation (1.9% *vs.* 0.9%). *(Article Selection: David Faraoni, M.D., Ph.D. Image: Adobe Stock.)*

Take home message: Noncritically ill patients with COVID-19 and therapeutic anticoagulation had a greater probability of survival to hospital discharge with reduced use of cardiovascular or respiratory organ support as compared to standard of care.



Dual antiplatelet therapy after PCI in patients at high bleeding risk. N Engl J Med 2021 Aug 28 [Epub ahead of print]. PMID: 34449185.

Patients with a high risk of bleeding were randomized to discontinue dual antiplatelet therapy immediately (abbreviated therapy) or to continue for at least 2 additional months (standard therapy) 1 month after receiving a biodegradable-polymer sirolimus-eluting coronary stent. Primary outcomes assessed at 335 days were adverse clinical events (death from any cause, myocardial infarction, stroke, or major bleeding), major adverse cardiac or cerebral events (death from any cause, myocardial infarction, or stroke), and major or clinically relevant bleeding. The first two outcomes were assessed for noninferiority in the per-protocol population (4,434 patients), and the third outcome for superiority in the intention-to-treat population (4,579 patients). Adverse events occurred in 165 abbreviated therapy patients (7.5%) and in 172 standard therapy patients (7.7%; −0.23 percentage point difference; 95% CI, −1.80 to 1.33; $P < 0.001$ for noninferiority). A total of 133 abbreviated therapy patients (6.1%) and 132 standard therapy patients (5.9%) had a major adverse cardiac or cerebral event (0.11 percentage point difference; 95% CI, −1.29 to 1.51; $P = 0.001$ for non-inferiority). Major or clinically relevant nonmajor bleeding occurred in 148 abbreviated therapy patients (7%) and in 211 standard therapy patients (9%) (−2.82 percentage point difference; 95% CI, −4.40 to −1.24; $P < 0.001$ for superiority) in the intention-to-treat population. *(Article Selection: BobbieJean Sweitzer, M.D., F.A.C.P. Image: J. P. Rathmell.)*

Take home message: After the implantation of a sirolimus-eluting coronary stent, dual antiplatelet therapy for 1 month was noninferior to at least 2 additional months with regard to adverse clinical events and major adverse cardiac or cerebral events, while resulting in a lower incidence of major or clinically relevant nonmajor bleeding.

Effect of low–normal vs high–normal oxygenation targets on organ dysfunction in critically ill patients: A randomized clinical trial. JAMA 2021; 326:940–8. PMID: 34463696.

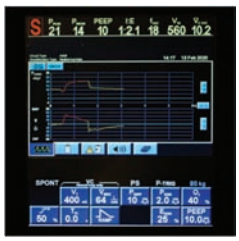
Controversy exists regarding the safety of hyperoxemia in patients with critical illness. This randomized clinical trial included 400 adult patients in The Netherlands (median age, 68 yr; 35% female; 72 to 73% intubated) admitted with two or more systemic inflammatory response criteria excluding elective surgical admissions. The low–normal oxygen target group (n = 205) had Pao_2 maintained between 8 and 12 kPa *versus* high–normal (n = 195) between 14 and 18 kPa. The primary outcome was a ranked outcome score of nonrespiratory organ failure quantified by components of the Sequential Organ Failure Assessment score (SOFARANK; lower scores indicate faster organ failure improvement) summed over the first 14 days, intensive care unit discharge or death. The median Pao_2 difference between the groups was −1.9 kPa (95% CI, −2.1 to −1.7; $P < 0.001$). The median SOFARANK score was −35 points in the low–normal Pao_2 group *versus* −40 in the high–normal Pao_2 group (median difference, 10; 95% CI, 0 to 21; $P = 0.06$). Median duration of mechanical ventilation (3.4 *vs.* 3.1 days; median difference, −0.15; 95% CI, −0.88 to 0.47; $P = 0.59$) and in-hospital mortality (32% *vs.* 31%; odds ratio, 1.04; 95% CI, 0.67 to 1.63; $P = 0.91$) were similar. *(Article Selection: Martin J. London, M.D. Image: J. P. Rathmell.)*

Take home message: Among patients admitted to the ICU with two or more systemic inflammatory response syndrome criteria, targeting a low–normal Pao_2 *versus* a high–normal Pao_2 had no significant impact on nonrespiratory organ dysfunction.

Haemodynamic-guided management of heart failure (GUIDE-HF): A randomised controlled trial. Lancet 2021; 398:991–1001. PMID: 31150790.

Hemodynamic-guided management *via* implantable pulmonary artery pressure monitors has been shown to reduce heart failure hospitalizations in patients with moderately symptomatic (New York Heart Association functional class III) heart failure irrespective of ejection fraction. Its role in patients across the spectrum of heart failure severity has not been determined. The hemodynamic-GUIDEd management of heart failure (GUIDE-HF) trial was a multicenter, single-blind study at 118 centers in the United States and Canada incorporating a randomized arm (among a larger ongoing single-arm observational study). One thousand patients of varying ejection fractions, New York Heart Association functional class II–IV chronic heart failure, and either a recent heart failure hospitalization or elevated natriuretic peptides with successful implantation of a pulmonary artery pressure monitor were randomized to either hemodynamic-guided heart failure or a usual care control group. The primary endpoint was a composite of all-cause mortality and total heart failure events (heart failure hospitalizations and urgent heart failure hospital visits) at 12 months. There were 253 primary endpoint events (0.563 per patient-year) in the hemodynamic-guided management group and 289 (0.640 per patient-year; hazard ratio, 0.88; 95% CI, 0.74 to 1.05; $P = 0.6$). A prespecified pre-COVID-19 impact analysis demonstrated a significant effect (hazard ratio, 0.81; 95% CI, 0.66 to 1.00; $P = 0.049$). *(Article Selection: Martin J. London, M.D. Image: Adobe Stock.)*

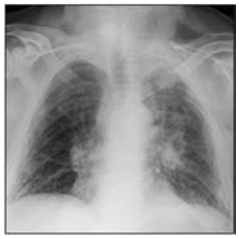
Take home message: Overall, hemodynamic-guided management of heart failure did not result in a lower composite endpoint rate of mortality and total heart failure events. However, a pre-COVID-19 impact analysis indicated a possible benefit of hemodynamic-guided management on the primary outcome in the pre-COVID-19 period, driven by a lower heart failure hospitalization rate.



Effect of lower tidal volume ventilation facilitated by extracorporeal carbon dioxide removal vs standard care ventilation on 90-day mortality in patients with acute hypoxemic respiratory failure: The REST randomized clinical trial. JAMA 2021; 326:1013–23. PMID: 34463700.

The role of extracorporeal carbon dioxide removal to facilitate further reduction in tidal volume below the current 6 ml/kg standard in patients with acute hypoxemic respiratory failure has not been tested. This multicenter, randomized, open-label, pragmatic clinical trial with a planned sample size of 1,120 from 51 intensive care units in the United Kingdom randomized patients to lower tidal volume ventilation (3 ml/kg ideal body weight) facilitated by extracorporeal carbon dioxide removal for 48 h to 7 days (n = 202) or conventional low tidal volume ventilation (6 ml/kg ideal body weight; n = 210). The primary outcome was all-cause mortality 90 days after randomization. Among 412 patients who were randomized (mean age, 59 yr; 35% female), 405 completed the trial. The trial was stopped early by the data monitoring and ethics committee for futility. There was no significant difference in the primary outcome (42% in the extracorporeal carbon dioxide removal group *vs.* 40% in the standard care group; risk ratio, 1.05; 95% CI, 0.83 to 1.33; difference, 2%; 95% CI, –7.6 to 11.5%; $P = 0.68$). Serious adverse events occurred in 31% in the extracorporeal carbon dioxide removal group *versus* 9% in the standard care group, including intracranial hemorrhage (5% *vs.* 0%). *(Article Selection: Martin J. London, M.D. Image: J. P. Rathmell.)*

Take home message: The use of extracorporeal carbon dioxide removal to facilitate lower tidal volume mechanical ventilation in patients with acute hypoxemic respiratory failure, compared to standard care, did not significantly reduce 90-day mortality and was associated with more adverse events.



Tracheal aspirate RNA sequencing identifies distinct immunological features of COVID-19 ARDS. Nat Commun 2021; 12:5152. PMID: 34446707.

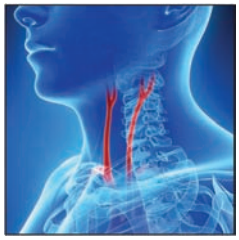
Transcriptional profiling of RNA from tracheal aspirates from ventilated patients with acute respiratory distress syndrome (ARDS) revealed dysregulated host responses with reduced proinflammatory gene expression in patients with COVID-19 compared to patients with other etiologies. The findings conflict with the classical "cytokine storm" hypothesis proposed in other studies of COVID-19 ARDS. A complex picture of upregulation of genes with nontraditional roles in inflammation and granulocyte colony-stimulating factor signaling were identified and were predicted to be therapeutically decreased by dexamethasone. Increased phosphatase and tensin homolog protein, interferon-γ and ciliary neurotrophic factor gene expressions were present with decreased genes classically activated by IL-10, an anti-inflammatory cytokine. These findings demonstrate that dysregulated inflammatory activation combined with impaired attenuation of inflammation (*e.g.*, decreased IL-10) may contribute to COVID-19 ARDS. *In silico* modeling was used to predict which therapeutics would target dysregulated gene expressions using a database containing 13,000 drug treatment-induced transcriptional profiles. Dexamethasone had the highest predicted likelihood to counteract the dysregulated gene expression patterns. This matching of *in silico* predictions with clinical data for dexamethasone provides a remarkable translational correlation with the identified dysregulated gene profiles herein. *(Article Selection: Charles Emala, M.D. Image: J. P. Rathmell.)*

Take home message: RNA profiling of genes in the tracheal aspirates of ventilated patients with ARDS from COVID-19 challenges the classical description of "cytokine storm" and instead reveals a complex upregulation of genes not classically linked to inflammation and immunity and the downregulation of anti-inflammatory genes. *In silico* profiling predicted dexamethasone would have beneficial effects on these dysregulated genes.

Battery-free, wireless soft sensors for continuous multi-site measurements of pressure and temperature from patients at risk for pressure injuries. Nature Commun 2021; 12:5008. PMID: 34429436.

Continuous monitoring of pressure and temperature at critical skin locations has the potential to reduce pressure injuries in a variety of hospitalized or immobile patients, including those undergoing prolonged surgical procedures. This article introduces the development and operating characteristics of a soft, skin-mountable sensor system incorporating a pressure-responsive element using membrane deflection and battery-free, wireless operation using multisite measurements on vulnerable locations. Pressure and temperature are transmitted using a pair of antennas mounted under the bedding to a multiplexer at the bedside. The pressure sensor can measure pressures across the entire relevant range (less than 10 kPa) without hysteresis or drift, and with high degrees of linearity, verified in benchtop studies and numerical simulations. Clinical trials were conducted of two hemiplegic and a tetraplegic patient verifying the feasibility, functionality, and long-term stability of this technology in the clinical setting. *(Article Selection: Martin J. London, M.D. Image: Adobe Stock.)*

Take home message: A new class of wireless, battery-free soft skin sensors capable of reporting local pressure and temperature at multiple body sites has been developed, which ultimately may assist in reducing pressure injuries in immobilized patients.



Lactate sensing mechanisms in arterial chemoreceptor cells. Nat Commun 2021; 12:4166. PMID: 34230483.

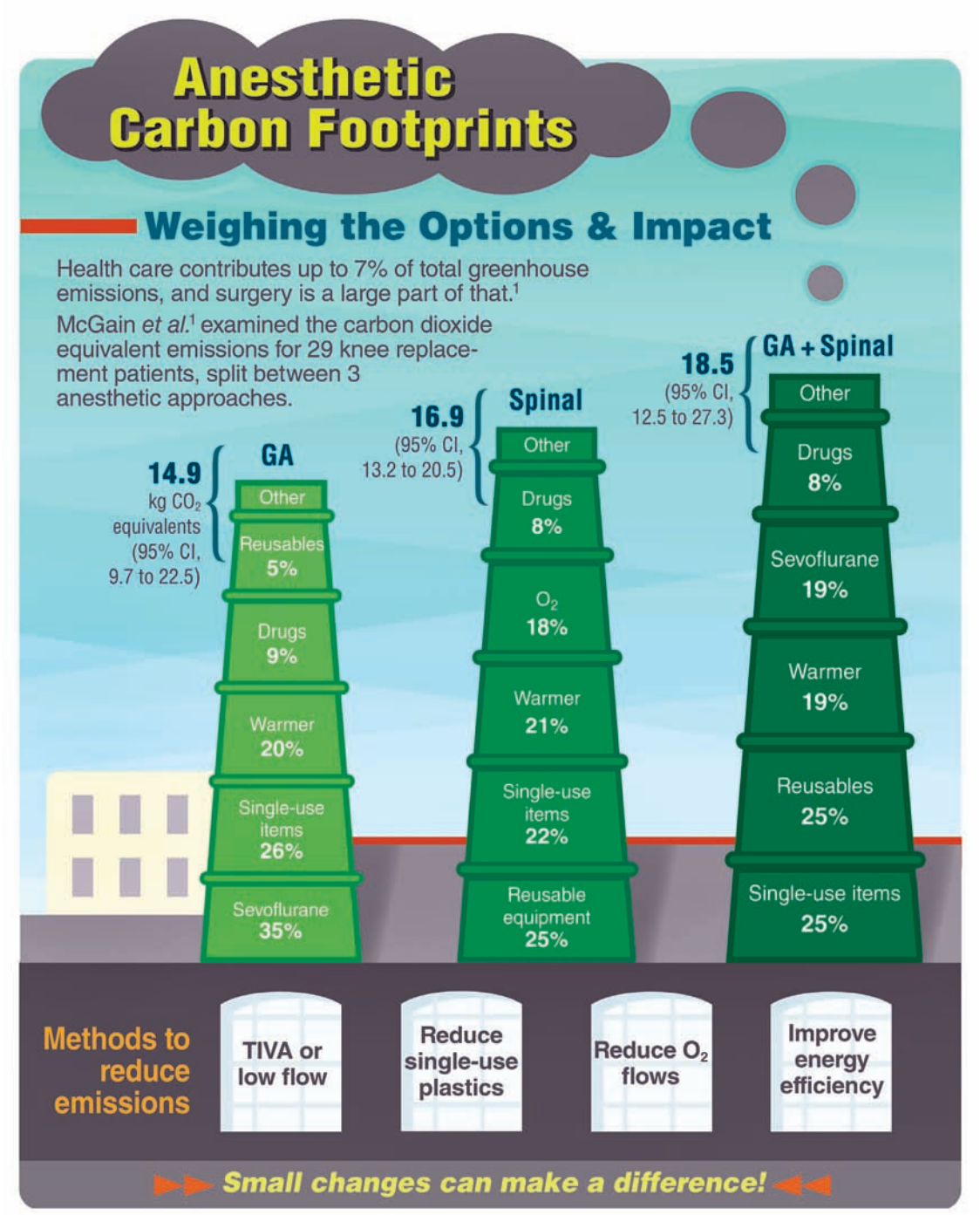
Although previously considered only a byproduct of anaerobic metabolism, lactate is gaining relevance as a signaling molecule. Murine models were used to evaluate the role of the carotid body in lactate signaling. Using mice with deficient carotid bodies and wild-type mice, they found that hypoxia-induced lactatemia was reduced by the carotid body. Lactate stimulated the carotid body in an external calcium-dependent manner, similar to the effects of hypoxemia. They found that lactate activates the carotid body specifically by binding to an atypical olfactory receptor (Olfr78) highly expressed in the glomus cells, the main oxygen-sensing arterial chemoreceptor cells of the carotid body. As lactate is transported into the glomus cells, it causes a rapid increase in the cytosolic NADH/NAD+ ratio, leading to action potential firing and calcium influx. It also leads to decreased intracellular pH and increased mitochondrial reactive oxygen species, further activating the glomus cells. These data demonstrate the importance of the carotid body to lactate homeostasis, and that lactate and hypoxia (although sensed by different mechanisms) share the same signaling pathway to activate the carotid body glomus cells and cause compensatory cardiorespiratory reflexes. *(Article Selection: Meghan Prin, M.D., M.S. Image: Adobe Stock.)*

Take home message: The carotid body glomus cells are lactate sensors and the carotid body is essential to lactate homeostasis. Lactate and hypoxia share the same signaling pathway to elicit compensatory cardiorespiratory responses.

Trends in prevalence of diabetes and control of risk factors in diabetes among US adults, 1999–2018. JAMA 2021; 326:704–16. PMID: 34170288.

Understanding the prevalence of diabetes as well as the control of risk factors for cardiovascular disease in diabetics are critical from a public health perspective. The data was evaluated from both the self-report interview and mobile examination components of the National Health and Nutrition Examination Survey (NHANES) reports from 1999 to 2000 through 2017 to 2018 to identify trends in the prevalence of diabetes and cardiovascular risk factors. They found that the age-standardized prevalence of diabetes increased significantly from 9.8% (95% CI, 8.6 to 11.1%) in 1999 to 2000 to 14.3% (95% CI, 12.9 to 15.8%) in 2017 to 2018 ($P < 0.001$). The trends in many subgroups, including men, women, and persons of all educational levels, showed similar patterns. Of particular concern, the prevalence of diabetes rose in populations already disproportionately affected, including Mexican Americans and those with abdominal obesity. Only 21% of those with diagnosed diabetes achieved their individualized hemoglobin A1c targets, blood pressure less than 130/80 mmHg, and low-density lipoprotein cholesterol level less than 100 mg/dl: three key goals in reducing the risk of cardiovascular disease. *(Article Selection: J. David Clark, M.D., Ph.D. Image: Adobe Stock.)*

Take home message: There has been a steady rise in the prevalence of diabetes in the American population over the past two to three decades with only approximately 20% achieving adequate control of cardiovascular risk factors.



GA, general anesthesia; TIVA, total intravenous anesthetic.

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

1. McGain F, Sheridan N, Wickramarachchi K, Yates S, Chan B, McAlister S: Carbon footprint of general, regional, and combined anesthesia for total knee replacements. Anesthesiology 2021; 135:976–91

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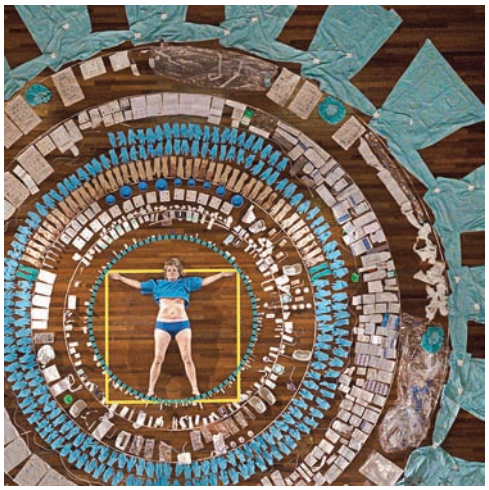
Environmental Footprint of Anesthesia: More than Inhaled Anesthetics!

Michel M. R. F. Struys, M.D., Ph.D., F.R.C.A., Matthew J. Eckelman, Ph.D.

Climate change is an increasingly apparent global reality. According to the new United Nations (New York, New York) Intergovernmental Panel on Climate Change report, published on August 9, 2021, the scientific consensus is that there is still time to act, but immediate action is required and "demands strong and sustained reduction in carbon dioxide and other greenhouse gases."[1] Although fossil fuel burning is still the major source of greenhouse gas emissions, each sector can take action to reduce its share of emissions, including indirect emissions that occur in the supply chain. A series of studies over the past half decade have revealed that the global environmental footprint of health care is significant[2]; its contribution to total global greenhouse gas emissions (in carbon dioxide equivalents) is nearly 5%.[2,3] These studies make it clear that clinicians and health care professionals have a vital role to play in tackling climate change, deemed by the World Health Organization (Geneva, Switzerland) as "the greatest threat to global health in the 21st century."



"[What is] the carbon footprint of general, regional, and combined anesthesia?"

In recent years, various (inter)national anesthesia societies have launched initiatives to minimize the environmental impact of our profession, largely focusing on the management of waste anesthetic gases.[4] Along with nitrous oxide, these halogenated ethers are themselves potent greenhouse gases with significant global warming potentials. Taken together, their direct emissions are responsible for an estimated 3% of the climate footprint of national healthcare systems in industrialized countries and can account for more than 50% of greenhouse gas emissions from the perioperative chain.[5] Recommendations include the utilization of low fresh gas flows, the avoidance of high-impact inhaled anesthetics (desflurane, nitrous oxide), the consideration of intravenous and regional techniques, and the investment in waste anesthetic gases trapping or destroying technology.[6]

While the greatest emphasis to date in the anesthesia literature has understandably been on the carbon footprint of inhaled anesthetics,[4] they are just one environmental consideration within the complex system of products and services that make up anesthesia practice. If we are to make evidence-based decisions on how to deliver perioperative care in the most sustainable manner, we need a holistic picture of what matters and what does not. "Life cycle" studies can provide this perspective and have been published on a range of products and procedures, often making comparisons among options. But as we all know, every case is unique. What has been mostly lacking to date is research that analyzes the environmental impacts of health care *across* multiple cases so that we can understand variations, quantify uncertainty, and test whether a recommendation is generally applicable or more case dependent.[7]

In this issue of Anesthesiology, McGain *et al*. provide a detailed comparison of the carbon footprint of general, regional, and combined anesthesia for total knee replacement in Australia, using a small cohort of 10 patients per group.[8] Aiming for a complete picture, they collected input data on anesthetic consumables, gases and drugs, and electricity for patient warming and the anesthesia machine. (In the general anesthesia group, sevoflurane or propofol was used, but no desflurane or nitrous oxide.) The investigators then conducted a Life Cycle Assessment to convert all of these input data into estimates of carbon footprint, with

Image: Maria Koijck/Eva Glasbeek.

This editorial accompanies the article on p. 976. This editorial has an audio podcast.

Accepted for publication October 4, 2021. From the Department of Anesthesiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands (M.M.R.F.S.); Department of Basic and Applied Medical Sciences, Ghent University, Ghent, Belgium (M.M.R.F.S.); and Department of Civil and Environmental Engineering, Northeastern University, Boston, Massachusetts (M.J.E.).

 Anesthesiology 2021; 135:937–9. DOI: 10.1097/ALN.0000000000004050

the hypothesis that spinal anesthesia would have the lowest impacts. They instead observed that the mean value was similar for general, spinal, and combination approaches, with significant overlap among the CIs. Within each group, there were large variations in results stemming from case-by-case differences in how anesthesia was administered. Examining the relative contributions of each input reveals some important trade-offs and offers lessons for our own practices.

First considering the anesthetic agents, sevoflurane was an important contributor but did not dominate results. For general anesthesia, sevoflurane contributed an average of 4.7 kg carbon dioxide equivalents (range, 2.7 to 8.6 kg carbon dioxide equivalents) or 35% of the total carbon footprint. (It should be noted that the contribution of inhalational gases would certainly have been higher if desflurane or nitrous oxide were used in the included cases.) Patients receiving total intravenous anesthesia were at the low end of the range of general anesthesia results. In the combined group, the contribution of sevoflurane was only 19% on average. The spinal group of course had zero contribution from inhaled anesthetics, but this relative carbon savings was more than offset (on average) by a large increase in emissions from washing and sterilization of surgical items (4.5 kg carbon dioxide equivalents) and the production of oxygen (2.8 kg carbon dioxide equivalents) for high-flow nasal cannula during locoregional anesthesia.

Other considerations were more consistent across groups. Single-use items have received much attention and contributed a substantial 25% of the total carbon footprint, with slightly higher results for the combined group. Perhaps surprisingly, the next largest contributor was electricity for the patient warmer at approximately 20%, while pharmaceuticals were nearly 10% of the total across groups.

What does this mean for clinical practice? Because of the large variations in results for each of the groups, the investigators were able to note practices that led to lower impacts. Some were specific to the anesthetic technique applied, such as using low-flow anesthesia or total intravenous anesthesia in general anesthesia or reducing oxygen flows when possible for spinal anesthesia. Other recommendations cut across all techniques, such as reducing single-use plastics or improving energy efficiency of patient warmers. The shift from single-use to reusable items has been a focus of multiple studies with results showing environmental and economic benefits in nearly every case.[9,10] Taking multiple actions to reduce emissions was found to be more beneficial than simply shifting to a different anesthetic technique.

Although the study expanded the boundaries of what is typically included in a clinical care Life Cycle Assessment, it is impossible to consider every possible input and permutation. Of particular note is the exclusion of heating, ventilation, and air conditioning systems and lighting systems, which are often a target of healthcare sustainability programs. Another important area is waste generation. Surgical and anesthesia procedures using mostly single-use items produce a significant amount of "medical trash," as illustrated in figure 1 by the Dutch artist Maria Koijck, who created an artwork using all disposable items from her own breast reconstruction surgery and anesthesia. The analysis from McGain *et al.*[8] assumed that nonpharmaceutical waste is either recycled or landfilled, with little consequence for the results. If instead this waste were incinerated (and its carbon liberated), then its contribution to emissions would be much higher. Also, it is important to remember that climate change is just one (albeit critical) environmental challenge we are facing. Air pollution, water pollution, depletion of finite resources, and numerous other impacts can also be modeled using Life Cycle Assessments.

The study by McGain *et al.*[8] is a small, single-center, prospective, nonrandomized, observational, unblinded study with various limitations that make comparison between anesthetic groups and between countries uncertain. The authors included only 10 patients per group ("convenience sample"), and the study is clearly underpowered to compare the footprint of various anesthetic techniques, as cautiously stated by the authors. As such, this study doesn't offer a definitive answer about which anesthetic method is the most detrimental to the climate, and it should not be misquoted to favor or reject the use of a specific anesthetic technique. What this study does offer is an interesting example of how clinical or cohort studies can be used for sustainability analysis (even with low numbers of included patients). As such, it shows a next step in a progression of research that has been slowly revealing different aspects of sustainability in clinical care.

Some aspects of a carbon footprint are location-dependent; for example, the emissions associated with electricity use depend on how electricity is generated locally. The Life Cycle Assessment is flexible in being able to test different assumptions about where different products originate or where certain processes take place, and the authors use this flexibility well to estimate how the results would change for clinical settings in Europe, the United Kingdom, or the United States. Those aspects of anesthesia that are electricity-intensive, such as steam sterilization,

Fig. 1. Dutch spatial artist Maria Koijck created an artwork with trash from her own surgery and anesthesia (photo: Maria Koijck and Eva Glasbeek, published with permission).

oxygen compression, and patient warming, had one fourth the emissions in Europe/United Kingdom than in Australia because of differences in the carbon intensities of electricity between the two regions. Therefore, a valuable lesson that the authors highlight is that recommendations for sustainable clinical care must consider local conditions. We cannot assume *a priori* that actions to reduce emissions in one clinical setting or country will have exactly the same effect somewhere else. Future studies, carbon accounting tools, and reporting frameworks that are developed for anesthesia and health care generally should ideally be flexible enough that clinicians can extract recommendations that are accurate for their own institutions, wherever they are.

Research Support

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

Competing Interests

Dr. Struys's research group/department received (over the last 3 yr) research grants and consultancy fees from The Medicines Company (Parsippany, New Jersey), Masimo (Irvine, California), Becton Dickinson (Eysins, Switzerland), Fresenius (Bad Homburg, Germany), Dräger (Lübeck, Germany), Paion (Aachen, Germany), Medtronic (Dublin, Ireland), and Medcaptain Europe (Andelst, The Netherlands). He receives royalties on intellectual property from Ghent University (Ghent, Belgium). Dr. Eckelman's research group/department received (over the last 3 yr) consultancy fees from the National Health Service (London, United Kingdom).

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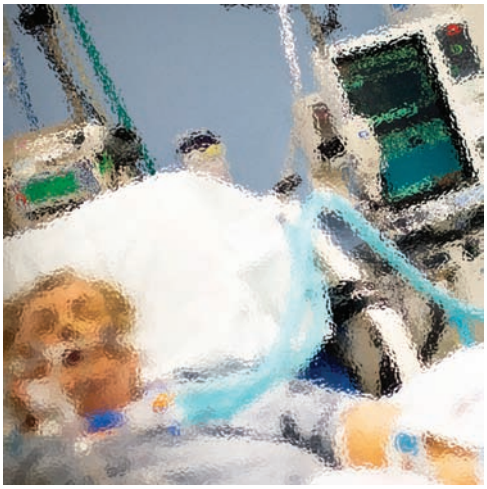
Baseline Vulnerabilities May Play a Larger Role than Depth of Anesthesia or Sedation in Postoperative Delirium

Pratik P. Pandharipande, M.D., M.Sc., Elizabeth L. Whitlock, M.D., M.Sc., Christopher G. Hughes, M.D., M.Sc.

Studies in mechanically ventilated patients have brought to the forefront the iatrogenic harm of deep sedation, particularly with continuous benzodiazepine infusions.[1,2] Interventional trials modifying sedation paradigms (*e.g.*, with nonbenzodiazepine medications)[3] and delivery patterns (*e.g.*, daily awakening trials, targeted light sedation),[4] as well as large-scale implementation trials of bundled supportive care (ABCDEF Bundle[5]; http://www.iculiberation.com, accessed August 1, 2021), have shown a decrease in sedative medication burden associated with clinically meaningful outcome benefits, including delirium, time on mechanical ventilation, and even mortality. The Society of Critical Care Medicine's Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption,[6] therefore, recommend targeting light sedation when needed, minimizing overall sedative medication exposure, and avoiding benzodiazepine infusions. With the high incidence and associated morbidity of postoperative brain dysfunction, there has been interest in utilizing similar techniques in the operating room. Unfortunately, it is unclear if the beneficial findings of reducing delirium by targeting lighter sedation in critically ill patients extrapolates to patients in the operating room undergoing general or regional anesthesia.



"Should we be surprised by the lack of an effect of depth of anesthesia or sedation on delirium outcomes during surgery, when studies in ICU patients have strongly suggested otherwise?"

In this issue of Anesthesiology, Brown *et al.* build on earlier work to elucidate the role of depth of sedation in the context of an anesthetic on delirium outcomes.[7] In the SHaping Anesthetic techniques to Reduce Postoperative delirium (SHARP) trial, investigators randomized 219 older patients undergoing lumbar fusion to either spinal anesthesia with propofol sedation titrated to a Bispectral Index (BIS) value greater than 60 to 70 (intervention) *versus* general anesthesia (control), where the anesthesiologist was blinded to the BIS values.[7] Patients were evaluated for delirium for the first 3 postoperative days using the Confusion Assessment Method. In the primary intention-to-treat analysis, median BIS values were 62 (interquartile range, 53 to 70) in the group that underwent spinal anesthesia with propofol sedation *versus* 45 (interquartile range, 41 to 50) in the group that underwent general anesthesia. Despite this, there were no statistically significant differences in delirium incidence rates: 25% in the spinal anesthesia with propofol group *versus* 19% in the general anesthesia group. Subgroup analyses factoring in age, comorbidities, and previous cognitive impairment did not yield any sufficiently powered results that would lend strong support to the use of one technique in favor of the other.

This study adds to the growing literature from randomized controlled trials that depth of anesthetic or sedation while undergoing regional anesthesia does not significantly alter delirium rates in the postoperative period in older patients. Two recent studies help contextualize this. In the ENGAGES (Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes) study,[8] patients (aged older than 60 yr and undergoing major surgery) were randomized to receive electroencephalogram (EEG)–guided anesthetic administration

Image: J. P. Rathmell.

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(n = 614) or usual anesthetic care (n = 618). The median end-tidal volatile anesthetic concentration and median cumulative time with EEG suppression was significantly lower in the EEG-guided group than the usual-care group. Delirium during postoperative days 1 to 5 was not different in the two groups and occurred in 26% in the EEG-guided group and 23% in the usual-care group. The double-blind STRIDE (Strategy to Reduce the Incidence of Postoperative Delirium in Elderly Patients) study[9] included older patients (aged 65 yr or older) who were undergoing nonelective hip fracture repair with spinal anesthesia and propofol sedation. Patients were randomized to heavier (Modified Observer's Assessment of Alertness and Sedation score of 0 to 2) or lighter (Observer's Assessment of Alertness/Sedation score of 3 to 5) levels of intraoperative propofol sedation. The overall incident delirium risk again was similar in both groups when measured on postoperative days 1 to 5.

Should we be surprised by the lack of an effect of depth of anesthesia or sedation on delirium outcomes during a surgical procedure, when studies in intensive care unit (ICU) patients have strongly suggested otherwise? Or are there fundamental differences in the patient populations, study design, and outcomes assessed that provide insight for future interventional trials? Baseline patient vulnerabilities may play the major role in development of delirium, with modifiable risk factors such as sedation/anesthetic depth and early mobilization, among others, providing some opportunity for targeting interventions.[10] Importantly, patients with greater vulnerabilities are probably more likely to benefit from addressing modifiable risk factors. The SHARP study patients had a median American Society of Anesthesiologists physical status classification of 2 (interquartile range, 2 to 3) and Charlson Comorbidity Index of 1 (interquartile range, 0 to 1), indicating a lower degree of comorbidity than ICU patients and highlighting a lower vulnerability risk. Like other studies in the operating room, including STRIDE,[9] the exposure to the intervention (deep *vs.* light sedation) was also brief (median, approximately 2 h) as compared with 2 to 3 days of sedation exposure in critically ill patients. Delirium was also not measured on postoperative day 0, a day where the contribution of sedation depth on delirium could have been higher.[11] These factors may help, in part, to explain the disparity in results between ICU and operating room studies. Additionally, currently identified surrogate markers of anesthetic or sedation depth using BIS or EEG may be inappropriate to target interventions aimed at addressing depth of anesthetic and sedation to make a significant impact on delirium outcomes. While there was a statistically significant difference between the groups in the SHARP trial[7] with regard to the BIS scores (62 in intervention; 45 in control), that difference may not be clinically meaningful in the context of the spinal anesthesia group still getting propofol in doses up to 125 mcg · kg^{-1} · min^{-1} (median highest dose, 80 mcg · kg^{-1} · min^{-1}), which may have contributed to higher-than-expected rates of delirium in the intervention. Future studies may help identify specific EEG patterns that are associated with worse delirium outcomes, allowing us to better focus interventions on a hypothetical vulnerable subpopulation (*e.g.*, the sensitive brain hypothesis, reduced cognitive reserve). ICU studies have shown that even a short duration of burst suppression (minutes) is associated with delirium after recovery from coma. The ENGAGES trial[8] was able to demonstrate a reduction in EEG suppression time from 13 min to 7 min, yet those 7 min may also be too much of an insult and something that perhaps can be avoided completely.

While the search for a surrogate marker of anesthetic or sedation depth with good specificity and sensitivity in the operating room is ongoing, adequately powered trials that help us understand the impact of anesthetic strategies on patients with high vulnerability and potential to benefit from modification of risk factors should be conducted. The current SHARP study was unfortunately powered assuming an almost 40% incidence of delirium and with an ambitious goal of reducing delirium by almost 50%, while in actuality the base rates of delirium were found to be much lower. This prevents a robust evaluation of statistical interactions between the interventions and key baseline vulnerabilities such as cognitive impairment, higher age, and comorbid status; although the cognitively impaired subgroup appeared to benefit from spinal anesthesia, the subgroup analysis itself was underpowered. Nonetheless, the authors' prespecified and *post hoc* subgroup analyses offer provocative hypotheses about the potential interactions of baseline cognitive impairment or of intrathecal morphine with the potential for harm or benefit of general anesthesia (some of which conflict with extant data in these areas). There is certainly more here that needs to be studied. Until we have stronger evidence to the contrary or higher fidelity measures to target anesthetic depth, it appears that baseline vulnerabilities and many determinants of the hospital course play larger roles in the multifactorial and complex underpinnings of delirium than the brief exposure to anesthetics and sedatives in the operating room does.

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Competing Interests

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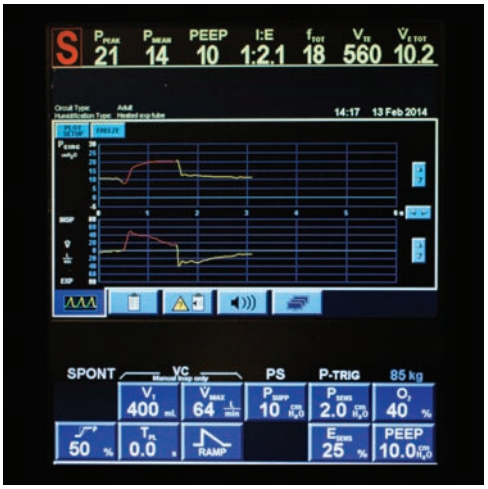
Pursuing the Importance of Postoperative Atelectasis

Luca Bigatello, M.D., Erland Östberg, M.D., Ph.D.

Atelectasis develops shortly after preoxygenation and induction of general anesthesia and impairs oxygenation by creating an intrapulmonary shunt. The pioneering use of computed tomography by Professor Göran Hedenstierna and collaborators in the 1980s[1] opened the way to understanding the pathophysiology of perioperative atelectasis. Atelectasis occurs in most anesthetized patients, generally affecting a small portion of dependent lung regions, but is more conspicuous in certain conditions such as patients who are overweight, have abdominal distention, or are in the Trendelenburg position.[2] Atelectasis may persist after surgery and may contribute to the development of postoperative pulmonary complications.[3]



"[What is] the link between optimal ventilatory strategies and a reduced incidence of postoperative pulmonary complications?"

Atelectasis during general anesthesia may be prevented by limiting the fraction of inspired oxygen ([F_{IO_2}] "absorption atelectasis")[4] and by promoting alveolar recruitment with positive end-expiratory pressure (PEEP) and recruitment maneuvers.[5] The effectiveness of these interventions has been thoroughly investigated during induction and maintenance of anesthesia. However, the same conditions that contribute to early formation of atelectasis are often present during, and shortly after, emergence from anesthesia. Therefore, ventilatory strategies during emergence may counteract evidence-based strategies used intraoperatively, facilitating the development of postoperative atelectasis.

In this issue of Anesthesiology, Jeong *et al.*[6] report the results of a clinical trial comparing the effects of pressure support ventilation with PEEP *versus* spontaneous ventilation during anesthetic emergence on postoperative atelectasis. In this randomized study, blinded to investigators of lung ultrasound and outcome assessments, 100 nonobese patients undergoing laparoscopic colectomies or radical prostatectomy received either the intervention of 5 cm H_2O pressure support over 5 cm H_2O PEEP throughout emergence, or the control where ventilation was provided manually as needed, without PEEP. Emergence was 8 to 9 min on average and F_{IO_2} was 0.4 in both groups. The main finding of the study is that maintaining a consistent positive pressure at the airway with pressure support and PEEP during emergence from general anesthesia results in lower incidence of atelectasis (measured by lung ultrasonography) and higher P_{AO_2} in the postanesthesia care unit. Unfortunately, but not unusually, no significant effect was detected in reducing the number of episodes of desaturation (S_{AO_2} less than 92%) nor of any predetermined clinical outcomes up to 48 h postoperatively.

More detailed information regarding the precise method of manual ventilation in the control group, especially the level of positive pressure, would have helped understanding to what extent the study groups differed in treatment other than in PEEP level. Also, the authors choice to omit preoxygenation before emergence is somewhat surprising: similar to the induction of anesthesia, increasing F_{IO_2} before extubation is a safeguard against the consequences of a problematic extubation. Finally, the quantitative difference in atelectasis between the two groups (table 2 in Jeong *et al.*[6]) is somewhat indistinct: while the number of atelectatic segments is significantly lower in the intervention group, the difference in atelectasis score does not reach significance. Regardless of these possible shortcomings, the study from Jeong *et al.*[6] is important for several reasons.

First, maintaining a consistent positive pressure at the airway throughout emergence from anesthesia for laparoscopic procedures limits the development of postoperative atelectasis. While numerous studies have demonstrated the

Image: J. P. Rathmell.

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beneficial effects of PEEP, individualized or not, during maintenance of anesthesia, the current study reminds us that this practice should be continued during emergence. From a physiologic point of view, and in accordance with the findings of the study, it is important to avoid airway closure and the development of areas with low ventilation/perfusion ratios (susceptible to atelectasis formation) during the entire course of anesthesia. This can be done by maintaining PEEP during emergence, with or without inspiratory support.

Second, Jeong *et al.*[6] limited F_{IO_2} to 0.8 during induction and 0.4 during maintenance and emergence, even with unexpected difficult intubations in nine study subjects. Given that the F_{IO_2} was equal between study groups, it is impossible to speculate on its effects on the development of atelectasis. The issue of F_{IO_2} on emergence remains an open one. Currently, we can only state that when concerns exist on the ability of a patient to maintain adequate oxygenation postoperatively because of difficult airway, morbid obesity, and obstructive sleep apnea, among others, an F_{IO_2} of 1 is indicated and recommended. In healthy patients undergoing nonabdominal procedures where a PEEP of 7 to 9 cm H_2O was maintained throughout the surgery, an F_{IO_2} of 1 during awakening did not produce clinically significant atelectasis.[7] This raises the question why one would refrain from emergence preoxygenation even in low-risk patients.

Third, computed tomography remains the accepted standard when measuring atelectasis. However, exposure to radiation and the need to transport the anesthetized or newly operated patient to the radiology department limits its use. Jeong *et al.*[6] used the still developing technique of ultrasonography, with its advantages of being portable, dynamic, and free of radiation. Lung ultrasound is judged to be reliable in detecting postoperative atelectasis, and one of several proposed scores has been shown to correlate with the volume of atelectasis measured by computed tomography.[8] Here, Jeong *et al.* looked at the incidence of atelectasis, and compared the number of patients in each group having a positive sign of atelectasis in more than 3 out of 12 examined lung sections. The numbers give a perhaps less intuitive appreciation of the extent of atelectasis formation and emphasizes that a standardized scoring system for lung ultrasound and atelectasis would be much welcomed.

A clear continuum between atelectasis and postoperative pulmonary complications is still elusive. Despite years of excellent research, the link between optimal ventilatory strategies and a reduced incidence of postoperative pulmonary complications does not consistently include preventing atelectasis. Despite much script and some important experimental data,[9] the clinical evidence is yet to come. Nearly 4 decades after the visual demonstration of atelectasis by chest computed tomography in humans undergoing general anesthesia, the knowledge in this field is orders of magnitude greater. However, we still need to add important pieces to the story to be able to link the prevention of atelectasis to the ability to improve outcomes. A possible feature of this process is the use of dynamic imaging that may complement what we know from computed tomography studies with a real-time exam with technologies such as ultrasonography and electrical impedance tomography. The study of Jeong *et al.* constitutes a small but significant building block in this trail.

Competing Interests

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Preoperative Chronic Opioid Trajectories: A Change (in Any Direction) Would Do You Good?

Patrick J. Tighe, M.D., M.S.

Aside from the risk of misuse, addiction, overdose, and/or death, chronic preoperative opioid use is associated with numerous facets of postoperative recovery, including rates of surgical complication, length of hospital stay, and hospital readmission.[1–3] Increasing recognition of these adverse events has driven efforts to wean opioids in the preoperative setting.[4–6] With more than one in four patients who present for surgery reporting preoperative opioid use, such efforts could potentially offer a significant public health impact.[7] Results from single-center prospective randomized controlled pilot studies suggest that preoperative opioid weaning interventions (*e.g.*, weekly phone calls guiding and supporting cessation efforts) are feasible and lead to a quicker return-to-baseline and/or cessation of opioids after surgery.[5] In a more generalized approach, a single-site retrospective cohort comparison of those patients achieving a 50% reduction in opioids before total joint arthroplasty through self- or physician-guided weaning with unweaned patients suggested that patients who successfully weaned their opioid dose had greater improvements in postoperative outcomes 6 to 12 months after surgery.[4] However, it remains unclear whether such weaning practices can translate to larger populations and practice settings. It is also unclear whether such findings generalize to practices outside of interventions specifically geared toward preoperative opioid weaning.

"[Are] decreasing or increasing opioid prescriptions in the weeks to months before surgery associated with differences in persistent postoperative opioid prescriptions?"

To answer the question of whether decreasing, or even increasing, opioid prescriptions in the weeks to months before surgery is associated with differences in persistent postoperative opioid prescriptions after surgery, Rishel *et al.*[8] examined a retrospective cohort of surgical patients using administrative health claims data. This study cohort comprised patients filling at least 10 opioid prescriptions, or 120 days of opioids, in the year before surgery. Surgeries included a selection of common elective (*e.g.*, total knee arthroplasty) and urgent/emergent (*e.g.*, appendectomy) procedures that were performed between 2004 and 2018. Importantly, a subset of these procedures (*e.g.*, total knee arthroplasty, mastectomy) have been previously associated with increased rates of persistent postsurgical pain.[9] The primary outcome was the amount of opioid(s) prescribed between 91 and 365 days after surgery, a time frame commonly associated with varying definitions of subacute to persistent postsurgical pain.[9] To examine the effect of preoperative opioid weaning, exposure was defined as patients with a 20% increase or decrease in average daily opioid dose across two sequential time intervals: 365 to 91 days before surgery and 90 to 7 days before surgery.

Surprisingly, Rishel *et al.*[8] found that after adjusting for confounding effects, either a 20% decrease or increase in opioids prescribed in the 90 days before surgery was linked to a lower rate that any opioids would be prescribed 91 to 365 days after surgery when compared with patients with stable opioid prescription rates before surgery. Notably, the absolute reductions were small: a 7% reduction for the group with decreasing preoperative opioid use, and 2.6% for the group with increasing preoperative opioid use, against a reference prevalence of 96.4% of patients with stable preoperative opioid use who continued to fill opioid prescriptions in this postoperative follow-up period. For patients who did receive an opioid prescription in this postoperative time frame, patients with increasing opioid prescriptions 90 days

Image: Adobe Stock.

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before surgery had a very slightly lower adjusted average daily dose of opioid (a decrease of just 2.2 oral morphine milligram equivalents against a reference adjusted average daily dose of 46.5 oral morphine milligram equivalents in the opioid-stable group) 91 to 365 days after surgery. Secondary analyses did not detect differences in the rate of postoperative adverse events, healthcare costs, or the number of days of postoperative hospitalization across the three groups of preoperative opioid trajectories.

Among other points of their methodology, Rishel *et al.*[8] should be particularly commended for their robust approach to sensitivity analyses used throughout their study; their careful consideration strengthens the support of their results and anticipates questions on whether select assumptions (*e.g.*, the definition of chronic opioid use) could have altered the findings.

As with many great research reports, these findings raise several interesting questions. First, how do we explain the decrease in longer-term opioid prescriptions for both preoperative opioid escalators and de-escalators? Without insight into the driving factors leading to opioid escalation or de-escalation before surgery, it remains impossible to define mechanisms explaining this linkage. Such conjectures become more challenging when one considers that between 2004 and 2018, our understanding of the dangers of perioperative opioids became much more widespread, as did alternative analgesic approaches. In one potential explanation, the authors posit that for patients with increasing preoperative opioid use, worsening pain may have driven increasing opioid use and a decision for surgery that then ameliorated the underlying pain generator. They do note, however, that the observed results held for nonelective procedures, whereby intentional reduction of opioids in preparation for surgery may not have been feasible. It may be that it is not the increase or decrease itself that is relevant, but rather the responsive practice dynamic that drove a minimum-necessary approach to opioid prescription. It is also possible that for subsets of both escalators and de-escalators, different motivations nevertheless lead to the same use of various behavioral, interventional, or multimodal analgesic strategies that influenced postoperative opioid prescriptions. In such cases, patients on a stable opioid regimen may not have had similar incentives to use such analgesic adjuncts. Given these and other possible explanations for the observed findings, it is important to consider that the health claims data used in this analysis originated with patient members of commercial and Medicare Advantage health plans; this may pose limitations in generalizability for other socioeconomic groups in the United States.

Relatedly, this article highlights opportunities to better understand which conditions initiated an analgesic prescription. Rishel *et al.*[8] wisely selected both elective and emergent procedures, as well as procedures associated and not associated with chronic preoperative and postoperative pain. Despite extensive sensitivity analyses, no major differences emerged between these procedure groups. Notably, 8.6% of patients on long-term preoperative opioids had cessation of opioid prescriptions 91 to 365 days after surgery. These findings comport with those of Jivraj *et al.*,[10] who found in a cohort of chronic opioid users that surgery was associated with increased likelihood of opioid discontinuation, especially if the mean preoperative opioid dose was less than 90 morphine milligram equivalents, and that discontinuation was greater for surgical *versus* medical patients.[10] It is plausible that for some of these patients, the surgery directly addressed the underlying pain generator and obviated the need for continued opioid therapy. However, such presumptions may be called into question if, for example, the opioids were prescribed for back pain and yet the patient underwent a laparoscopic appendectomy for appendicitis. Such discernments are simply not feasible with contemporary data commonly used in pharmacoepidemiology. It is worth highlighting that opioid consumption is not the same as opioid prescription, that previous works highlighting the number of opioids prescribed after surgery can substantially exceed the amount consumed, and that increased prescriptions are associated with increased consumption.[11]

This research project also highlights more systematic opportunities in how health data are collected and managed. Following established approaches to pharmacoepidemiology, Rishel *et al.*[8] carefully define exposures, which in this case are opioid trends (escalating, de-escalating, stable). In effect, these trends represent decisions, or perhaps a series of decisions over time, that establish the observed trends. But what drove these decisions? Was there a particular state change that led the prescribers to modify their analgesic approach? Without this sequence of state–action–outcome, it becomes difficult to understand how we might more fully incorporate these results into our day-to-day decision-making. Such opportunities are systematic throughout health outcomes research. While causal inference and related methods can plausibly address some of these shortcomings, they remain constrained by the features and organization of data commonly found in outcomes research.

Another opportunity relates to how outcomes surrounding pain are collected in both clinical and research constructs. While this study captured information pertaining to opioid prescriptions, it is reasonable to presume that such opioids were most likely prescribed due to increased pain intensity. After surgery, pain intensity absent context provides little support for clinical decisions; a pain intensity rating of 8 out of 10 may be reassuring (at least, from an analgesic titration perspective) as a postoperative patient continues to lap the ward at an 8-min mile pace, yet 0 out of 10 would be quite concerning in a patient with respiratory compromise. Similarly, data on opioid use (whether prescription or administered doses) absent context on pain intensity, pain quality, and normalized indices of patient function provide only limited insight into quality of recovery.

In summary, the report by Rishel *et al.*[8] suggests that regarding preoperative opioid therapy, a change in use in any direction may be associated with small improvements in postoperative opioid requirements, at least as measured by opioids prescribed. We look forward to learning more about the potential clinical relevance of these findings, as well as the practice patterns that could motivate such trends in both perioperative opioid–related exposures and outcomes.

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Competing Interests

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The Big Match: Lung Ventilation and Blood Flow during Inhalational Anesthesia and Recovery—Is There a Winning Combination?

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For most anesthesiologists, volatile anesthetic agents remain a core tool that we use on a daily basis. Real-time tidal gas concentration measurement is one great strength of inhalational anesthesia. However, an end-tidal concentration is just one intermediate point in the complex process between a dialed vaporizer concentration and drug effect. While many of the principles of this process are taught during training, we suggest that achieving the highest standards of patient care in our specialty requires an understanding, and the daily application, of the principles of inhalational pharmacokinetics.

"The practice of anesthesiology prides itself on having a strong basis in science."

In two papers in this issue of Anesthesiology,[1,2] Kretzschmar *et al.* and Baumgardner *et al.* present data from animal studies exploring the changes in blood concentrations of sevoflurane and desflurane during uptake and elimination of these agents. This work was conducted at the Hedenstierna laboratory in Uppsala, Sweden.

There are two salient features of these studies. As the authors point out, there is very little published *in vivo* work on elimination of inhalational anesthetic agents, and yet this phase of anesthesia is important for several reasons. As many texts on inhalational anesthesia point out, in contrast to induction, where we can use "over-pressure" to accelerate onset, we are limited in our ability to manipulate the partial pressure gradient in the same way to accelerate elimination and recovery. Second, the primary focus of these studies was blood content. Most studies of inhalational agents use concentrations in end-expired gases as a questionable surrogate for blood partial pressures. However, it is the partial pressure gradient between inspired gas, blood, and tissues that drives onset and offset of effect.

There are several key findings from these studies. First, they show how, at any given cardiac output, overall lung alveolar ventilation quickly becomes the main determinant of the rate of rise or fall of the partial pressure of the agent in arterial and mixed venous blood, and that this effect persists for at least the first 45 min after commencement or cessation of administration of these agents. The authors further find that after 10 min into the washout phase, volatile agent elimination can be represented by a simple model consisting of just two body compartments: the muscle group and the lungs.

Interestingly, the authors have in the process confirmed *in vivo* the findings of previous theoretical analyses that posed the question, "What effect does cardiac output have on the rate of elimination of a volatile agent?" These studies predicted that a higher cardiac output slowed the washout or rate of fall in partial pressure of volatile agents in the vessel-rich tissues such as the brain during emergence, in a similar fashion to its slowing of washin during induction.[3] While computer models are instructive, their inherent simplifications can deceive us and need to be challenged or validated with real measurements to reassure us of their reliability. Kretzschmar *et al.* have supported this in their piglet model, where the overall alveolar ventilation/perfusion ratio ($\dot{V}_A/\dot{Q}$) was manipulated by either doubling, or almost halving from baseline, cardiac output using dobutamine or atrial occlusion, respectively, accompanied by more modest opposite changes in ventilation. They found the rate of decline in venous blood partial pressure is slowed by a lower overall $\dot{V}_A/\dot{Q}$, *i.e.*, a higher cardiac output, and

Image: J. P. Rathmell.

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accelerated by lower cardiac output. The authors have gone on to interpret this as *in vivo* evidence that overall alveolar ventilation rate persists into the postoperative period as the rate-limiting step in the elimination of modern volatile agents from the body.

The implications for the physiology and conduct of anesthesia in humans need to be critically examined. First, under clinical conditions, we do not deliberately modulate global $\dot{V}_A/\dot{Q}$ ratio by manipulation of cardiac output, beyond ensuring adequate fluid and volume resuscitation and blood pressure support to attempt to optimize the patient's circulation. Rather, the tool we have most readily at hand in everyday practice is the ability to modulate overall alveolar ventilation rate through control of lung minute ventilation. What does this do to the variables measured in this study, where global tissue perfusion remains relatively steady? We may have to rely on computer simulations a little longer to answer this question. In the meantime, the data from Kretzschmar *et al.* are reassuring that the assumptions we have relied upon and taught for some years are largely correct. These results suggest maintaining minute ventilation during emergence will enhance clearance of inhalation agents from body tissues, and this effect continues into the recovery period. Conversely, factors decreasing minute ventilation such as postoperative opioid-induced respiratory depression may slow elimination of these drugs.

A second reason to question simple extrapolation of these findings to our patients is the assumption that the lungs can be treated as a single uniform compartment with no significant variation in $\dot{V}_A/\dot{Q}$ ratio throughout the lung (*i.e.*, no $\dot{V}_A/\dot{Q}$ scatter). Increased $\dot{V}_A/\dot{Q}$ scatter manifests as widening of end-tidal or alveolar to arterial partial pressure gradients for gases being taken up or eliminated by the lung. This simplification is commonly made in computer simulations of inhalational pharmacokinetics and was not unreasonable for their piglet model where the degree of $\dot{V}_A/\dot{Q}$ scatter appears relatively small, as indicated by the alveolar to arterial gradients measured for carbon dioxide. For this reason, the end-tidal volatile agent partial pressures in the piglets are likely to have been close to the measured arterial partial pressure.

However, these assumptions generally do not hold true in the anesthetized patient. As first shown elegantly almost 40 yr ago by Goran Hedenstierna and colleagues in Stockholm using the multiple inert gas elimination technique, significant scatter in distributions of alveolar ventilation rate and cardiac output is the norm even in healthy human lungs under general anesthesia.[4] Consequently, relatively large alveolar to arterial partial pressure gradients for volatile agents persist for the duration of surgery.[5] Nevertheless, there is no *a priori* reason to think that the typical reduction in efficiency of lung gas exchange seen in anesthetized humans should contradict the authors' finding[1,2] that alveolar ventilation acts as the primary brake on volatile agent elimination from the body at any given level of cardiac output.

The characteristics of the main phase of elimination found by the authors were relatively rapid and similar to those seen from muscle alone. That may surprise some. Does this mean that obesity and volatile anesthesia are not such uncomfortable bedfellows as is often assumed? In clinical practice, we are generally a long way from equilibrium with our inhaled volatile agents. In particular, the body fat compartment has relatively low perfusion, thus taking a long time to reach equilibrium. Even with desflurane, the time constant for the fat compartment is 22.5 h.[6] The effect of this extremely slow uptake into fat has recently been neatly shown by Weber *et al.*, who, using computer simulation with GasMan (Med Man Simulations, Inc., USA), showed that after 10 h of anesthesia, desflurane partial pressure in fat is only about one third of that in the brain.[7] This modeling is supported by clinical data, with Lemmens *et al.* observing that the effect of increasing body mass index on uptake is minimal,[6] while McKay *et al.* found that duration of volatile agent administration had a much greater effect on recovery times than increasing body mass index.[8] These various results support the suggestion of the data from Baumgardner *et al.* that fat plays a lesser role than generally assumed in onset and offset of activity, at least over short-term anesthetic and postoperative time frames.

The practice of anesthesiology prides itself on having a strong basis in science. This compels us to continue to push the boundaries of what we know about what we do, and to practice based on an understanding of the underlying processes rather than taking a one-size-fits-all cookbook approach to drug administration. Kretzschmar *et al.* and Baumgardner *et al.* have added valuable insight into sevoflurane and desflurane pharmacokinetics, as well as hints about models that can help simplify our understanding of their pharmacology. In the process, the authors have reminded us of the importance of seeking a better understanding of the physiology behind our practice, and have shown us that there is much in the world of inhalational anesthesia that is yet to be explored.

We conclude by sadly acknowledging the recent passing of Goran Hedenstierna. During a research career spanning several decades, Professor Hedenstierna led an innovative and wide-ranging program of both clinical and preclinical studies with particular focus on the factors that impact lung function and ventilation/perfusion matching during anesthesia and critical care, and the potential interventions to ameliorate these effects. The global anesthesiology community has lost a distinguished leader, and many of us have lost a great friend and mentor, whose warmth, good humor, and generosity of knowledge will be greatly missed.

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ANESTHESIOLOGY

Elastomeric Respirators for COVID-19 and the Next Respiratory Virus Pandemic: Essential Design Elements

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ABSTRACT

Respiratory viruses are transmitted *via* respiratory particles that are emitted when people breath, speak, cough, or sneeze. These particles span the size spectrum from visible droplets to airborne particles of hundreds of nanometers. Barrier face coverings ("cloth masks") and surgical masks are loose-fitting and provide limited protection from airborne particles since air passes around the edges of the mask as well as through the filtering material. Respirators, which fit tightly to the face, provide more effective respiratory protection. Although healthcare workers have relied primarily on disposable filtering facepiece respirators (such as N95) during the COVID-19 pandemic, reusable elastomeric respirators have significant potential advantages for the COVID-19 and future respiratory virus pandemics. However, currently available elastomeric respirators were not designed primarily for healthcare or pandemic use and require further development to improve their suitability for this application. The authors believe that the development, implementation, and stockpiling of improved elastomeric respirators should be an international public health priority.

(ANESTHESIOLOGY 2021; 135:951–62)

Elastomeric respirators are reusable respirators made of plastic or non–latex-containing rubber materials with exchangeable filter cartridges or canisters. Elastomeric respirators have been widely used in industry, but not in health care. We believe there is an urgent need to develop elastomeric respirators specifically for respiratory protection from pandemic respiratory viruses. While such elastomeric respirator development may not take place in time for widespread use during the current COVID-19 pandemic, it is vitally important to be prepared for the next respiratory pandemic, which could occur at any time.[1] There is also the possibility that immune escape of SARS-CoV-2 variants could result in a protracted COVID-19 pandemic, heightening the importance of effective respiratory protection.[2] In this article, we explain why respiratory protection is important, describe the major types of respiratory protection, and elaborate on the potential role for elastomeric respirators.

Airborne Pathogens

Respiratory viruses may spread by fomite (touching a contaminated surface and then transferring the virus to the respiratory tract), droplet, or airborne routes (table 1). Determining the relative importance of these routes for an individual virus is difficult and may be controversial; for SARS-CoV-2, the fomite route of transmission is thought to be less important.[3,4] Many experts now believe that there is a continuous spectrum of different sized respiratory particles produced by persons infected with respiratory viruses, and that the traditional distinction between droplet and airborne transmission is arbitrary and obsolete.[5–7] During the current COVID-19 pandemic, there has been controversy, as in previous respiratory virus pandemics, concerning whether respiratory protection should protect against only droplet or droplet and airborne particles.[8] However, there is now substantial evidence that airborne transmission of SARS-CoV-2 transmission is likely[5,9–12]; inhalation of respiratory particles may be the predominant route of transmission. Difficulty in culturing putative airborne pathogens from air samples because of various technical obstacles does not rule out airborne transmission.[5,12] Therefore, it seems prudent to protect healthcare workers (and the public) accordingly, by using respiratory protection whenever possible. The two major categories of respirators used for respiratory protection in health care include negative and positive pressure mode respirators.

Negative Pressure Mode Respirators

The wearer of a negative pressure mode respirator draws air through a filter and into a facepiece during inhalation. There are two main types of negative pressure respirators: disposable filtering facepiece respirators[13] (such as the N95 filtering facepiece respirators, familiar to many healthcare workers), and elastomeric respirators,[14] which are reusable (table 1; fig. 1). The effectiveness of respiratory protection depends upon fit, filtering efficiency, and resistance to breathing (table 1).

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Table 1. Respiratory Protection Terminology

Terminology	Alternative Terminology	Major Characteristics
Airborne particles	Smaller respiratory particles; aerosols	Typically smaller than droplets, with the limiting size being a bare virus, approximately 0.1 μm in diameter (airborne particles typically contain water and other molecules in addition to viruses). May remain suspended in the air for longer periods of time and travel over longer distances in comparison to droplets. Transmission of infection typically involves inhalation directly into the lungs.
Assigned Protection Factor		The workplace level of protection that a class of respirators is expected to provide if it is fit and used appropriately. A somewhat arbitrary number, representing the ratio of the concentration of contaminant in the ambient air compared to the concentration of contaminant inside the respirator based on typical performance of a particular class of respirator. For example, an Assigned Protection Factor of 10 means that the concentration of particles inside the mask will be reduced to 10% of the concentration in the ambient air. The Assigned Protection Factors for filtering facepiece and elastomeric half-mask respirators are both 10.
American Society for Testing and Materials F2100 Standards		Standards for surgical masks concern repelling blood or other fluids, filtering submicron particles and bacteria, fire resistance, and breathability; the American Society for Testing and Materials (West Conshohocken, Pennsylvania) has defined three barrier levels.
Barrier face covering	Cloth mask, homemade mask	Protects others mainly by preventing the release of large respiratory droplets; no or very limited prevention of small particle release; very limited protection of the wearer from droplets and aerosols.
Droplets	Larger respiratory particles	Traditionally defined as respiratory particles > 5 μm in diameter. Tend not to be suspended in the air for long periods of time, as they are relatively heavy. Traditional concept of droplet transmission of infection involves direct contact between droplets and mucous membranes such as the nose, mouth, or eyes, not inhalation of particles directly into the lungs.
Elastomeric respirator	Reusable respirator	Plastic or rubber mask, typically with filter cartridges or canisters; depending upon filter type, can be used for protection against chemicals as well as particles; regulated by the National Institute for Occupational Safety and Health (Washington, D.C.) in the United States.
Filtering efficiency		The filtration efficiency of a respirator is the degree to which the filter material removes particles from air passing through the filter. Filtering efficiency of respirators rated by National Institute for Occupational Safety and Health as 95, 99, or 100, corresponding to filtration of 95%, 99%, or 99.97% of 0.3-μm particles, which are usually the most penetrating particle size. In addition, the filters are designated with the letter N, R, or P, corresponding to "not resistant to oil," "somewhat resistant to oil," and "very resistant to oil," respectively. Oil resistance is not a factor in health care, and N, R, or P filters can be used. A National Institute for Occupational Safety and Health 100 filter rating is very similar to a high-efficiency particulate air filter rating, originally devised by the United States Department of Energy (Washington, D.C.).
Filtering facepiece respirator	Disposable respirator; examples include N95 (National Institute for Occupational Safety and Health); FFP2 (European Union); other designations depending upon origin and filtering characteristics	Protect against droplets and aerosols when seal against face is effective; regulated by National Institute for Occupational Safety and Health in the United States; may also be cleared for marketing by the Food and Drug Administration (Silver Spring, Maryland) for use as a surgical mask; National Institute for Occupational Safety and Health–certified respirators are required by the Occupational Safety and Health Administration (Washington, D.C.) in workplaces for personal protection.
Fit factor		A concept similar to the Assigned Protection Factor, but based on how well a specific respirator fits a specific individual. Measures the degree to which particles can enter through gaps between the face and the respirator. Does not test the filtering efficiency. For most respirators, gaps between the face and the respirator are a more significant route of entry than through the filtering material. The fit factor is the measured ratio of the contaminant concentration in ambient air to the concentration inside the respirator required to pass a quantitative fit test. The required fit factor for both a filtering facepiece and elastomeric respirator is 100. This is 10 times the Assigned Protection Factor of 10, which adds a "margin of safety."
Powered air purifying respirator	Reusable respirator	A fan draws air through a filter and then forces purified air into the face covering. The exhausted air escapes around the edges of the face covering and is not filtered. Level of respiratory protection generally greater than filtering facepiece respirators; regulated by National Institute for Occupational Safety and Health in the United States.
Surgical mask	Procedure mask, medical mask	Mainly protects from respiratory droplets, limited protection from aerosols; a few are cleared for marketing in the United States by the Food and Drug Administration and meet American Society for Testing and Materials F2100 standards.
User seal check		A maneuver performed each time a respirator is donned in an attempt to verify that there is an adequate seal to the face. Should be performed regardless of whether the user has passed a formal Occupational Safety and Health Administration fit test with the respirator. Difficult to execute for a filtering facepiece respirator because air can pass through the entire mask body, making it difficult or impossible to completely occlude the entire mask body to test whether air can be inhaled around the edges of the respirator. Relatively easy to execute for an elastomeric respirator by simply covering the breathing inlets with the palm of the hand.

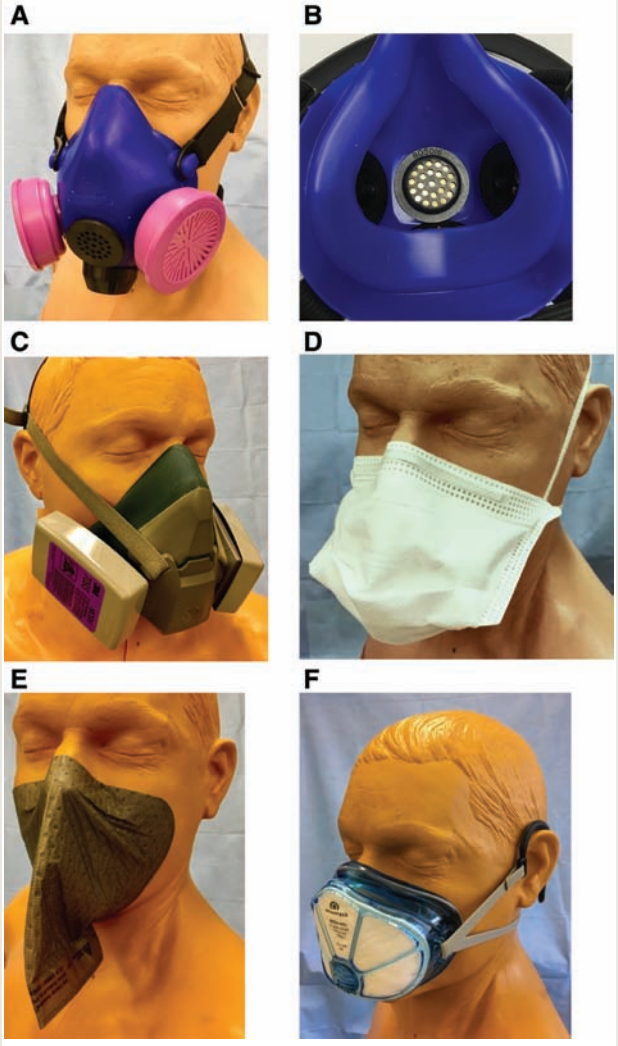

Fig. 1. Examples of filtering facepiece respirators, elastomeric respirators, and a hybrid respirator. Elastomeric respirators with P100 filters enclosed in plastic cartridges are shown in *A* and *C*. Both elastomeric respirators have exhalation valves at the bottom of the front of the mask. The respirator in *A* also has a "speaking diaphragm" in the center front of the respirator. A closeup view of the speaking diaphragm is shown in *B*. The filtering facepiece respirator in *D* is a typical N95. The filtering facepiece respirator in *E* is a unique strapless N95 that is attached to the face by an adhesive strip around the edge of the mask. An example of a hybrid respirator design is shown in *F*, combining a plastic mask body and sealing surface with a melt-blown fabric filtering area. The example shown is a "quarter face" respirator that does not cover the chin; the other respirators shown are "half face" respirators; quarter face respirators have an Assigned Protection Factor of 5, while half face respirators have an Assigned Protection Factor of 10 (see table 1).

Negative Pressure Mode Respirator Fit

Fit defines the extent to which there is an occlusive seal of the respirator with the face, preventing leakage and forcing all inhaled and exhaled air to pass through the filtering material (or in some cases through an exhalation valve). In contrast, barrier face coverings[15] ("cloth masks") and surgical masks[16] are not designed to make a tight seal to the face (table 1). Only when there is an occlusive seal with the face, as with a respirator, does almost all of the air entering the facepiece pass through the filtering material, providing the optimal opportunity to remove particles from the air.[17,18] In the United States, the Occupational Safety and Health Administration (Washington, D.C.) Respiratory Protection Standard[19] requires that employees must be medically cleared to wear a respirator and that employers must measure the fit of respirators for employees upon first selection and annually thereafter using standardized tests that may be qualitative or quantitative.[19] Numerous studies have shown that the fit of a filtering facepiece respirator varies considerably depending upon the particular design and materials, and the facial characteristics of an individual user; not all respirators fit the full range of human faces.[20] The face must be clean-shaven in order to obtain an effective fit. A recent American Society for Testing and Materials (West Conshohocken, Pennsylvania) standard for "respirator fit capability" may be used to characterize how well a particular respirator will fit a variety of facial characteristics.[21] Moreover, filtering facepiece respirators are disposable, and the quality of the fit may deteriorate with repeated use.[22]

Negative Pressure Mode Respirator Filtering Efficiency

Filtering facepiece respirators typically utilize a layer of melt-blown polypropylene (or other synthetic material) fabric as the filter. The randomly oriented fibers of the melt-blown fabric filter particles by a combination of impaction, diffusion, and interception.[23] In addition, an electrostatic charge is often added to enhance filtration, causing the material to function as a permanent magnet, or "electret."[24]

Elastomeric respirators are constructed of various solid plastic or rubber materials that form the mask body and the portion of the mask that seals to the face. Filtering is accomplished by one or more exchangeable filters, constructed of material similar to that of filtering facepiece respirators, that attach to the mask body. The filtering material may be protected within a canister or cartridge (figs. 1 and 2). In the United States, the National Institute for Occupational Safety and Health (Washington, D.C.), a branch of the Centers for Disease Control and Prevention (Atlanta, Georgia), certifies the filtering efficiency of respirators using standardized tests[25] (table 1).

Negative Pressure Mode Respirator Resistance to Breathing

In addition to fit and filtration, resistance to breathing is an important property. Increased resistance to breathing results in increased negative and positive pressures inside the respirator during inhalation and exhalation, respectively, which could

Fig. 2. Examples of elastomeric respirator filters. The outer facing side of the filters is shown in the *upper photos*, and the side of the filters that attaches to the respirator is shown in the *lower photos*. Both filters are P100 (equivalent to high-efficiency particulate air). The filtering material of the *left* filter is exposed, while the filtering material of the *right* filter is completely enclosed in plastic. The *right* filters are also shown mounted on an elastomeric respirator in fig. 1C.

increase leakage around the respirator facepiece. Resistance to breathing also affects comfort and tolerability.[26] In the United States, the National Institute for Occupational Safety and Health requires that respirator filtering material be tested for the pressure gradient across the filtering material at 85 l/min constant airflow; the "inspiratory" pressure gradient must be less than 35 mm H_2O (343 Pa), and "expiratory" pressure gradient must be less than 25 mm H_2O (245 Pa). Methods for testing the pressure gradient across filtering material typically specify the cross-sectional area of the material to be tested, since the cross-sectional area affects the pressure gradient under conditions of constant volumetric flow rate. The National Institute for Occupational Safety and Health method for certifying filtering facepiece respirators specifies that the entire respirator is sealed onto a plate for testing; approved filtering facepiece respirators typically have inspiratory and expiratory pressure gradients in the approximate range of 5 to 15 mm H_2O at 85 l/min airflow.[27] Currently, there is not a standardized test for measuring the pressure gradient across a respirator during actual use. A study of a single model of a filtering facepiece respirator found peak pressure gradients of less than 20 mm H_2O during exercise.[28]

Positive Pressure Mode Respirators

Powered air purifying respirators employ a fan or pump that brings air through the filter and into the facepiece. Filtration is important, but fit is less so; a powered air purifying

respirator with a loose-fitting hood offers greater protection to the wearer than an N95 filtering facepiece respirator because it provides more than enough filtered air to overcome any inward airflow between the hood and the wearer's head.[29] Powered air purifying respirators with a loose-fitting hood generally have an Assigned Protection Factor (table 1) of 25, or 2.5 times the Assigned Protection Factor of 10 for a filtering facepiece or elastomeric respirator.[19] Loose-fitting powered air purifying respirators have the advantage of not requiring fit testing, and contrary to negative pressure mode respirators, do not increase resistance to breathing. Their performance is not affected by the presence of facial hair as they do not make a tight seal to the face. It is important to understand that the exhaled air passes around the edges of a loose-fitting powered air purifying respirator hood without filtration; only the inhaled air is filtered.

Disadvantages of powered air purifying respirators include their greater complexity of use (*i.e.*, fan motors and batteries), higher cost, and the possibility of impaired communication caused by fan noise. A potentially serious shortcoming of loose-fitting powered air purifying respirators is that the exhaled air is exhausted into the ambient air without filtration. This could hypothetically result in contamination of a sterile field or transmission of a respiratory pathogen by the wearer.[30] The unfiltered exhaust from a powered air purifying respirator is analogous to an unfiltered exhalation valve on a negative pressure mode respirator. We suggest that powered air purifying respirators should be available for healthcare workers who, because of facial features or facial hair, are unable to be fitted for a filtering facepiece or elastomeric respirator, or when an increased Assigned Protection Factor is desired. However, we also suggest that during a pandemic, negative pressure mode respirators (*i.e.*, filtering facepiece respirators or elastomeric respirators) are likely to be a better solution for providing respiratory protection for large numbers of healthcare workers.

Tight-fitting half facepiece powered air purifying respirators are also available, although they have been used much more widely in industry than in health care (fig. 3). Tight-fitting powered air purifying respirators require fit testing and would not be suitable for use with facial hair that interferes with the seal of the mask body to the face. An Assigned Protection Factor of 50 is possible, five times that of a negative pressure elastomeric respirator and twice that of a typical loose-fitting powered air purifying respirator,[19] making this an attractive option when higher levels of protection are desired.

Full Face Respirators

Full face elastomeric respirators (sometimes referred to as "gas masks") that cover the eyes, nose, and mouth within a single mask body are another option to consider. Such respirators are used routinely by the military, police, and fire fighters and for industrial applications in which infectious agents, chemical toxins, or radioactive particles can irritate or damage the eyes or gain entry to the body through the eyes, as well as the respiratory system. While eye protection in the form of glasses or goggles has been advised for protection from SARS-CoV-2,[31] the evidence for respiratory viruses causing infection from contact with the conjunctiva is not strong.[32–37] In general, full face masks are heavier, are less comfortable in warm environments, and may have greater interference with the field of vision in comparison to half masks (which do not cover the eyes). Nevertheless, a study of acceptability to healthcare workers of military-style elastomeric full face respirators in comparison to filtering facepiece respirators (used with eyeglasses or goggles) found a high level of acceptance for the full face respirators when worn for brief periods (up to 40 min).[38]

Surgical Masks

It is important to note that while surgical masks are typically constructed from melt-blown fabric, and bear some superficial physical resemblance to filtering facepiece respirators, surgical masks are not respirators. Some surgical masks are cleared for marketing (in the United States) by the Food and Drug Administration (Silver Spring, Maryland) and meet American Society for Testing and Materials F2100 standards[16] (table 1). Surgical masks are intended to block large droplets, splashes, sprays, or splatter from reaching the mouth or nose and to prevent the user's droplets from exposing others. Surgical masks may capture some but not all of the particles contained in a wearer's cough or sneeze.[39] Since surgical masks are not designed to make an occlusive seal with the face, the protection from inhalation or exhalation of infectious particles will be limited in comparison to a properly fitted respirator.[40–46] The American Conference of Governmental Industrial Hygienists (Cincinnati, Ohio) has published an informative graphic illustrating the comparative effectiveness of cloth face coverings, surgical masks, and respirators.[47]

Filtering Facepiece *versus* Elastomeric Respirators

Filtering facepiece respirators such as N95 or the European Union equivalent FFP2 have been avidly sought during the COVID-19 pandemic; public health authorities initially advised that these respirators should only be used by healthcare workers, but recently some governments have recommended or even required their use by the public.[48] While filtering facepiece respirators provide effective respirator protection when properly fitted, they have significant shortcomings (table 2). A major shortcoming is the overwhelming number of respirators required during a respiratory pandemic, inevitably resulting in acute shortages, even when respirators are stockpiled in advance. During the COVID-19 pandemic, due to the shortage of respirators, there were numerous attempts to construct homemade respirators using three-dimensional printed materials, respiratory therapy equipment, anesthesia circuit filters, and other available components.[49–51] This situation revealed the critical shortage of commercially available respiratory protection. To the contrary, elastomeric

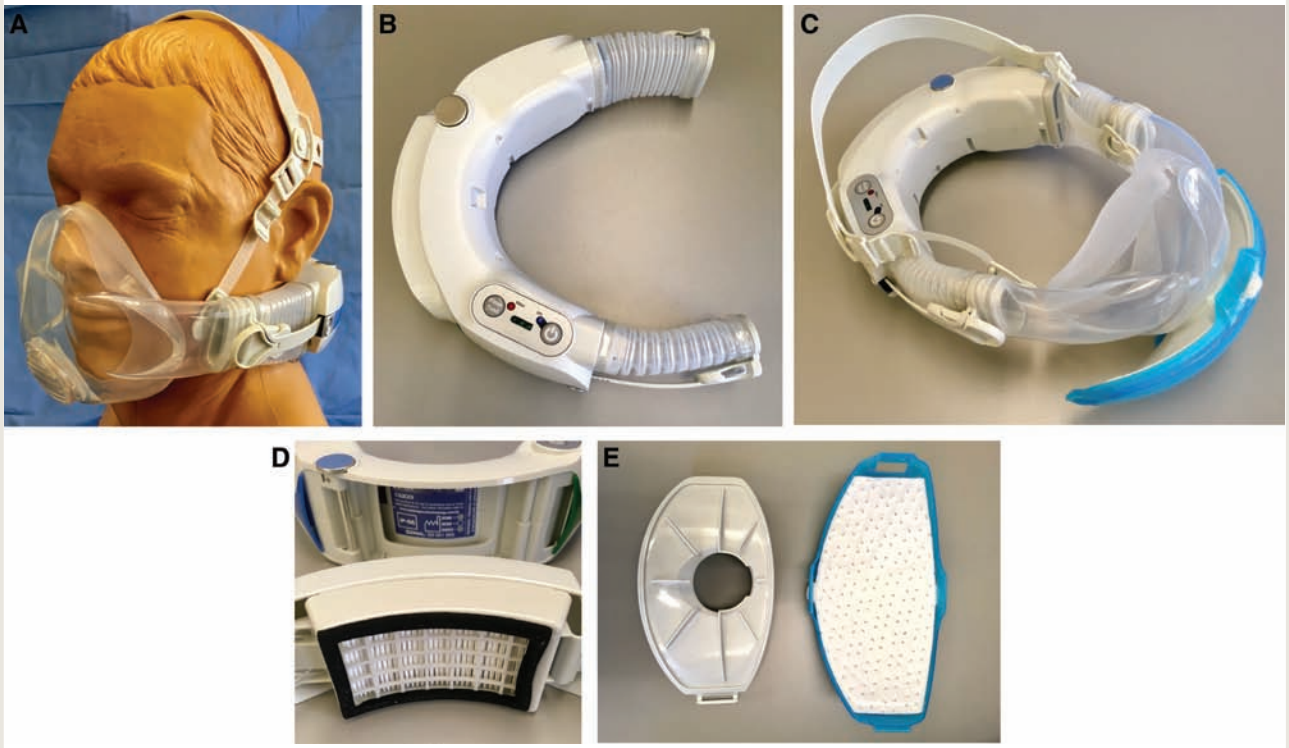

Fig. 3. An example of a tight-fitting, half facepiece powered air purifying respirator is shown in *A* (CleanSpace Technology; Australia); the unfiltered exhalation valve is in the center of the facepiece. In *B*, another view of the battery and fan unit is shown. In *C*, a view of the accessory N95 filter attachment for the exhalation valve is shown; when used, filtration of the exhalation valve provides "source control," preventing the wearer of the respirator from exhaling respiratory pathogens into the surrounding air. This respirator is intended to make a highly effective seal against the face, and should be fit tested before use, just as with a negative pressure elastomeric respirator or filtering facepiece respirator. Air is drawn through a high-efficiency particulate air filter (shown in *D*) and pushed into the respirator under positive pressure by the battery-powered fan located behind the wearer's head. Exhalation occurs through an unfiltered valve on the front of the respirator, unless the accessory N95 filter is attached to the exhalation valve (the replaceable N95 filter is shown inside of the filter holder in *E*). This respirator has at least three advantages compared to a loose-fitting powered air purifying respirator. First, because this respirator has both a tight seal against the face and positive pressure produced by the battery powered fan, the Assigned Protection Factor is 50, twice that of a typical loose-fitting powered air purifying respirator, or five times that of a negative pressure elastomeric respirator. Second, it is possible to filter the exhaled air, which is not possible with a loose-fitting powered air purifying respirator. Third, if the power source or fan fails (for example, if the battery is exhausted), the respirator will function as an ordinary negative pressure elastomeric respirator, with the wearer pulling inhaled air through the high-efficiency particulate air filter; if a loose-fitting powered air purifying respirator power source or fan fails, there is no respiratory protection.

respirators can be used for prolonged periods of time, and thus provide a durable solution during a pandemic.

Elastomeric respirators are widely used outside of health care for protection from aerosols and harmful vapors and gases. Their use in health care has been limited, but successful implementation has been reported.[52–54] In 2019, before the COVID-19 pandemic, a consensus report from the National Academy of Sciences, Engineering, and Medicine (Washington, D.C.) concluded that "reusable elastomeric respirators could be a viable option for use in surge situations" and that surge use would be enhanced if "reusable elastomeric respirators were a part of healthcare facilities' day-to-day respiratory protection program."[55] However, the report also acknowledged the shortcomings of existing elastomeric respirator products, and recommended "design of innovative reusable respirators and the implementation of robust respiratory protection programs…taking into account the distinctive characteristics of the healthcare workplace…" In light of the experience gained with respirators during the COVID-19 pandemic, this document now seems prescient.

There are several potential advantages of elastomeric respirators in comparison to filtering facepiece respirators (table 2).[56] Elastomeric respirators are ideally suited to pandemic surge use because they can be reused indefinitely, and filter cartridges or canisters can last for extended periods of time (see the Durability of Elastomeric Respirators section). Elastomeric respirators are capable of robust user seal checks because occlusion of the filter ports completely

Table 2. Elastomeric Respirator Compared to Filtering Facepiece Respirator

	Elastomeric Respirator	Filtering Facepiece Respirator
Value during a surge	Extended use, could last for entire pandemic. Filters can last for extended periods.	Disposable. Very large numbers of masks required during a sustained pandemic.
User seal check	User seal check is robust.	User seal check is not robust.
Cost	Individual respirator and set of filters more expensive than a single filtering facepiece respirator but much less expensive during prolonged usage.	Individual respirators less expensive than an elastomeric respirator and filters but more expensive during prolonged usage due to the large numbers of respirators required.
Cleaning and disinfection	Required.	Disposable.

prevents breathing if the mask makes an effective seal to the face. In addition, elastomeric respirators tend to have better fit[57] than filtering facepiece respirators.

Durability of Elastomeric Respirators

As already mentioned, the advantage of elastomeric respirators is that a set of filters can last for an extended period of time[58]; however, the precise longevity is uncertain because the concentration and nature of particles to be filtered will have a significant effect on the lifetime of the filter. High-efficiency filters such as 95 (FFP2), 99 (FFP3), 100 series (N, R, or P), or high-efficiency particulate air filters can be used until they load with particles to the point that the resistance to breathing becomes excessive. Particles that are filtered become tightly bound to the filtering material by Van der Waals forces and do not come out of the filter in significant quantitites.[59] When filters are used in relatively dust-free environments such as hospitals, they would be expected to be highly durable, possibly allowing users to work through a pandemic with one or two sets of filters. Filters can be encased in plastic enclosures that can be handled without touching the filter material itself, allowing for external cleaning by, for example, disinfecting wipes (figs. 1 and 2). An ideal elastomeric respirator for a pandemic should be designed with filter ports able to accommodate filters from multiple manufacturers (to prevent supply chain disruptions). Since there is not a universal filter connection design, the use of filters from multiple sources would require the use of adapters specifically made for this purpose.[38] Sources of filters during a surge might include anesthesia and ventilator breathing circuit filters.[60] In the United States, the National Institute for Occupational Safety and Health would need to be involved in the design and certification of novel elastomeric respirators designed for use with a variety of filters.

Developing Elastomeric Respirators

Existing elastomeric respirators should undergo further development to improve their functionality. The properties of ideal elastomeric respirators are shown in table 3, and an artist's conception of a future respirator is shown in fig. 4 (filters removed to show the respirator facepiece more clearly). Elastomeric respirators can make verbal communication difficult, in most cases more so than filtering facepiece respirators.[61,62] A few elastomeric respirators are equipped with a "speaking diaphragm" (fig. 1), which transmits sounds by a thin disc located in a circumscribed area of the mask body. For elastomeric respirators to succeed in health care, sound transmission must be improved substantially by the use of "speaking diaphragms" or other measures. Transparent mask materials may also assist with effective communication by making facial expressions and lip movement discernable.[63] Management of moisture is also a potential challenge since condensation of exhaled water vapor inside the mask can result in accumulation of moisture.

All but a few available elastomeric respirators have an unfiltered, valved exhalation port, which is undesirable in healthcare settings. Unfiltered exhaled air may contaminate a sterile field during a procedure, or result in transmission of a respiratory pathogen if the person wearing the respirator is infected. While these exhalation ports can be overcome by user modifications, such as by covering the exhalation port and removing the inhalation port valves, a respirator designed either without an exhalation port or with an exhalation port that can be switched off would be preferable. In some nonpandemic situations, unfiltered exhaled air may be acceptable—for example, if the person wearing the respirator is extremely unlikely to be infected with a specific transmissible respiratory pathogen (*e.g.*, *Mycobacterium tuberculosis* in low prevalence areas). Some users have worn surgical masks over an elastomeric respirator with the idea of providing filtration for the exhaled air; however, this solution is unreliable due to the shortcomings of surgical masks described in the Surgical Masks section.

Cleaning Elastomeric Respirators

One of the potential challenges for elastomeric respirators is cleaning. Reusable respirators require periodic cleaning and decontamination. Elastomeric respirators have typically been designed for low-level disinfection such as cleaning with soap and water, disinfectant wipes, dishwasher disinfection at low temperature, or immersion in relatively weak chemicals such as diluted bleach.[64] While the SARS-CoV-2 virus is inactivated by low-level disinfection, many other pathogens are resistant to this method. The elastomeric respirator is in close proximity to the user's mouth, nose, and airway, has contact with respiratory secretions, and has potential contact with a wide variety of

Table 3. Properties of an Ideal Pandemic Elastomeric Respirator

Desired Property	Details
Possibility for high level disinfection*	Would tolerate heat or chemicals required for disinfection.
Good fit for most users	The design of the mask body and straps would result in such good fit for most users that a user seal check could reasonably replace the need for formal fit testing during emergency or surge use. Currently such respirators do not exist, and regulators in the United States require fit testing of all respirators. Manufacture an adequate range of sizes to accommodate all users.
Comfortable for prolonged use	Lightweight, with a sealing surface that is comfortable for several hours of continuous use.
High-efficiency filter cartridges could be subjected to low level decontamination of the plastic enclosing the filter	High-efficiency filters enclosed in plastic cartridges can be subjected to low-level surface decontamination with disinfectant wipes. Filter life expectancy during use in relatively dust-free environments could be measured in months to years.
Adaptable to filters from diverse sources	In anticipation of supply chain disruption during a pandemic, the filter ports should be designed with adaptors for compatibility with filters from multiple sources, possibly including filters for anesthesia machine and ventilator circuits. In the United States, such designs would require approval by National Institute for Occupational Safety and Health (Washington, D.C.).
Low resistance to breathing	Filter surface area would be large enough to minimize resistance to breathing.
Unfiltered exhalation valve would either be eliminated or could be disabled	Exhalation filtered through the same filter cartridges as inhalation.
Designed for communication	Ease of communication would be a key design feature including a transparent mask body and a speaking diaphragm, or other speech-enhancing features.
Moisture management	Mitigation of condensation of moisture inside the mask body.
Compatibility with eyeglasses, goggles, and face shields with good field of view	The body of the respirator should not interfere with eye protection such as goggles or face shields. Filters should be kept small enough not to interfere with field of view.
Magnetic resonance image scanner compatibility	Ferromagnetic parts should be avoided for magnetic resonance image scanner compatibility.
Long storage life	Mask bodies and filters should be stable during prolonged storage to facilitate stockpiling.
Minimize environmental impact	Recyclable materials are preferred when possible.
Minimize costs	Minimizing costs facilitates stockpiling and implementation in middle- and low-income countries.

*High-level disinfection is the process of complete elimination of all microorganisms in or on a device, with the exception of a small numbers of bacterial spores.

pathogens commonly found in the healthcare environment, including multidrug-resistant organisms. Therefore, an argument could be made that elastomeric respirators are semicritical devices that should be subject to high-level disinfection.[65] Semicritical devices are those that come into contact with intact mucous membranes. High-level disinfection destroys all microorganisms except some bacterial spores. High-level disinfection could be particularly important if elastomeric respirators are processed by a hospital central processing unit and reissued to multiple users. High-level disinfection would require that elastomeric respirators be submersible (with the filter cartridges removed), and that the materials be resistant to heat or chemicals required for high-level disinfection. During surge conditions when other disinfection processes may be in short supply, heat-resistant respirator materials could be disinfected with boiling water.[66] The hard surfaces of reusable filter cartridges or canisters (fig. 2) could be cleaned with disinfectant wipes (low-level disinfection) between uses.

Hybrid Filtering Facepiece and Elastomeric Respirator Designs

There are several examples of respirators that combine a plastic or rubber mask frame and sealing surface with melt-blown fabric filtering, rather than filter cartridges or canisters. Thus, these respirators have features of both traditional filtering facepiece respirators and elastomeric respirators. An example of such a hybrid respirator is shown in fig. 1.

Environmental, Equity, Diversity, and Economic Considerations

The environmental impact of elastomeric respirators in comparison to disposable filtering facepiece respirators has not been well-studied. The environmental impact of cleaning reusable respirators should be considered. Respiratory protection must be effective and available for all people who need it. The experience of the COVID-19 pandemic has clearly shown that control of viral transmission must occur everywhere in the world in order to prevent the selection of more fit and dangerous variants of the virus. Respirators must be designed to effectively fit the wide variety of facial shapes and sizes found around the globe. Respirators must be produced in large enough numbers and at a low enough cost to ensure availability to low- and middle-income countries.

Conclusions

Elastomeric respirators have significant advantages during respiratory pandemics due to their durability and capacity for repeated use. Unlike filtering facepiece respirators, elastomeric respirators allow for robust user seal checks. However, to optimize their utility in healthcare settings, elastomeric respirators should be further enhanced with respect to ease of communication, moisture control, suitability for high-level disinfection, capacity to filter exhaled air, and adaptability to filters from multiple manufacturers. The authors believe that the development, implementation,

Fig. 4. Artist's conception of improved elastomeric respirator, with filter ports on either side of the respirator facepiece; the filters are deliberately not shown. The respirator body is transparent, and there is a speaking diaphragm to facilitate communication. The respirator would accommodate a wide variety of filters through the use of adapters, which could make the respirator more suitable to surge situations in which the supply chain for filters could be interrupted. The sealing surface is highlighted. There is no exhalation port; inhalation and exhalation take place through the same filters. Straps that hold the respirator onto the face are deliberately not shown, but are an important feature for fit and comfort. In the United States, respirators are certified for use by the National Institute for Occupational Safety and Health (Washington, D.C.); thus, the National Institute for Occupational Safety and Health would need to be involved in improved elastomeric respirator design.

and stockpiling of improved elastomeric respirators around the world should be an international public health priority.

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Competing Interests

The authors declare no competing interests.

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Lulling Carnations to Sleep, Ethylene Ripens with Anesthetic Powers

In 1878, famed French physiologist Claude Bernard reported on ether's ability to "anesthetize" *Mimosa pudica*, a plant known for its rapid movements to touch. Placing an ether-soaked sponge next to the species had abolished its sensitivity to contact. Thirty years later, North American carnation growers mourned the mysterious narcotization of their flowers (*right*) in Chicago's greenhouses. Scientists at the University of Chicago soon determined that ethylene (*left*), a fruit-ripening greenhouse gas, had caused open carnation petals to droop and nascent buds to remain closed. Physiologists A. B. Luckhardt and J. B. Carter then tried to determine ethylene's toxicity in animals, only to discover its anesthetizing properties instead. In 1923, they reported in *JAMA* (8:765–70) ethylene-induced surgical anesthesia first in animals and then in humans (*i.e.*, the study authors and two surgeons). That same year, Isabella Herb, M.D., chief physician anesthetist at Chicago's Presbyterian Hospital, became the first to administer ethylene clinically. Initially lauded as a superior alternative to nitrous oxide for both faster onset and deeper anesthetic effect, ethylene's popularity bloomed for a time but then wilted, given its odor and explosivity. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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ANESTHESIOLOGY

The Evolution of the Anesthesia Patient Safety Movement in America: Lessons Learned and Considerations to Promote Further Improvement in Patient Safety

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ABSTRACT

Ellison C. Pierce, Jr., M.D., and a small number of specialty leaders and scientists formed a remarkable, diverse team in the mid-1980s to address a dual crisis: a safety crisis for anesthetized patients and a medical malpractice insurance crisis for anesthesiologists. This cohesive team's efforts led to the formation of the Anesthesia Patient Safety Foundation, the American Society of Anesthesiologists's Committees on Standards of Care and on Patient Safety and Risk Management, and the society's Closed Claims Project. The commonality of leaders and members of the Anesthesia Patient Safety Foundation and American Society of Anesthesiologists initiatives provided the strong coordination needed for their efforts to effect change, introduce standards of care and practice parameters, obtain financial support needed to grow patient safety–oriented new knowledge, integrate industry and other relevant leaders outside of anesthesiology, and involve all anesthesia professions. By implementing successful patient safety initiatives, they promoted the recognition that anesthesiology and patient safety are inextricably linked.

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The anesthesia patient safety movement in the United States, heralded by the development and implementation of the American Society of Anesthesiologists' (ASA; Shaumburg, Illinois) *Ad Hoc* Committee on Patient Safety and Risk Management in 1984 and Committee on Standards in 1985 and the Anesthesia Patient Safety Foundation (APSF) in 1985, has been lauded as a landmark of successful collaboration between a national professional society and a related foundation.[1] The impact of the movement has been recognized as one of the most influential medical advances of the past century. By any account, the ASA and APSF have formed a remarkable team during the past 36 yr and have stimulated changes that improved the safety of patients who undergo anesthesia.

As with any collaboration in a dynamic, changing environment, the strength of the relationship between partners may fluctuate over time and require periodic reassessment and adjustment to maintain or improve outcomes. The ASA, specifically its Committee on Patient Safety and Education (formerly the Committee on Patient Safety and Risk Management), its Committee on Standards and Practice Parameters (formerly the Committee on Standards), its Committee on Professional Liability, and the APSF have recently or currently are making adjustments to their missions and charges. Therefore, this period in 2021 provides an excellent opportunity to review the historical links between the two entities, understand the dynamics and shared goals that produced such a positive impact on anesthesia patient safety, and contemplate opportunities to promote additional collaboration into the future.

For the purposes of this paper, the years 1982 to 2000 are considered the era of the origin of the anesthesia patient safety movement. Born out of an increasing awareness of anesthetic-related injuries to patients and a growing malpractice insurance crisis, the nascent anesthesia patient safety movement during this period generated highly successful and innovative patient safety initiatives. A remarkable group of dedicated ASA and APSF leaders led these initiatives during a time of a dramatic reduction in patient harm associated with anesthesia.

The Origins of the Anesthesia Patient Safety Movement

The 1970s and early 1980s in the United States saw a rapid increase in innovative procedural practices in medicine and surgery. Technological advances boomed concomitant with the acceleration of the space programs, computerization, and other disruptive innovations. These advances were supported by increased governmental funding, an expansion of academic programs in science and mathematic fields, and an influx of both men and women into the biologic sciences and medicine. Surgical, nonsurgical procedural, and anesthetic disciplines were transformed by the resulting evolution of biomedical equipment, biologic monitoring, and medications and adjuvant agents. The advances also increased pressure to offer these procedural services to a greater breadth of the population, particularly reaching out to patients of advanced ages and a growing level of medical and surgical conditions and general dysfunction or disability.

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Anesthesiology adapted to these rapid changes, but not always in synchrony with the pace of the growing complexity of the procedural practice and surgical patient population. As a result, the risk of patient harm increased during this period, and medicolegal actions against anesthesiologists grew rapidly.[2] Medical malpractice insurers quickly responded to the increase in anesthesia-related lawsuits, and rates for malpractice insurance coverage jumped dramatically. Malpractice insurance coverage became difficult to obtain in certain geographic locations of the United States. An insurance crisis was looming. In addition, the public was becoming increasingly aware of patient harm associated with anesthesia care. This awareness peaked on Thursday evening, April 22, 1982, when the ABC television network aired its *20/20* production "The Deep Sleep: 6,000 Will Die or Suffer Brain Damage."[3] Public concern spiked, as did the desire of ASA members for actions that would address both the malpractice insurance crisis and the public's concerns. The stage was set for leaders to step forward and improve anesthesia patient safety.

Fortunately, anesthesiology had leaders in place who advocated for the resources and changes needed in the specialty to significantly address these issues. The key leaders who participated in the anesthesia patient safety movement are shown in figure 1. Figure 2 provides a timeline of the historical developments that are described in this paper.

Development of Anesthesia Monitoring Standards

The Controlled Risk Insurance Company in Boston, Massachusetts, provider of malpractice insurance for the Harvard University hospitals, noted in 1983 that 11% of its payments to patients for harm were associated with malpractice claims against its insured anesthesiologists despite these anesthesiologists representing only 3% of their insured physicians.[4] James F. Holzer, J.D., a director at the Controlled Risk Insurance Company and leader of Harvard's Risk Management Foundation, asked the nine chiefs of the Harvard-affiliated hospitals to determine how to solve this (Jeffrey B. Cooper, Ph.D., Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts, April 20, 2021, verbal communication; John H. Eichhorn, M.D., emeritus Anesthesia Patient Safety Foundation Newsletter Editor-in-Chief, April 21, 2021, San Jose, California, verbal communication). The chiefs subsequently formed a Risk Management Committee to review this issue. The committee had representatives from six Boston-area hospitals and was led by Eichhorn, then of Beth Israel Hospital. In addition to Eichhorn, the department chiefs and members of the Risk Management Committee consisted of several individuals who would become key leaders in the anesthesia patient safety movement. These included Ellison C. ("Jeep") Pierce, Jr., M.D.; Richard J. Kirtz, M.D.; and Cooper.

The Risk Management Committee determined during its efforts in 1984 and 1985 that the major anesthesia-related malpractice payouts by the Controlled Risk Insurance Company were associated with a handful of patients who suffered severe injuries, and that most of these injuries may have been preventable with continuous monitoring of patients. They subsequently recommended that the Harvard-affiliated hospitals adopt monitoring standards, a recommendation accepted by each anesthesiology department chair.[5] The standards faced initial resistance in the Harvard-affiliated hospitals, but their implementation in 1985 was supported by strongly aligned anesthesia chiefs and bolstered by a promise from Holzer and his insurance company to reduce anesthesia malpractice expenses by 15% or greater, a reduction that occurred by 1986.

Pierce was particularly influenced by this attention given to anesthesia patient safety. He had been interested in the issue for several years (Cooper, verbal communication; Eichhorn, verbal communication).[6] In 1982, as First Vice-President of the ASA, he was hearing often from ASA members and malpractice attorneys about catastrophic anesthetic-related harm to patients. He vowed to use his ASA leadership position to address this issue, a promise that would have a remarkable impact on not only the acceptance of anesthesia monitoring standards in the United States but also anesthesia patient safety in general around the world in the coming decades.

Development of the ASA Committee on Patient Safety and Risk Management

In July 1983, the ASA's Section on College recommended the production of a videotape program entitled "Patient Safety and Risk Management" by the Subcommittee on Resources and the Section on College. A sum "not to exceed $100,000" was budgeted "to plan and produce this program."[7] Subsequently, President-elect Pierce affirmed the recommendation in his annual report to the ASA House of Delegates.[8] In his report, Pierce noted, "The broadcast in 1982 of the ABC 20/20 program concerning anesthesia accidents caused many of us to reflect anew on the problem. Over 135 yr, numerous studies and commissions have examined morbidity and mortality in our field but produced little progress in modifying them. Most have suggested that the majority of anesthesia deaths are preventable… It is indeed possible that there may be some 5,000 anesthetic deaths each year in the United States out of some 20 million administrations of anesthesia… Leadership must come from the world's anesthesia societies, however, not from insurance companies and federal regulatory agencies… ASA and component educational programs will be costly but are essential to provide understandings of why mishaps occur. It is my belief that significant relief from ever-increasing premiums for medical liability insurance will come only when the number of mishaps is significantly reduced."

In that same report, Pierce further proposed the formation of an *Ad Hoc* Committee on Patient Safety and Risk Management.[8] Since it was an *ad hoc* committee, he did not require ASA Board of Directors or House of Delegates approval. He appointed Howard L. Zauder, M.D., Ph.D., as

Fig. 1. Photographs of anesthesiology leaders who advocated for the resources and changes needed in the specialty to significantly improve anesthesia patient safety and reduce patient harm during the years 1982 to 2000 during the evolution of the anesthesia patient safety movement.

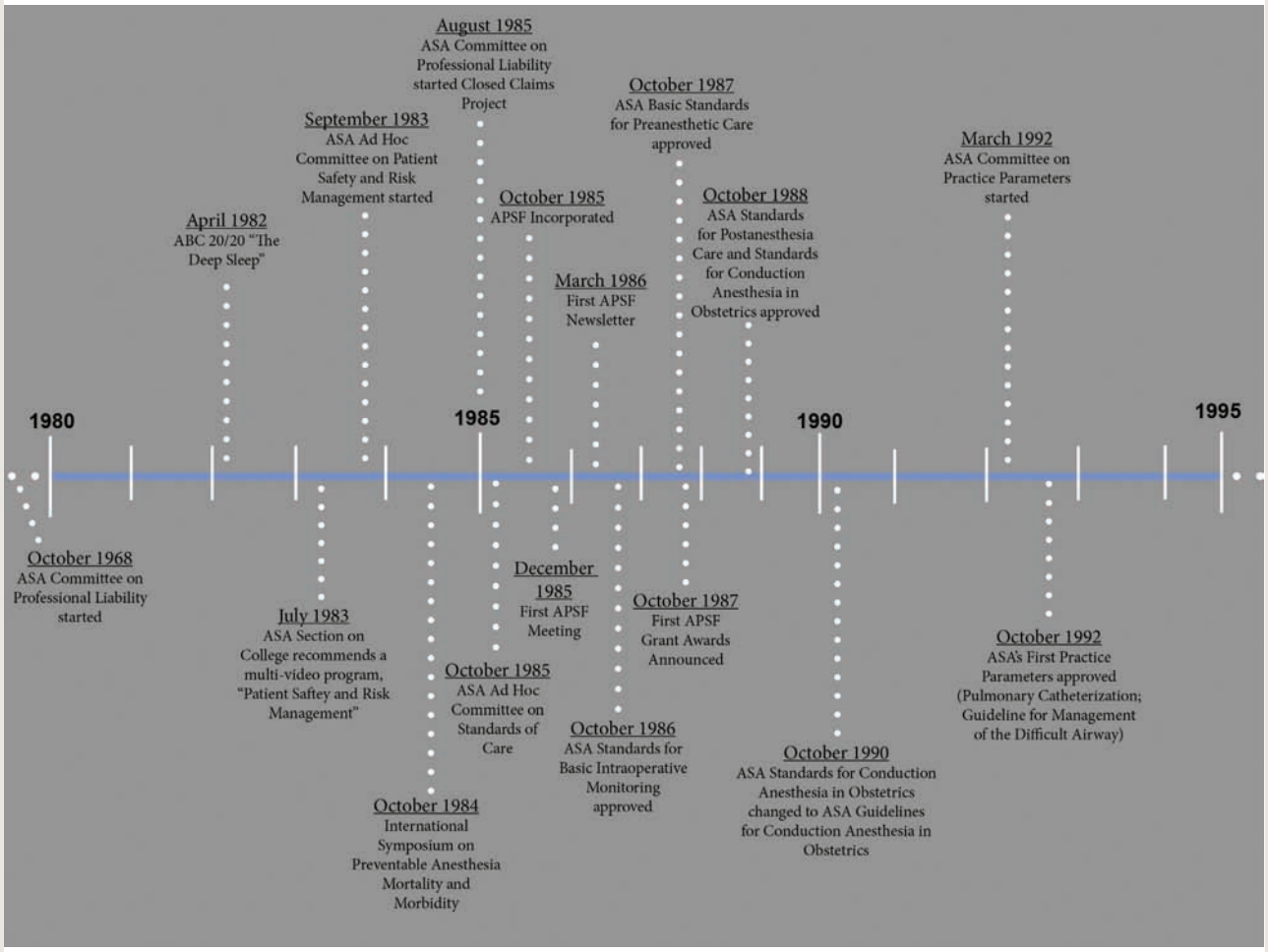

Fig. 2. This timeline depicts major events that contributed to anesthesiology's lead role in improving patient safety during the years 1968 to 1992. ABC, American Broadcasting Corporation; APSF, Anesthesia Patient Safety Foundation; ASA, American Society of Anesthesiologists.

the *ad hoc* committee's chair. Future APSF directors on that *ad hoc* committee included Cooper; William K. Hamilton, M.D.; Arthur S. Keats, M.D.; and Holzer. Zauder reported in July 1984 that the *ad hoc* committee's primary functions included education and the acquisition of data related to adverse events in anesthesia.[9] In his March 1984 report, Zauder noted that the ASA Board of Directors had directed the responsibility for production of videotapes related to patient safety to be shared by the ASA Committee on Resources of the Section on College and the *ad hoc* committee.[10] The first two tapes were "Introduction/Index" and "Anatomy of an Anesthesia Machine." The third was "Disconnection in Breathing Circuits."[9] This initial anesthesia patient safety videotape production initiative continued for 16 yr, ending in 2000 with its 24th videotape.[11] The *ad hoc* committee became the Committee on Patient Safety and Risk Management in 1985 upon a recommendation of then ASA President Pierce in 1984.[12] It first met in 1986 with Pierce as its inaugural chair.

Development of the ASA Committee on Standards (Subsequently the Committee on Standards and Practice Parameters)

Encouraged by Pierce, his predecessor as ASA president, H. Ketcham Morrell, M.D., promoted the development of standards of care, stating in his August 1985 Board of Directors Report, "There have, in the past, been discussions centered around the subject of 'standards of care' and whether or not ASA could or should publish what it believes is a standard of care in anesthesiology. I believe we owe it to our membership as well as the American public for ASA to set down guidelines concerning standards of care…"[13] In his subsequent September 1985 report to the Board of Directors, he commented further, "The time has come to 'get off the dime' and promulgate standards of care satisfactory not only to the House of Delegates, but to the entire membership. When this element of patient care is attended to, quality of care must improve. The conduct of an anesthetic will be even safer than it is currently. We will

eventually have a significant drop in morbidity and mortality and the people in the professional liability industry will have to take notice."[14] He appointed an *Ad Hoc* Committee on Standards of Care, and Burton S. Epstein, M.D., was made the committee's first chair. The initial committee included Pierce as a member and first met on October 14, 1985.

By July 1986, the *ad hoc* committee had met twice and decided to first tackle the issue of minimal monitoring for anesthetized patients. After a review of existing, relevant recommendations and standards and hearing from Eichhorn of the 1985 implementation of the Harvard monitoring standards,[15] the committee members agreed with all of them and recommended their approval in the *ad hoc* committee's first annual report to the ASA Board of Directors.[16] The board approved the recommendation with a minor adjustment, and the ASA House of Delegates approved the "Standards for Basic Intra-Operative Monitoring" in final form on October 18, 1986.[17] This approval established ASA as a national leader in standards of care and accelerated the specialty's anesthesia patient safety movement.

Development of the ASA Committee on Professional Liability

The ASA *Ad Hoc* Committee on Professional Liability Insurance was established in 1968 with a goal of implementing professional liability resolutions passed by the 1968 House of Delegates.[18] In its 1969 annual report, the *ad hoc* committee suggested that the group continue with a main function to act as a clearinghouse for information about professional liability insurance and to assist with educational programs pointed toward the prevention of malpractice claims.[19] Harold L. Engel, M.D., chair of the *ad hoc* committee, sagely noted in that report, "Satisfied patients do not sue."

The *ad hoc* committee had a temporary setback in late 1970 after a series of recommendations, including one that promoted the transition of the *ad hoc* committee into a standing Committee on Medical-Legal Affairs, were disapproved by the Board of Directors.[20] The disapprovals, at least in part, led to the abrupt resignation of William H. L. Dornette, M.D., J.D., the *ad hoc* committee chair. Into his place stepped J. Gerald Converse, M.D.[21]

The malpractice insurance crisis continued over the next decade. Both the costs of insurance and the financial awards to plaintiffs in anesthesia-related legal actions escalated. In 1984, Frederick W. Cheney, Jr., M.D., was the committee's chair and contemplated the nascent concept of using closed malpractice claims to gain information on anesthesia patient harm. It was clear to Cheney and other anesthesia patient safety leaders that the single most effective way to reduce malpractice insurance expenses and plaintiff awards was to reduce patient harm.[8,22] While attending the inaugural International Symposium on Preventable Anesthesia Mortality and Morbidity (October 8 to 10, 1984) organized by Pierce, Cooper, Kitz, and T. Cecil Gray, M.D., of the United Kingdom, he watched as Richard W. Solazzi, M.D., and Richard J. Ward, M.D., presented their analysis of anesthesia mishaps gleaned from medical liability cases.[23] Encouraged by ASA Immediate Past President Pierce, Cheney asked Ward to help the ASA start a closed claims project and recruited Karen B. Domino, M.D., and Karen L. Posner, Ph.D., to assist. The Closed Claims Project, now one of the world's most successful and sustained studies of anesthesia patient harm, benefited from Cheney's prolonged leadership as he served as chair of the Committee on Professional Liability through 1995. Starting with the Closed Claims Project's first peer-reviewed article by Robert A. Caplan, M.D., in 1998,[24] investigators associated with the project produced 67 novel peer-reviewed papers through the end of 2020. These papers have informed many patient safety changes and helped the ASA committees and APSF prioritize the issues that they have addressed over the years.

Development of the APSF

The initial International Symposium on Preventable Anesthesia Mortality and Morbidity meeting in 1984 proved to be a pivotal point in the rise of the anesthesia patient safety movement. It was held October 8 to 10 in Boston and was attended by approximately 50 anesthesiologists from the United States, Australia, the United Kingdom, South Africa, France, and Belgium with the goal of holding a candid discussion of anesthesia morbidity and mortality.[6] After that meeting, a small subgroup consisting of Pierce, Cooper, Kitz, Gray, and Eichhorn met and decided that a patient safety foundation was needed to advance the ideas expressed at the (Cooper, verbal communication; Eichhorn, verbal commmunication). These included the concept that a separate foundation was needed to promote input from all anesthesia professionals (in this case, specifically nurse anesthetists), the industry, the legal profession, the American Medical Association (Chicago, Illinois), and the Joint Commission on Accreditation of Healthcare Organizations (now The Joint Commission, Oakbrook Terrace, Illinois). In addition, the subgroup was convinced that it was important for patient safety initiatives to be supported financially by industry and foundations. The ASA, designated by the U.S. Internal Revenue Service as a 501(c)(6) organization, could not accept foundation funding at that time and had to be very specific in intent when receiving industry support. On the other hand, a new foundation, crafted to achieve designation by the Internal Revenue Service as a 501(c)(3) organization, could accept funds from these sources as long as conflict of interest issues were addressed appropriately. The APSF was granted 501(c)(3) status on December 5, 1986.[25]

Several other crucial decisions and initiatives related to the anesthesia patient safety movement arose from the initial International Symposium on Preventable Anesthesia Mortality and Morbidity meeting. It was clear to the subgroup that the foundation should be U.S.-centric. Attaching it to entities such as other anesthesiology societies and the World Health Organization (Geneva, Switzerland) would most likely be controversial, impeding the pace of change needed to improve patient safety in the United States (Cooper, verbal communication; Eichhorn, verbal communication).[6] On

the other hand, the group didn't wish to place restrictions on itself that would limit its ability to reach out internationally. At the subgroup meeting, Cooper proposed naming the foundation "The Anesthesia Patient Safety Foundation,"[26] avoiding any mention of country of origin that might hinder one of the APSF's initial missions, "[the] international exchange of information and ideas on patient safety."

As he did with other key ASA initiatives on patient safety, Pierce led the development of the APSF. He arranged the organizing meeting on July 10, 1985, in Washington, D.C. He was joined by Cooper; Kitz; Michael Scott, J.D.; and Zauder.[27] After subsequent consultation with Pierce, ASA President Morrell recommended the formation of the foundation in his August 1985 President report to the ASA Board of Directors.[28] Pierce, as the first chair of the Committee on Patient Safety and Risk Management, asked at that same meeting that the ASA approve APSF funding of $100,000 annually, using a voluntary "checkoff" on the ASA dues form to add a contribution of $25 per member to offset the $100,000 commitment.[29] The ASA Board of Directors initially disapproved his recommendation and expressed a desire to see the draft bylaws of the foundation in order to better understand the proposed relation between the ASA and the APSF. Pierce and Scott produced the draft bylaws and on October 12, 1985, the ASA House of Delegates agreed to the $100,000 annual funding support and elected Pierce and Scott as the APSF's first two directors.[30]

As there were 30 APSF director positions approved in the bylaws, it fell to Pierce and Scott to arrange the election of the remaining directors.[31] They met on November 22 and December 13 that year, both times in New York City, to select a slate of nominees. Twenty-seven additional directors were recommended and elected on December 14, 1985.[32] Their election was followed immediately by the APSF's first Board of Directors meeting.[33] A 30th director position was held open for a potential, unrealized nominee. The new board consisted of 16 anesthesiologists; 5 anesthesia and monitoring equipment representatives; 3 insurance company leaders; a single nurse anesthetist; and one director each from the Food and Drug Administration (Silver Spring, Maryland), the American Hospital Association (Chicago, Illinois), the pharmaceutical industry, and the legal profession.

The addition of a nurse anesthetist to the APSF as a board member was controversial at the time. Key leaders within the ASA were initially against the nomination of a nurse anesthetist, but Pierce believed strongly that the nurse anesthesia profession must be represented (Cooper, verbal communication; Eichhorn, verbal communication). In a compromise, it was agreed that a nurse anesthetist should be an APSF director, but the nominee could not be a leader within the American Association of Nurse Anesthetists (AANA; Park Ridge, Illinois). Pierce nominated Beverly Nichols, C.R.N.A., and she was subsequently elected unanimously. Ironically, two additional nurse anesthetists, including Jeffery M. Beutler, Deputy Executive Director of the AANA, had been elected by 1991. This act of compromise by Pierce has arguably driven the overall success of the APSF for its first 35 yr. He used this compromise to demonstrate his extraordinary belief in the importance of including all relevant people in the anesthesia patient safety movement. The culture of inclusivity that he sought through compromise continues to this day as the APSF Board of Directors and others on its committees consist of individuals from various anesthesia-related industries, the insurance and medicolegal fields, nurse anesthesia and anesthesiologist assistant professions, surgeons, perianesthetic nurses, operating room nurses, regulatory agency representatives, and others.

Industry, in a broad definition that includes manufacturers (*e.g.*, those producing anesthesia-related equipment, physiologic monitors, and pharmaceuticals) and medicolegal insurance companies, was well represented on the initial APSF Board of Directors and played a vital role in improving the safety of anesthesia care.[32] Industry leaders such as Burton A. Dole, Jr. (Puritan-Bennett Corporation, Overland Park, Kansas), William New, M.D. (Nellcor Corporation, Hayward, California), George Griffiths (Janssen Pharmaceuticals, Beerse, Belgium), James F. Holzer (Risk Management Foundation, Boston, Massachusetts), Mark D. Wood (St. Paul Fire and Marine Insurance Company, St. Paul, Minnesota), and W. Dekle Roundtree, Jr. (Ohmeda, Atlanta, Georgia) added credibility to the APSF within their fields of industry. They were major contributors to the APSF missions personally. Equally important, they were able to use their considerable collective influence to assist APSF and the specialty pursue changes within their industries and address major patient safety issues. For example, Wood collaborated with Cheney and the ASA Committee on Professional Liability to open the St. Paul Companies' (St. Paul, Minnesota) closed claims files on anesthesia-related lawsuits and persuaded additional malpractice insurers to do the same, all of which made the ASA Closed Claims Project possible.[34] These leaders also raised money to support the initial activities of the APSF, getting their own companies to support the foundation but also helping obtain funding from other corporations and foundations. Perhaps the most important example in the first several years of the APSF's existence was Dole's influence in obtaining a grant of $450,000 over 3 yr (1986 to 1988) from the Parker B. Francis Foundation (Kansas City, Missouri).[35] Francis was founder of Dole's Puritan-Bennett Corporation. Puritan-Bennett also provided in-house publishing support for the first years of the *APSF Newsletter* (Eichhorn, verbal communication). The newsletter was particularly important for the dissemination of patient safety information and was distributed to all members of the ASA and AANA in its first year, 1986.

Historical Links between Key ASA Committees and the APSF

The APSF and these three ASA committees were very strong partners during the crucial development of the anesthesia patient safety movement from 1985 through 1995. Pierce played a very significant role in building these partnerships, either directly appointing overlapping membership between the APSF directors and the committees or arranging it

through his influence on receptive and supportive ASA leaders such as ASA Presidents Morrell, Franklin B. McKechnie, Zauder, and Arens (Cooper, verbal communication).[6,36] The interdigitation of members of the APSF Board and the ASA committees was crucial to coordinating an evolving, broad anesthesia patient safety movement. For example, during the first decade of its existence, 29 to 60% of the members of the ASA Committee on Patient Safety and Risk Management were APSF directors.[37] Pierce took this concept a step further by influencing the selection of the chairs of these ASA committees, many of whom were either APSF directors or ASA leaders who strongly supported the anesthesia patient safety vision that Pierce promoted (Cooper, verbal communication; George A. Schapiro, M.S.I.A., emeritus Anesthesia Patient Safety Foundation Executive Vice-President, April 22, 2021, Hillsborough, California, verbal communication). APSF director Cheney was notified in mid-1984 that he would be appointed to chair the 1985 ASA Committee on Professional Liability and its Closed Claims Project. He remained in that position for the entire first decade of the anesthesia patient safety movement (1985 to 1995). Epstein was appointed in 1985 to become the inaugural chair the Committee on Standards of Care. He led that committee for its first 9 yr. Pierce himself chaired the ASA Committee on Patient Safety and Risk Management from 1984 through 1990 and was followed by Caplan, also an APSF director. This interdigitation of APSF directors onto these key ASA committees as members and chairs led to a strong union of forces and coordination of efforts to reduce patient harm from anesthesia.

During that time, the ASA Committee on Patient Safety and Risk Management was the primary resource for the ASA initiative to produce a series of videotapes on anesthesia patient safety issues. The APSF served as a conduit for industry funding to support the initiative. APSF directors also provided insights and guidance. The ASA Committee on Professional Liability, especially with its leadership role with the ASA Closed Claims Project, provided crucial information to guide APSF patient safety initiatives and promote anesthesia patient safety in general within anesthesiology. The ASA Committee on Standards was tightly linked to the APSF during that same period. The committee recommended the ASA's adoption of clinical standards.[16] The adoption of clinical standards was novel for a medical entity at the time, propelling anesthesiology and ASA to the forefront of patient safety in general worldwide.[38] The APSF and the three ASA committees shared their minutes or ASA reports starting in 1986, and a significant number of their members and leaders overlapped. This interdigitation of members and leaders led to a coordinated, collaborative effort to improve anesthesia patient safety. In many ways, it is reasonable to suggest that this coordination between these four groups markedly accelerated interest in and actions toward anesthesia patient safety, in essence starting the exponential rise of the anesthesia patient safety movement and patient safety across the broad spectrum of medical care. Pierce was the common link and was primarily responsible for this coordination.

From 1986 through 2000, the ASA Committee on Patient Safety and Risk Management augmented the education and training component of the APSF. The committee produced the ASA patient safety videotape series. The last of the initial series of 24 videotapes was finalized in 2000.[11] Of course, the committee also had ASA-specific roles. These included serving the society as a resource for patient safety–related questions and requests, assisting the annual meeting and other education leaders in selecting speakers for specific patient safety-oriented topics, identifying potential patient safety–oriented authors for *ASA Newsletter* articles and other educational enduring materials, and generally advising the society and its members on methods to enhance the safety of anesthesia care.[39]

The relationship between the APSF and the ASA Committee on Patient Safety and Risk Management was very effective during the initial 14-year period of 1986 to 2000. During these years, the percentage of APSF directors who served on the committee ranged from 29 to 60%.[37] With completion of the videotape series, a major component of the committee's role fell away, and the committee went through a period of transition. In 2000, committee chair Casey D. Blitt, M.D., also an APSF officer, noted, "The direction and charge of the committee continues to be somewhat nebulous."[11] Successive committee chairs made similar comments in their reports to the ASA House of Delegates and asked for a closer, official relationship with APSF.[39,40] By 2009, the percentage of APSF directors serving on the committee as members had decreased to less than 20%, and that downward trend has continued. From 2014 through 2020, less than 5% of the committee members were APSF directors, and the interchange in ideas between the committee and APSF faltered. However, the committee has continued to fulfill its ASA charge and assists the Committee on Annual Meeting Oversight and other ASA committees by suggesting topics and speakers for patient safety courses and lectures. It provides input to ASA patient-directed materials and other patient safety publications (*e.g.*, a recent *International Anesthesiology Clinics* text), supported and maintained a now-inactive ASA Frequently Asked Questions webpage that primarily dealt with issues that impact patient safety, and has been asked by ASA leaders to serve as a resource for patients and members who have questions related to patient safety–oriented issues.

The ASA Committee on Professional Liability and Committee on Standards of Care never had a significant percentage of their members who were APSF directors.[37] However, the chairs of these committees from 1986 through 1999 were primary either APSF directors or ASA leaders who were strong supporters of the anesthesia patient safety movement. For the Committee on Professional Liability, the chairs were Cheney (10 yr) and Caplan (4 yr). For the Committee on Standards of Care, the chairs were Epstein (9 yr), Ronald A. Gabel, M.D. (1 yr), and Eichhorn (4 yr). The sustained leadership of these committees by individuals who believed strongly in the anesthesia patient safety movement influenced the many contributions of the committees

to advances that resulted in a dramatic reduction in patient harm during this remarkable 14-year period. For example, the Committee on Standards of Care recommended and supported the ASA's adoption of minimal standards for the monitoring of anesthetized patients. The Committee on Professional Liability oversaw the implementation of the Closed Claims Project and the many influential publications produced by it that led to patient safety improvements.

The APSF and AANA have intermittently pursued similar links. Three of the AANA's chief operating officers have been APSF directors. These include Beutler; Wanda O. Wilson, C.R.N.A., Ph.D.; and Randall Moore, II, C.R.N.A., D.N.P.[41] The APSF Board of Directors has included at least one nurse anesthetist representative of the AANA since 1991 and has had as many as four at any one time. Although APSF is apolitical and inclusive, the relationship between the APSF and the AANA has fluctuated over the foundation's 36-year history. The relationship has been impacted, at times, by disagreements on a variety of issues but especially scope-of-practice differences between anesthesiologists and nurse anesthetists. In general, however, the relationship has provided very valuable collaborative interactions and exchanges of perspectives that have helped to advance anesthesia patient safety.

Reflections

This history of the evolution of the anesthesia patient safety movement expands on the development of each major contributing component (*i.e.*, APSF and the three relevant ASA committees) and reveals how Pierce and his colleagues deliberately built a diverse but like-minded, highly regarded leadership team across the spectrum of anesthesia professionals and industry leaders. Pierce also recruited key governmental and healthcare leaders such as Marlene E. Hoffner, M.D., Director of the Office of Health Affairs for the Food and Drug Administration; Martin J. Hatlie, Esq., General Counsel for the Joint Commission on Accreditation of Healthcare Organizations; and Mary Ann Kelly, Clinical Services, American Hospital Association, to the APSF Board of Directors.[41] He courted liaisons with our surgical colleagues, and C. Rollins Hanlon, M.D., was appointed as the APSF's first representative from the American College of Surgeons (Chicago, Illinois).[41] Colleagues from surgical fields have been continuously represented on APSF's Board of Directors or committees since the organization's inception and have provided unique perspectives that have contributed to patient safety initiatives that have expanded into the entire perioperative period.

Importantly, Pierce and his team provided sustained leadership as they all contributed in their roles for the first decade of the evolution of the movement. During that period, the anesthesiologist leaders on the team also each contributed to the mentoring of the next generation of patient safety advocates and leaders. These future leaders of the movement included, but were not limited to, Robert K. Stoelting, M.D. (President, APSF); Caplan and Blitt (Committee on Patient Safety and Risk Management); Domino, Eichhorn, and Caplan (Committee on Professional Liability); and Eichhorn (Committee on Standards of Care). The movement's industry leaders mentored future key supporters such as George A. Shapiro (Andros Analyzers, Berkeley, California) and David Swedlow, M.D. (Nellcor Puritan-Bennett, Pleasanton, California). Together, Pierce's diverse leadership team shaped an expansive, sustained anesthesia patient safety movement.

Missing in the movement's first decade, however, was any specific attempt to add the perspective of patients and patient advocates. No public members or patient advocates outside of the anesthesia professions were added to the APSF Board of Directors or integrated into its committees.[41] This apparently was not for lack of trying to recruit patient advocates or public members to the ASPF Board (Eichhorn, verbal communication). Patient advocates and public members were not prevalent on medical boards and foundations in the mid-1980s. The only public member of the APSF Board of Directors has been Harry Schwartz, Ph.D., in 1993.[41] He remained only until 1995. His contributions to the APSF Board discussions were minimal during his time as a director (Eichhorn, verbal communication).

The pace of progress in reducing patient harm during the evolution of the anesthesia patient safety movement was rapid at first and then appears to have slowed and fluctuated. Initial reports of 10-fold and higher reductions in anesthesia-related mortality in the early 1990s were greeted with exuberance.[42–44] These results even triggered comments that anesthesiology had made patient care so safe that the need to continue supporting patient safety initiatives had dwindled. Factions within ASA sought to reduce or even eliminate further financial support for APSF and unique ASA patient safety initiatives. Pierce recognized this growing undercurrent by 1989. He and his patient safety leadership team sought the support of influential ASA members and the leaders of the ASA's other foundations, the Foundation for Anesthesia Education and Research and the Wood Library-Museum of Anesthesiology. They encouraged them to become advocates for expanded ASA funding of all three foundations, and in October 1990, the ASA House of Delegates approved a dues increase of $60 annually, with the increase specifically targeted to greater financial support of the foundations, including APSF.[45] To further remind ASA members of the continued need for support of anesthesia patient safety, Pierce noted in his 1995 Rovenstine Lecture at the ASA Annual Meeting, "Patient safety is not a fad. It is not a preoccupation of the past. It is not an objective that has been fulfilled or a reflection of a problem that has been solved. It must be sustained by research, training, and daily application in the workplace."[6]

The Importance of Coordinated Efforts

Pierce built a strong team of like-minded leaders to initiate the anesthesia patient safety movement. They did not all agree on every issue and initiative, and they were dissimilar in many

ways. Yet they worked as a team and established a tradition of working respectfully together, a culture that carried through the first several decades of the movement. As the rapid improvements in patient safety peaked by the mid-1990s, the general sense of excitement about these improvements within the specialty started to wane. The malpractice insurance crisis relented, and expenses for insurance dropped dramatically. The motivation and urgency to improve patient safety fell.

The anesthesia patient safety movement was entering a phase of slower progress by the early 1990s. The ASA House of Delegates became increasingly wary of adding more standards of care. Members expressed concern that the scientific evidence to support expanded standards of care was lacking. To compensate and still provide practice guidance, House of Delegates members suggested that the society develop practice parameters (*i.e.*, guidelines and practice advisories). These practice parameters would not require the same level of adherence as standards of care but would provide recommendations and insights to guide clinical practices. In a report to the ASA Board of Directors in August 1990, Immediate Past President Arens recommended the appointment of a task force to develop a proposal on the issue of producing practice parameters in anesthesiology.[46] The task force met over the winter of 1991 and recommended a standing Committee on Practice Parameters to the ASA Board of Directors in March 1991.[47] Still wary of adding restrictions on the independence of the clinical practices of its members, the board disapproved of the recommendation. However, ASA President Betty P. Stephenson, M.D., a close colleague of Arens and a strong supporter of the movement, did not let the idea die. Instead, she appointed Arens as chair of an *Ad Hoc* Committee on Practice Parameters. After a year of concerted effort by Pierce, Arens, Stephenson, and other patient safety leaders to influence reluctant ASA directors,[6] the ASA Board of Directors approved the standing committee in March 1992.[48] Arens remained as chair of the new standing committee, and the committee developed a number of important patient safety–oriented practice parameters over the next decade. By 2005 it was becoming clear that the ASA House of Delegates was unlikely to add more standards of care. In March 2005, Alexander A. Hannenberg, M.D., Chair of the ASA's Division on Professional Affairs, recommitted that the Committee on Standards of Care be merged with the Committee on Practice Parameters.[49] This was approved, and the Committee on Standards and Practice Parameters was implemented in 2006 with Arens as chair. In essence, practice parameters had become the method by which patient care changes to improve safety would be advanced within the ASA.

By the late 2000s, many of the initial leaders of the anesthesia patient safety movement had retired or died. Specifically, key leaders such as Pierce, Eichhorn, Arens, Caplan, Epstein, and Cheney were no longer serving as chairs of the ASA Committee on Professional Liability, Committee on Standards (and Practice Parameters), and Committee on Patient Safety and Risk Management (renamed as the Committee on Patient Safety and Education in 2008). By 2009, the overlap of APSF directors and memberships of these committees had dwindled. For example, the overlap of committee members and APSF directors on the Committee on Patient Safety and Education dropped from a typical 40 to 60% to less than 20% in 2009, and this decrease continued during the past decade, reaching the point of no overlap in 2018.[37] Successive committee chairs after 2009 recommended that ASA approve an APSF liaison member position for the committee, recommendations that were disapproved by the ASA Board of Directors in 2011 and 2014.[39,40] Similarly, APSF directors were included infrequently as members of the ASA Committee on Standards and Practice Parameters. After Arens stepped down from his committee chair position at the end of 2008, linkage back to the APSF was diminished. Since then, APSF requests for practice guidelines or practice advisories for several of its priority issues (*e.g.*, monitoring for residual neuromuscular blockade) have been declined, deferred, or delayed. Pierce's grand vision of coordinated efforts between APSF and the ASA committees had tumbled.

Despite the transition of anesthesia patient safety leaders by 2000, the APSF and ASA have continued to make advances in reducing perioperative patient harm. The APSF continues to fund important anesthesia patient safety research. Through its annual consensus conferences, it develops recommendations and then uses its extensive international outreach to advocate for them. APSF has strongly encouraged the inclusion of patient safety education and simulation in certification requirements of the American Board of Anesthesiology (Raleigh, North Carolina) and accreditation requirements of the Accreditation Council for Graduate Medical Education (Chicago, Illinois). It's been a leading advocate for the development and use of adjuncts such as crisis manuals and the integration of these adjuncts into electronic medical records. The ASA has funded and staffed the Anesthesia Quality Institute and its Anesthesia Incident Reporting System registry, developed many patient safety–oriented educational programs, and promoted patient safety though its publications and support of APSF. There is more progress to be made, and APSF and ASA are linked in tandem to further reduce perioperative patient harm.

Future Considerations

Based on this research and close, firsthand observations of the anesthesia patient safety movement, the authors suggest the following four considerations to the APSF and the ASA.

First, the APSF and ASA should increase cross-membership, and leadership, between APSF and the ASA Committee on Professional Liability, Committee on Standards and Practice Parameters, and Committee on Patient Safety and Education. This recommendation could be readily achieved with either the addition of *ad hoc* or *ex officio* members of each, or encouragement for each to accept guests from the others. This interdigitation of APSF directors and committee members would promote shared ideas and collaborations.

Second, leaders of the APSF and these committees should meet regularly and share information about their patient safety priorities and initiatives. This union of leaders could promote coordinated efforts to reduce patient harm and, when appropriate, shared resources. For example, the ASA Committee on Patient Safety and Education and the APSF's Committee on Education and Training might share a number of their responsibilities as both have common charges. A similar partnership is already present between the Foundation for Anesthesia Education and Research and the ASA. In 1988, the ASA Committee on Research was appointed as the *de facto* study section for Foundation for Anesthesia Education and Research.[50] It continues in this role today while retaining its unique ASA-related roles. Overall, a common APSF and ASA patient safety leadership group could share the outcomes of its discussions with APSF and ASA leaders, increasing awareness of potential patient safety issues and opportunities for improvement.

Third, to paraphrase an oft-used statement, anesthesia patient safety is a team sport. The anesthesia patient safety movement achieved much of its success from a union of forces. No single group "owns" anesthesia patient safety. In the United States, approximately half of anesthesia professionals involved in the day-to-day, in-room provision of anesthesia care are not anesthesiologists. It is crucial for nurse anesthetists and anesthesiologist assistants to be involved in discussions about patient safety and the development and implementation of patient safety initiatives. The enthusiastic involvement of anesthesia and monitoring equipment and pharmaceutical manufacturers is vital for enhancing anesthesia patient safety. To achieve perioperative care improvements, operating room nurses, perianesthetic nurses, and other postoperative nurses must be engaged and contribute their ideas on patient safety. Our surgical and other procedural colleagues need to be tightly linked to perioperative patient safety efforts. Experts from the medicolegal fields, insurance industry, and governmental and regulatory agencies also must be actively engaged. For this reason, it is imperative for the APSF to continue to be a wide-open tent, including directors and committee members who have all of these backgrounds.

Fourth, the APSF should remain an affiliated foundation of the ASA but continue to function independently. Harkening to its origin, it is imperative to have an independent foundation that includes representation from the many entities that impact anesthesia patient safety. An independent foundation, unencumbered by a large membership, has the ability to rapidly address new, potentially time-sensitive patient safety issues and shift resources quickly to support targeted initiatives and meet its missions and its vision, "that no one shall be harmed by anesthesia care."

Potential Biases

The authors readily acknowledge their potential biases in this report. One (M.A.W.) is a past President of the APSF, ASA, and American Board of Anesthesiology and past executive committee member of Foundation for Anesthesia Education and Research. The other (M.E.W.) is a past, long-serving ASA House of Delegate member, past President of the Wood Library-Museum of Anesthesiology, and current Vice President of the Anesthesia Foundation. Together, they have been longtime supporters of all of the ASA-affiliated foundations. Both have received grant funding from the APSF and have written multiple articles on anesthesia patient safety–related topics.

In most instances, they have referenced publications, archival sources such as ASA and APSF reports and minutes, and videotaped interviews to support their conclusions. However, these references do not always provide context or the sense and/or sensibilities of specific issues. In those instances, they have relied on and referred to personal communications from individuals who were present at unique meetings to provide their perspectives. As authors who have been fairly involved in the ASA, American Board of Anesthesiology, and APSF during most of the 36 yr of the anesthesia patient safety movement and who have personally known most of the individuals discussed in this report, their own perspectives have undoubtedly influenced the presentation of this history. Every effort has been made to reference source materials.

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Competing Interests

The authors declare no competing interests.

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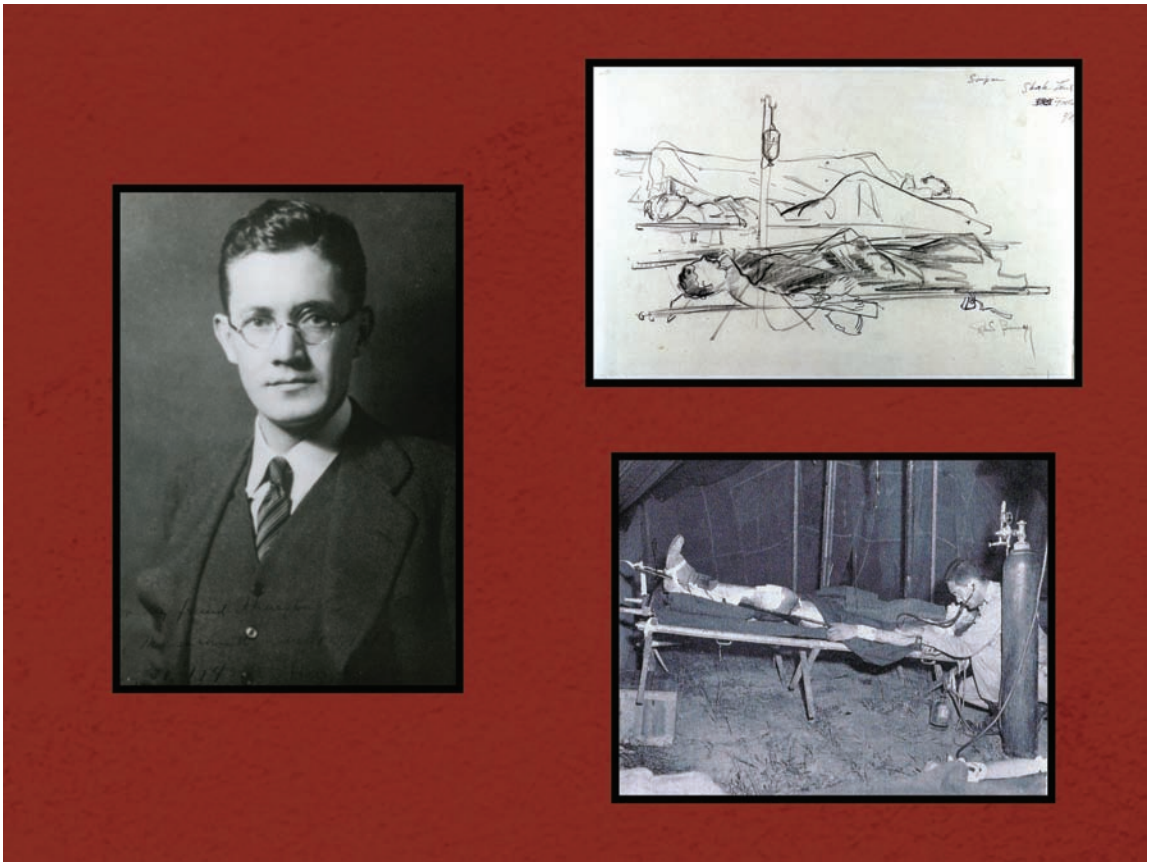
ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Henry K. Beecher, Battlefield Professor: Research Meets Practice during World War II



Henry K. Beecher, M.D. (*left*), Harvard's first Anaesthetist-in-Chief, grew up in Kansas as Harry Unangst, a bookish and self-sufficient lad. Young Harry would adopt the surname Beecher before matriculating at Harvard Medical School. As a medical student, Beecher's research prowess impressed Edward Churchill, M.D., Professor of Surgery. In 1936, Churchill would appoint Beecher, then merely a novice anaesthetist, as Chief of Anaesthesia at the Massachusetts General Hospital (MGH). Seven years later, Beecher would follow his mentor into the Mediterranean Theater of World War II, where battles were "bitterly contested." Away from the MGH's hallowed halls, the battlefield became both Beecher's laboratory, and Beecher's clinic. When he was not resuscitating wounded soldiers in "shock tents" (*upper right*) near the front lines, Beecher was scribbling furious notes and analyzing copious data on patients in hemorrhagic shock. Within two years, his investigations would lead to more efficient and effective rescue measures. Several treatments—elevation of the foot of the bed, nasal oxygen supplementation, whole blood transfusion, gastric drainage, and close monitoring of blood pressure—became the standard of care (*lower right*, from Beecher HK, *Resuscitation and Anesthesia for Wounded Men*, Charles C. Thomas, 1949). For his exceptional efforts in wartime, Lieutenant Colonel Henry K. Beecher would receive the prestigious Legion of Merit. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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ANESTHESIOLOGY

Carbon Footprint of General, Regional, and Combined Anesthesia for Total Knee Replacements

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Health care produces greenhouse gases both directly (electricity and gas) and indirectly from emissions associated with consumption of goods and services
- For anesthesiologists to reduce their workplace carbon footprint, they must understand the sources and amounts of the greenhouse gases produced as they care for patients in the operating room

What This Article Tells Us That Is New

- The carbon footprint in carbon dioxide equivalent emissions associated with general anesthesia (n = 9), spinal anesthesia (n = 10), and combined (general and spinal) anesthesia (n = 10) for total knee replacement surgery in Melbourne, Australia, were similar
- Single-use equipment, electricity for the patient air warmer, and pharmaceuticals were major sources of carbon dioxide equivalent emissions across all anesthetics
- Sevoflurane was a significant source of the carbon dioxide equivalent emissions of both general anesthesia and combined anesthesia
- Washing and sterilizing reusable items contributed substantially to the carbon dioxide equivalent emissions of both spinal and combined anesthesia
- Oxygen use was an important contributor to the carbon footprint of spinal anesthesia

ABSTRACT

Background: Health care itself contributes to climate change. Anesthesia is a "carbon hotspot," yet few data exist to compare anesthetic choices. The authors examined the carbon dioxide equivalent emissions associated with general anesthesia, spinal anesthesia, and combined (general and spinal anesthesia) during a total knee replacement.

Methods: A prospective life cycle assessment of 10 patients in each of three groups undergoing knee replacements was conducted in Melbourne, Australia. The authors collected input data for anesthetic items, gases, and drugs, and electricity for patient warming and anesthetic machine. Sevoflurane or propofol was used for general anesthesia. Life cycle assessment software was used to convert inputs to their carbon footprint (in kilogram carbon dioxide equivalent emissions), with modeled international comparisons.

Results: Twenty-nine patients were studied. The carbon dioxide equivalent emissions for general anesthesia were an average 14.9 (95% CI, 9.7 to 22.5) kg carbon dioxide equivalent emissions; spinal anesthesia, 16.9 (95% CI, 13.2 to 20.5) kg carbon dioxide equivalent; and for combined anesthesia, 18.5 (95% CI, 12.5 to 27.3) kg carbon dioxide equivalent. Major sources of carbon dioxide equivalent emissions across all approaches were as follows: electricity for the patient air warmer (average at least 2.5 kg carbon dioxide equivalent [20% total]), single-use items, 3.6 (general anesthesia), 3.4 (spinal), and 4.3 (combined) kg carbon dioxide equivalent emissions, respectively (approximately 25% total). For the general anesthesia and combined groups, sevoflurane contributed an average 4.7 kg carbon dioxide equivalent (35% total) and 3.1 kg carbon dioxide equivalent (19%), respectively. For spinal and combined, washing and sterilizing reusable items contributed 4.5 kg carbon dioxide equivalent (29% total) and 4.1 kg carbon dioxide equivalent (24%) emissions, respectively. Oxygen use was important to the spinal anesthetic carbon footprint (2.8 kg carbon dioxide equivalent, 18%). Modeling showed that intercountry carbon dioxide equivalent emission variability was less than intragroup variability (minimum/maximum).

Conclusions: All anesthetic approaches had similar carbon footprints (desflurane and nitrous oxide were not used for general anesthesia). Rather than spinal being a default low carbon approach, several choices determine the final carbon footprint: using low-flow anesthesia/total intravenous anesthesia, reducing single-use plastics, reducing oxygen flows, and collaborating with engineers to augment energy efficiency/renewable electricity.

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Climate change has become a considerable healthcare threat of the 21st century,[1] yet health care itself produces greenhouse gases directly (electricity and gas), but also from indirect emissions associated with consumption of goods and services.[2,3] The Australian healthcare system is responsible for approximately 7% of the total Australian greenhouse gas emissions.[4] Within hospitals, the intensive care unit[5] and operating rooms[6] are the most demanding of natural and financial resources. Operating rooms require

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large amounts of medical equipment, produce much waste,[7] and have large energy requirements.[6,8] As climate change has become an environmental (and health) emergency,[1] health systems need to investigate ways in which high-quality health care can be delivered while minimizing the environmental impact.

MacNeill *et al.*[6] studied three hospitals, one each in Canada, the United States, and the United Kingdom, finding that anesthesia could have greater carbon dioxide equivalent emissions than (1) all surgical equipment and procurement, and (2) all operating room–associated energy requirements including heating, ventilation, and air conditioning.[6] Multiple studies have focused on the surgical side of carbon dioxide equivalent emissions for different operations (*e.g.*, hysterectomies,[8] cesareans,[9] and cataracts[10]). The carbon dioxide equivalent emissions associated with the anesthetic gases desflurane and nitrous oxide are significant.[11] Similar to the United Kingdom hospital in the study by MacNeill *et al.*,[6] we observed minimal desflurane and nitrous oxide use in our hospital, although we recognize variability in Australian anesthetic practice.[12] There are calls for studies to investigate the effects of general *versus* regional anesthetic choice upon carbon dioxide equivalent emissions,[13] as this could be important even in the absence of desflurane or nitrous oxide.

We asked what was the carbon footprint of the anesthetic component of a total knee replacement, a common operation for which there is clinical equipoise between alternate anesthetic approaches. We aimed to quantify the carbon dioxide equivalent emissions of general anesthesia, spinal anesthesia, and combined general and spinal anesthesia.

Materials and Methods

This prospective, nonrandomized, single center life cycle assessment was performed and follows the observational study Strengthening the Reporting of OBservational studies in Epidemiology checklist (www.strobe-statement.org.). The hospital ethics committee gave study approval (HREC/2018/Western Health/64), deeming that patient consent was not required (observational study not requiring patient data). We considered that 10 patients to each group (general anesthesia, spinal, and combined [general and spinal] anesthesia) provided an adequate convenience sample. We enrolled patients who were having elective total knee replacements consecutively, only excluding patients due to researcher unavailability. Life cycle assessment is a scientific method used to quantify the environmental footprint of a product or service throughout an entire life cycle.[14] Previous studies have examined the carbon footprint of anesthetic equipment, which we have incorporated.[15–17] Our study focused on the carbon footprint of anesthesia as climate change is becoming increasingly important. Appendix 1 and previous reviews[13,18] contain further information about life cycle assessment methods.

Using the International Organization for Standardization (Geneva, Switzerland) ISO-14040 standards,[14] we defined our study's *functional unit* as all anesthesia for a total knee replacement in a hospital in Victoria, Australia. The ISO-14040 standards[8] life cycle assessment *system boundary* defines inclusions/exclusions (fig. 1). We did not include data for heating/ventilation/air conditioning, or any surgical equipment. Electricity consumption for anesthesia devices was estimated (not measured) from manufacturer data[19] or from previous publications.[20,21]

We obtained patient anesthetic start and stop times. General anesthetics could be either volatile gas anesthetics or total intravenous anesthesia, with all cases requiring an airway device (laryngeal mask/endotracheal tube). Spinal anesthetics were delivered with sedation and by definition required no airway device. We present carbon dioxide equivalent emissions as total data, not per hour. For many items (drugs, plastic syringes, spinal anesthetic trays and gowns, inhalational induction), considerably more were used during the first hour of anesthesia than subsequently.

We examined the composition and weights of reusable and disposable consumables: gloves, gowns, syringes, airway devices, patient warming blankets, temperature probes, intravenous fluids, drugs, and gases, and associated immediate packaging. Volumes of oxygen, medical air, volatiles, and nitrous oxide use were obtained from the anesthetic machine (Aisys CS^2, GE Healthcare, USA) computer at the end of each case. Oxygen flows for sedated patients were manually recorded. We used the Andersen *et al.* study's[11] global warming potential data for anesthetic gases. We used two life cycle inventories (Ecoinvent,[22] Switzerland, and the Australian Life Cycle Inventory[23]) to obtain carbon dioxide equivalent emissions associated with devices and processes.

For reusable items, previous data were used to estimate the environmental impacts of cleaning (sterile gowns,[24] face masks, anesthetic breathing circuits, laryngoscope blades,[15] and drug trays[17]). We thus attributed the energy costs of reusable anesthetic equipment, *i.e.*, kilowatt-hour/size of item as a proportion of washer load,[25,26] and 1.9 kilowatt-hours/kg[27] items sterilized (appendix 1). The reusable anesthetic breathing circuits were changed weekly unless contaminated,[28] so their contribution to total carbon dioxide equivalent emissions was small (conservatively 25 operations per operating theater per week). Also included were the carbon dioxide equivalent emissions from carbon dioxide absorbent use (0.13 kg carbon dioxide equivalent emissions/h from Zhong *et al.*[29]). Energy requirements for liquid oxygen were 0.001 kilowatt-hours/l for oxygen gas and 0.0003 kilowatt-hours/l for compressed medical air (Ecoinvent[22] for electricity data, Australian Life Cycle Inventory[23] for carbon dioxide equivalent emissions per kilowatt-hour).

Since we knew equipment mass, we used average production data about carbon dioxide equivalent emissions/kilogram waste from the Ecoinvent[22] and Australian[23] life cycle inventories as appropriate. We assumed general waste for all disposables except for some polyvinyl chloride recycling[7] (face masks, oxygen tubing, and intravenous fluid bags), and polypropylene (spinal tray sterile wrap). Contaminated items (*e.g.*, suction tubing) were

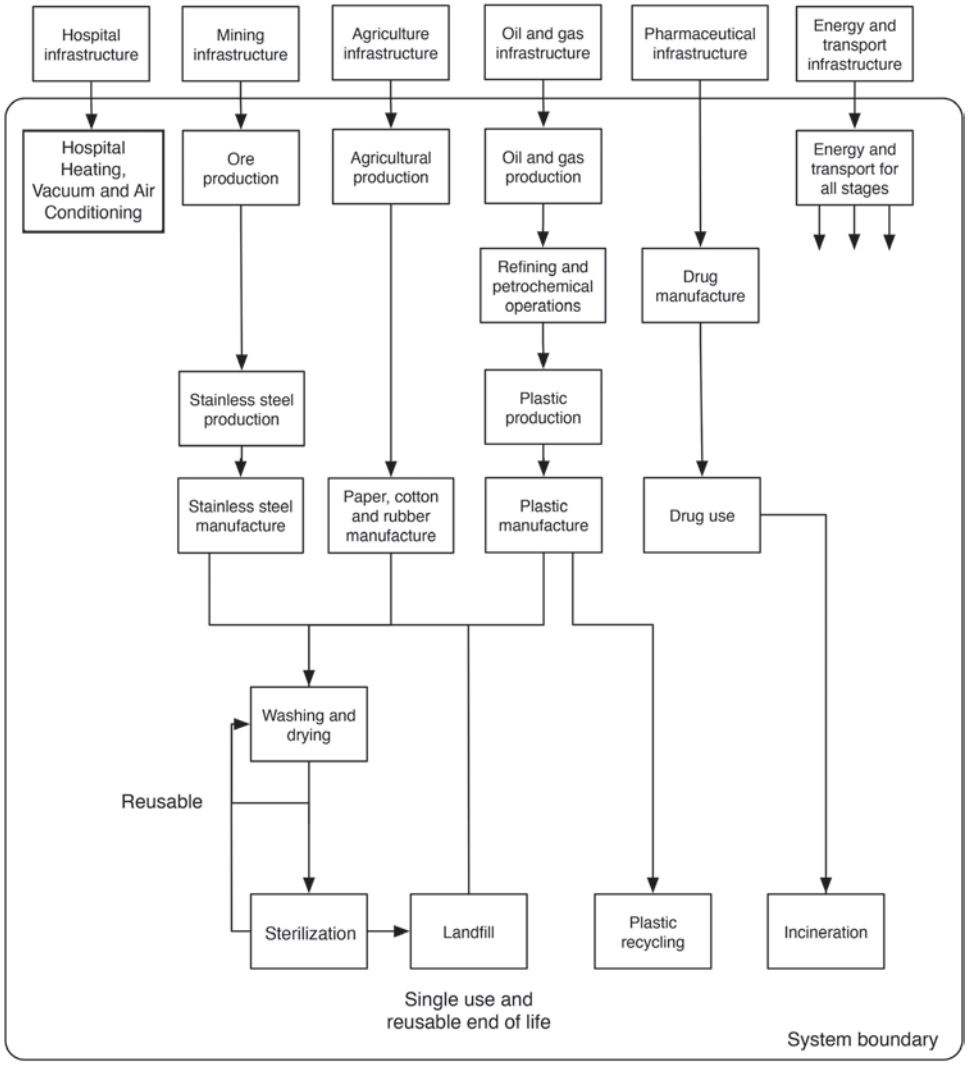

Fig. 1. System boundary.

assumed infectious/clinical waste (higher carbon dioxide equivalent emissions/kilogram, Ecoinvent), and pharmaceutical waste was assumed to undergo high-temperature incineration.

No public life cycle inventory data exist for most pharmaceuticals.[30] We used the Parvatker *et al.* study's carbon dioxide equivalent emissions data approximations for 20 common anesthetic pharmaceuticals.[31] From Parvatker *et al.*, the average/mean g carbon dioxide equivalent emissions/g drug across the 20 drugs was 340 g carbon dioxide equivalent emissions/g drug, with, for example, propofol at 21 g carbon dioxide equivalent emissions/g propofol, and midazolam 444 g carbon dioxide equivalent emissions/g midazolam.[31] Cefazolin, paracetamol, or tranexamic acid were unstudied, but we used this average 340 g carbon dioxide equivalent emissions/g drug[31] to calculate carbon dioxide equivalent emissions. We estimated carbon dioxide equivalent emissions associated with intravenous fluid manufacture from our previous morphine life cycle assessment study (including production and sterilization of 0.9% NaCl bags).[30] Some recycling was already occurring in the operating room (plastics/paper/cardboard).[7,32]

Data were modeled in SimaPro-9 life cycle assessment software (PRé Consultants, The Netherlands). We developed an inventory that quantified materials and energy used, and modeled this using the Ecoinvent[22] (version 3.5) and Australian Life Cycle Inventory[23] databases. We used Monte Carlo software algorithms (SimaPro) to obtain results and 95% CIs. We modeled our results with those for identical anesthetics being provided in China, the European Union, and the United States. We give the 95% CIs (from Monte Carlo analysis) only for the means/averages, and only for group aggregates (rather than individual components, *e.g.*, plastics or electricity use), as the same assumptions are

inherent in modeling the components that make up the aggregates (producing CIs for each component is lengthy and the numbers small). The 95% CI of the mean (indirectly obtained by Monte Carlo) indicates what the variability of the results could be if the study was performed many times, and may not closely reflect the directly obtained minima/maxima results. Further details about life cycle assessment methods are contained within appendix 1.

Results

Between January 9, 2019, and June 10, 2019, 36 patients underwent total knee replacements in operating room 4 at Williamstown Hospital, Western Health, Melbourne. As planned for this convenience sample and dependent upon researcher availability, we obtained anesthesia data for 30 patients: 10 patients in each group of general anesthesia, spinal anesthesia, and general plus spinal (combination). We excluded 1 patient (from combined general and spinal group) as they received nitrous oxide, leaving 29 patients (discussed later). The average/mean knee replacement anesthesia duration times (and ranges) were as follows: general anesthesia, 161 (113 to 193) min, spinal, 200 (168 to 288) min, and combination, 189 (128 to 241) min. Eight general anesthesia patients received sevoflurane, one total intravenous anesthesia, and one sevoflurane/total intravenous anesthesia combination. Six general anesthesia patients were intubated, while four had a laryngeal mask placed. All 10 patients receiving spinal anesthesia had sedative propofol infusions. For the patients receiving combination anesthesia, six received sevoflurane, and three received total intravenous anesthesia, while eight were given laryngeal masks, and two were intubated.

Background Data: Masses and Types of Disposables, Gases, and Electricity Used for Reusable Equipment

Appendices 1 and 2 give background data and calculations about the masses and energy required to wash reusable equipment. Appendix 3 gives masses of pharmaceuticals, led by cefazolin, tranexamic acid, paracetamol, and propofol, which are given in larger quantities/masses than other drugs. Intravenous paracetamol was given to one or two patients per group. Note (from Materials and Methods) that propofol has a carbon footprint of only 21 g carbon dioxide equivalent emissions/g propofol,[31] so using 3-h total intravenous anesthesia propofol at 700 mg/h will have carbon dioxide equivalent emissions of less than 50 g carbon dioxide equivalent.

Table 1 gives the equipment types used including the mean, 25%, 75% (interquartile range), and minimum–maximum (range). The total masses of single-use equipment used were as follows: general anesthesia (mean, 996 g; interquartile range, 873 to 1,033 g; range, 725 to 1,392 g), spinal anesthesia (mean, 997 g; interquartile range, 934 to 1,076 g; range, 885 to 1,184 g), and combination anesthesia (mean, 1,237 g; interquartile range, 1,100 to 1,285 g; range, 1,009 to 1,687 g). For single-use equipment, the majority of waste was from total plastics: average for general anesthesia, 783/996 g (78%); spinal, 729/997 g (73%); and combination, 932/1,237 g (75%). Glass was the next most common discarded material. There were minor (less than 100 g total mass) masses of other materials discarded (copper, cotton, latex, neoprene, and steel).

Table 1 also indicates that delivered oxygen was much greater for spinal anesthesia (mean, 1,328 l; interquartile range, 1,080 to 1,545 l; range, 990 to 1,950 l) *versus* general anesthesia (mean, 197 l; interquartile range, 116 to 271 l; range, 74 to 320 l), or combination anesthesia (mean, 256 l; interquartile range, 131 to 332 l; range, 53 to 824 l). Seven patients having spinal anesthesia received oxygen flow rates of 6 l/min, and three of 8 to 10 l/min. For the nine general anesthesia patients who received sevoflurane, the range was 14 to 44 ml (range, 6 to 15 ml/h), and for the seven combined anesthesia patients, the range of sevoflurane use was 11 to 50 ml (5 to 16 ml/h). Using 6 ml/h of (liquid) sevoflurane for 3 h will have carbon dioxide equivalent emissions of approximately 6 ml × 3 h × 1.5 (density) × 130 global warming potential in carbon dioxide equivalent emissions for sevoflurane[13] = 3.5 kg carbon dioxide equivalent emissions.

Desflurane was unused, and nitrous oxide used for one patient. Both desflurane and nitrous oxide are known to have high global warming potential (2,540[11] and 265,[33] respectively), which could easily skew overall results for this 30-patient convenience sample. The one patient who received nitrous oxide had 111 l N_2O over 3.25 h. The carbon dioxide equivalent emissions for the nitrous oxide alone are 111/24.5 = 4.5 moles = 4.5 × 44 g = 200 g (0.2 kg) N_2O = 0.2 × 265[33] = 53 kg carbon dioxide equivalent emissions. Thus, compared with using sevoflurane alone, the carbon dioxide equivalent emissions from using nitrous oxide are more than 10-fold greater.

Table 2 indicates carbon dioxide equivalent emissions from anesthesia per patient anesthetic items as calculated from the types and masses of consumables used (appendices 1 and 2), and the electricity requirements for washing/sterilizing reusable equipment, patient warming, anesthetic gas scavenging, and the anesthesia machine. Note in table 2 the column heading "Carbon dioxide equivalent emissions per kg, item, ml, or l," which indicates the differing carbon intensities of materials for their entire life cycle. Cotton has high carbon dioxide equivalent emissions per kilogram due to decomposition emitting methane (*vs.* steel and plastic, which are nonbiodegradable).[22] Considerably more plastics were used than *disposable* cotton; thus, plastics contributed the majority of the carbon dioxide equivalent emissions for disposable equipment. The summary carbon dioxide equivalent emissions for each group in the last two lines of table 2 indicate the directly measured averages, and the indirectly measured 95% CIs as calculated by Monte Carlo analysis. As noted in the Materials and Methods, the 95% CIs may not be reflective of the directly measured interquartile ranges and minima/maxima seen in figure 2.

Table 1. Masses of Items Used by Anesthetists

Items	General Anesthesia		Spinal Anesthesia		General + Spinal Anesthesia	
	Average (Range), g/case	[Interquartile Range, 25–75%], g/case	Average (Range), g/case	[Interquartile Range, 25-75%], g/case	Average (Range), g/case	[Interquartile Range, 25-75%], g/case
Reusable items, g						
Cotton hand towel washed* and sterilized† (with sterile gown)	0	0	143	0	143	0
Plastics washed‡ (drug trays)	178 (178–178)	[178–178]	178 (178–178)	[178–178]	178 (178–178)	[178–178]
Plastics washed (anesthetic breathing circuits)§	0.1 kilowatt-hours/operation		0		0.1 kilowatt-hours/operation	
Plastics washed‡ and sterilized† (Proseal laryngeal mask, spinal tray, sterile surgical gown for spinal procedure). Note: Some spinal cases required > 1 gown (training, contamination, and so forth).	14 (0–72)	0–0	1,492 (1,227–1,828)	[1,227–1,728]	1,227 (1,227–1,227)	[1,227–1,227]
Silicone washed‡ (face mask)	78 (78–78)	[78–78]	0	0	78 (78–78)	[78–78]
Stainless steel washed‡ and sterilized§ (laryngoscope blade)‖	86 (0–123)	[31–123]	0	0	13 (0–123)	[0–0]
Single-use items,# g						
Copper**	5 (0–10)	[0–10]	1 (0–6)	[0–0]	3 (0–10)	[0–10]
Cotton	12 (0–25)	[0–23]	15 (3–28)	[6–25]	22 (11–28)	[23–25]
Glass††	161 (97–357)	[118–185]	180 (91–305)	[123–218]	186 (103–270)	[133–224]
Plastics, non–polyvinyl chloride‡‡ trash	486 (164–755)	[388–501]	451 (374–512)	[433–473]	583 (393–1040)	[482–630]
Plastics, non–polyvinyl chloride polypropylene recycled§§	0	0	42 (42–42)	[42–42]	42 (42–42)	[42–42]
Plastics, polyvinyl chloride trash	186 (89–252)	[166–222]	111 (28–236)	[92–121]	181 (98–284)	[137–250]
Plastics, polyvinyl chloride recycled‖‖	111 (91–123)	[91–123]	125 (91–151)	[123–123]	123 (91–151)	[91–123]
Rubber, latex	3 (0–29)	[0–0]	41 (28–57)	[29–57]	41 (29–57)	[29–57]
Rubber, neoprene, nitrile	30 (26–38)	[26–32]	33 (0–77)	[19–53]	42 (0–77)	[26–51]
Stainless steel##	4 (1–7)	3–6	13 (7–23)	[11–13]	13 (7–17)	[7–17]
Total, single-use items	996 (725–1,392)	[873–1,033]	997 (885–1,154)	[934–1,076]	1,237 (1,009–1,687)	[1,100–1,285]
Gases (volumes in l or ml)						
Oxygen, l	197 (75–320)	[116 – 271]	1,328 (990–1,950)	1,080–1,545	256 (53–824)	[131–332]
Compressed air, l	80 (14–273)	52–76	0	0	76 (9–193)	[42–94]
Sevoflurane,*** ml as a liquid)	24 (0–44)	0–29	0	0	16 (0–44)	[0–28]
Sevoflurane, ml/h	9.6 (6.2–14.6)	8.2–10.3	0	0	8.1 (4.8–19.0)	5.0–9.0
Sevoflurane: total intravenous anesthesia + sevoflurane: total intravenous anesthesia	8: 1: 1				5: 1: 3	

Pharmaceutical data are located in appendix 2.

*Laundered cotton data taken from Carre's Royal Melbourne Institute of Technology (Melbourne) study within Overcash.[24] †Energy required to sterilize equipment obtained from McGain *et al.*[25–27] ‡Energy required to wash (thermally disinfect trays) taken from McGain *et al.*[17]

§Circuits changed weekly. Total 6.2 kilowatt-hours per wash load[17,28] with minimum of six circuits within and used for 25 operations. No energy attributed to spinal anesthetic as unused. ‖Stainless steel laryngoscope handles were wiped down with an antiseptic wipe between patient use. #Minimal paper/cardboard was disposed of within the operating room as the cardboard packets were routinely separated from the drug ampoules before entry into the operating room. No mattresses were used for heavy/obese patient transfers as most such patients are electively preferentially operated upon elsewhere in our health service. **Copper was found in the temperature probe. ††Glass arose mainly from drug ampoules. ‡‡Plastics, non–polyvinyl chloride were, from inspection and reference to our previous study of operating room plastics,[32] almost entirely polypropylene and polyethylene/polypropylene combinations (syringes). One plastic reusable ventilator circuit (436 g) was found to be leaking (thus discarded) for a general anesthesia + spinal patient, considerably increasing the maximum mass of plastics. §§Non–polyvinyl chloride recycling (of polypropylene) was occurring in the operating room.[7] ‖‖Polyvinyl chloride recycling of intravenous fluid bags was occurring in the operating room.[7] ##Stainless steel was contained within needles. ***Desflurane was not used for any cases. Nitrous oxide was used in one general anesthesia + spinal combination case, but this case was removed as the effect of nitrous oxide upon the total carbon dioxide emissions for the combination group excessively skewed the data.

Table 2. Carbon Dioxide Equivalent Emissions from Anesthesia per Patient

Item (Equipment, Gases, Energy)	Carbon Dioxide Equivalent Emissions per Kilogram, Item, Milliliter, or Liter	General Anesthesia: Average Kilogram Carbon Dioxide Equivalent Emissions per Patient	General Anesthesia: % Total	Spinal: Average Kilogram Carbon Dioxide Equivalent Emissions per Patient	Spinal: % Total	General Anesthesia + Spinal: Average Kilogram Carbon Dioxide Equivalent Emissions per Patient	General Anesthesia + Spinal: % Total
Average anesthesia duration		161 min (2.7 h)		200 min (3.3 h)		189 min (3.2 h)	
Electricity directly associated with anesthesia (Victorian electricity = 1.12 kg carbon dioxide equivalent emissions/kilowatt-hour							
Patient air warmer (3M, USA) 0.8 kilowatt-hours/h (product information) = 0.9 kg carbon dioxide equivalent emissions/h use		2.46 kg carbon dioxide equivalent	20%	2.96	21%	2.86	19%
Anesthesia machine 0.08 kilowatt-hours/h[18] = 0.09 kg carbon dioxide equivalent/h use		0.24 kg carbon dioxide equivalent	2%	0.30	2%	0.29	2%
Reusable equipment: electricity for washing, sterilizing (Victorian electricity = 1.12 kg carbon dioxide equivalent emissions/kilowatt-hour)[29]							
Washing plastic trays[17]	0.16 kg carbon dioxide equivalent emissions/tray[17]	0.16	1%	0.16	1%	0.16	1%
Washing[17] and sterilizing plastic, cotton, silicone, and stainless steel (sterile surgical gown and towel for spinal, combined anesthesia)	3.0 kg carbon dioxide equivalent emissions/kg washed[17] and sterilized[23–25]	0.49	4%	4.52	29%	3.96	24%
Single-use Items (Australian Government National Greenhouse Accounts Factors)[29]							
Copper	11.9 kg carbon dioxide equivalent emissions/kg	0.06 kg carbon dioxide equivalent	0%	0.01 kg carbon dioxide equivalent emissions	0%	0.05 kg carbon dioxide equivalent emissions	0%
Cotton	27.2 kg carbon dioxide equivalent emissions/kg	0.35	3%	0.44	3%	0.64	4%
Glass	3.6 kg carbon dioxide equivalent emissions/kg	0.58	4%	0.65	4%	0.65	4%
Plastics, non–polyvinyl chloride	3.3 kg carbon dioxide equivalent emissions/kg	1.72	13%	1.60	10%	2.07	12%
Plastics, non–polyvinyl chloride recycled	1.8 kg carbon dioxide equivalent emissions/kg	0.12	1%	0.07	< 1%	0.07	< 1%
Plastics, polyvinyl chloride	2.6 kg carbon dioxide equivalent emissions/kg	0.49	4%	0.30	2%	0.46	3%
Plastics, polyvinyl chloride recycled	1.1 kg carbon dioxide equivalent emissions/kg	0.12	1%	0.12	1%	0.12	1%
Rubber, synthetic and natural	2.0 kg carbon dioxide equivalent emissions/kg	0.02	< 1%	0.14	1%	0.16	1%
Stainless steel	6.8 kg carbon dioxide equivalent emissions/kg	0.03	< 1%	0.09	1%	0.09	1%
Gases							
Oxygen	0.0021 kg carbon dioxide equivalent emissions/l	0.41 kg carbon dioxide equivalent	3%	2.76 kg carbon dioxide equivalent emissions	18%	0.53 kg carbon dioxide equivalent emissions	3%
Compressed air	0.00051 kg carbon dioxide equivalent emissions/l	0.04	< 1%	0		0.04	
Sevoflurane global warming potential = 130)[11]	0.196 kg carbon dioxide equivalent emissions/ml liquid	4.70	35%	0	0%	3.14	19%
Pharmaceuticals, total	Variable carbon dioxide equivalent emissions[27]	1.20	9%	1.26	8%	1.26	8%
Average and range of all carbon dioxide equivalent emissions (kg carbon dioxide equivalent)		13.3 (8.1–20.8)	100%	15.4 (11.7–19.0)	100%	16.7 (10.6–25.7)	100%
95% CI of carbon dioxide equivalent emissions		11.4–17.9		13.7–18.3		14.6–23.6	

Carbon Dioxide Equivalent Emissions: Effects of Anesthetic Duration

As table 2 and figure 3 indicate, the average/mean duration of spinal and combined anesthesia were approximately 40 and 30 min more (*i.e.*, 20% longer) than general anesthesia. The increased duration for spinal/combined anesthesia is at least partly due to increased time to undertake the spinal anesthetic. The longer spinal and combined anesthetic duration increased the carbon footprint of electricity for the patient air warmer and scavenging by 0.8 and 0.6 kg carbon dioxide equivalent emissions, respectively. Further, because spinal anesthesia was 20% longer than general anesthesia, this added approximately 2.76 × 0.2 = 0.6 kg carbon dioxide equivalent emissions to oxygen use for the spinal anesthetic. A spinal anesthetic of 20% shorter duration would thus have approximately 1.4 kg carbon dioxide equivalent less emissions. The effects of anesthetic duration had a much lower magnitude of effect upon the carbon footprint of other anesthetic activities.

Carbon Dioxide Equivalent Emissions: Averages, Ranges, and Components

Using Monte Carlo modeling, we found that the carbon dioxide equivalent emission means/averages were similar for all three approaches, and that the 95% CIs overlapped considerably, resulting in difficulty in making group comparisons. For general anesthesia, the mean was 14.9 kg carbon dioxide equivalent emissions (95% CI, 9.7 to 22.5); spinal anesthesia, 16.9 kg carbon dioxide equivalent emissions (95% CI, 13.2 to 20.5); and combination anesthesia, 18.5 kg carbon dioxide equivalent emissions (95% CI, 12.5 to 27.3). Figure 2 provides graphical contextualization of the means, interquartile ranges, and minimum-maximum ranges of the carbon dioxide equivalent emissions for the three anesthesia approaches. Figure 2 indicates that the interquartile ranges are relatively close, but there are considerable *intragroup* outliers. The range for spinal anesthesia was less than for general or combination anesthesia as there was a more standard approach (spinal procedure, propofol infusion, no variability in [unused] anesthetic gas use, minor variation in oxygen delivery/hour).

Table 2 and figure 3 indicate that electricity for the patient air warmer was responsible for at least 2.46 kg carbon dioxide equivalent (16%) emissions of all anesthesia approaches. Total single-use plastics, glass, and so forth were responsible for 3.5 (general anesthesia), 3.4 (spinal), and 4.3 (combination) kg carbon dioxide equivalent emissions, respectively (20 to 25% total, with the majority from single-use plastics). All pharmaceuticals beyond gases were responsible for 1.2 to 1.3 kg carbon dioxide equivalent emissions, 7 to 8% total for all three approaches. For general anesthesia, sevoflurane (global warming potential = 130 times carbon dioxide)[11] for 9/10 patients was the principal contributor; average 4.7 kg carbon dioxide equivalent emissions (32% total), range 2.7 to 8.6 kg carbon dioxide equivalent emissions. The patient who received total intravenous anesthesia represented the minimum 8.4 kg carbon dioxide equivalent emissions in the general anesthesia group. For the combination anesthesia group, sevoflurane contributed an average 3.1 kg carbon dioxide equivalent emissions (17% total), range 0.6 to 10.0 kg carbon dioxide equivalent

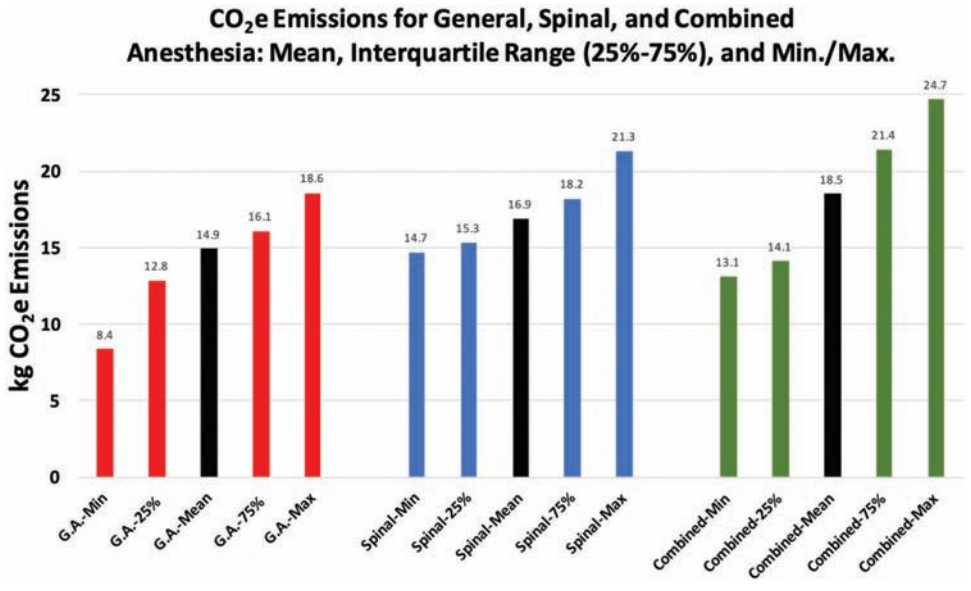

Fig. 2. Carbon dioxide equivalent emissions for general, spinal, and combined anesthesia: mean, interquartile range (25%–75%), and minimum/maximum.

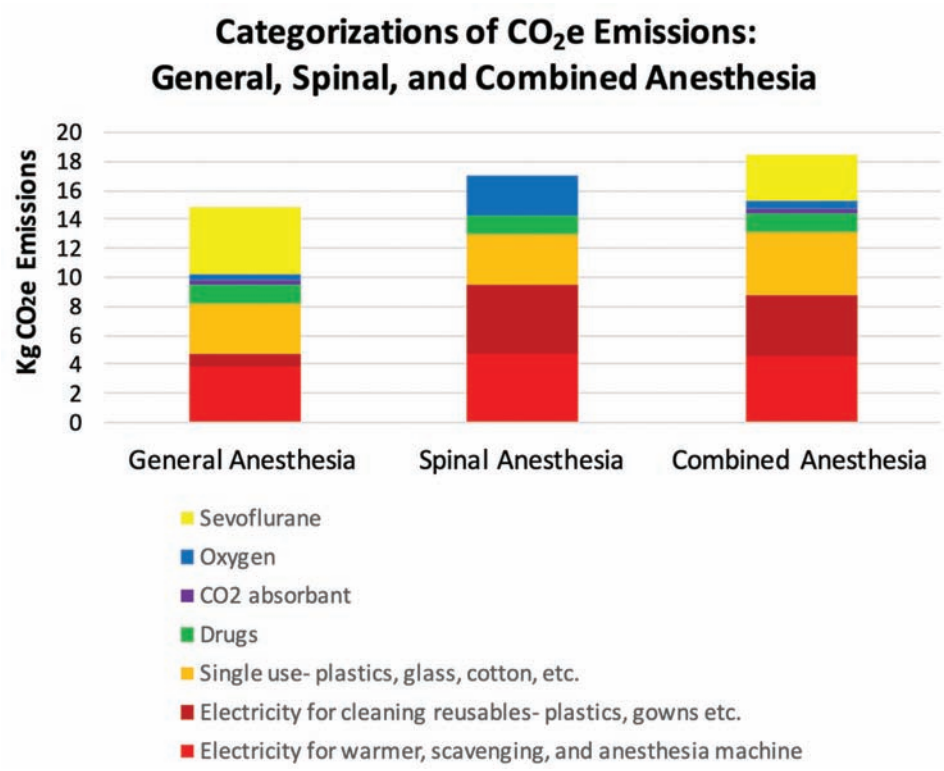

Fig. 3. Categorizations of carbon dioxide equivalent emissions: general, spinal, and combined anesthesia.

emissions. For spinal and combination anesthesia, washing and sterilizing reusable gowns, plastic spinal trays, and so forth contributed 4.5 kg carbon dioxide equivalent and 4.0 kg carbon dioxide equivalent emissions, respectively (coal was 75% of electricity for Melbourne, with 1.1 kg carbon dioxide equivalent emissions/kilowatt-hour).[23,34] Oxygen use was also important to carbon dioxide equivalent emissions for spinal anesthesia (2.8 kg carbon dioxide equivalent emissions, 16% total) as O_2 flow rates were 6 to 10 l/min, compared with 0.5 to 3 l/min for general and combination anesthesia approaches.

Environmental Impacts: International Comparisons

Figure 4 indicates the modeled results of our data with electricity sourced in three other countries/regions: China, the European Union, and the United States (source: Ecoinvent).[22] The carbon dioxide equivalent emissions per kilowatt-hour varies due to different energy sources. Australia and China have similar "carbon intensities" (carbon dioxide equivalent emissions per kilowatt-hour) due to their reliance on coal, while the European Union (and the United Kingdom) has large nuclear and hydro/wind/solar sources for electricity generation, and the United States is moving rapidly toward greater renewable electricity generation. Such modeling changed the carbon dioxide equivalent emissions for washing and sterilizing reusable equipment, and electricity for patient warming. We assumed that the carbon dioxide equivalent emissions due to the use of single-use equipment were identical between countries, *i.e.*, produced in China, as this is the major source for single-use items in Australia and anecdotally elsewhere.

From figure 4, as expected, the carbon dioxide equivalent emissions for all three anesthesia approaches for Australia and China are close. For the European Union and the United States, the carbon dioxide equivalent emissions for spinal anesthesia are decreased compared to Australia due to the greater predominance of renewable electricity used to clean reusable equipment/gowns. In the European Union, spinal anesthesia has a carbon footprint of approximately 60% (9.9/16.9 kg carbon dioxide equivalent emissions) that in Australia. Comparing the results of figure 2 (Australian data) with figure 4 (international modeling), the *minimum* carbon dioxide equivalent emissions for general anesthesia in Australia (total intravenous anesthesia) is less than the European Union general anesthesia *average* (8.4 *vs.* 11.9 kg carbon dioxide equivalent emissions), but the *minimum* for spinal anesthesia for Australia (14.7 kg carbon dioxide equivalent emissions) is considerably higher than the European Union *spinal average* (9.9 kg carbon dioxide equivalent emissions) due to high carbon intensity

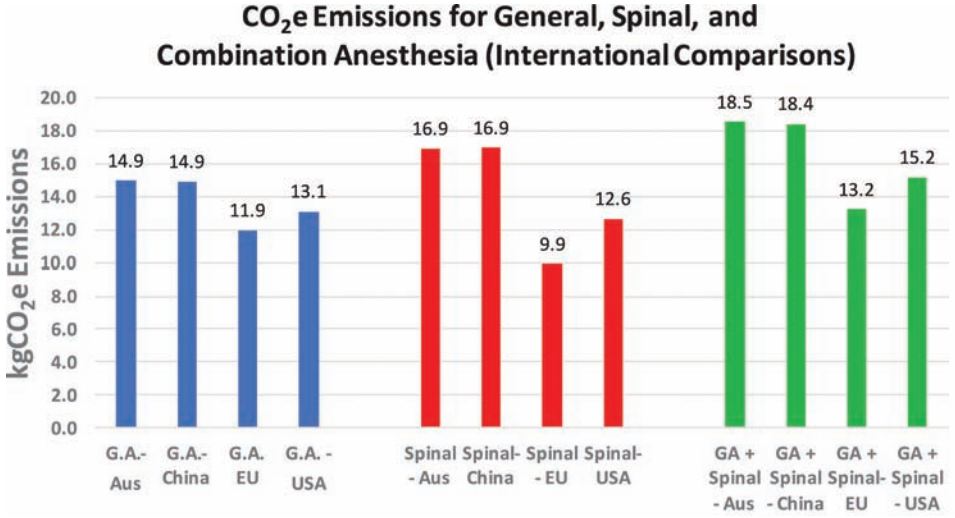

Fig. 4. Carbon dioxide equivalent emissions for general, spinal, and combination anesthesia (international comparisons).

Australian electricity required to clean reusable anesthesia equipment.

Discussion

The carbon footprints of anesthesia for a knee replacement were similar for general, spinal, and combination approaches, with significant overlap between the CIs. There was considerable *within-group* variation for general and combination anesthesia (a twofold difference in minimal-maximal carbon dioxide equivalent emissions), but only 50% difference for spinal anesthesia. The three major components of carbon dioxide equivalent emissions across all groups were (with approximations) single-use equipment (20 to 25%, mainly plastics), electricity for the patient air warmer (15%), and pharmaceuticals (8%). Carbon dioxide equivalent emissions from sevoflurane use for general anesthesia (32% total) and combination anesthesia (17% total) were considerable. Carbon dioxide equivalent emissions for cleaning reusable equipment were more than 25% total for spinal, and 20% for combined anesthesia. Oxygen use was about 15% of carbon dioxide equivalent emissions for spinal anesthesia. Importantly, the duration of anesthesia was 20% longer for spinal *versus* general anesthesia. Procedure duration contributes to carbon dioxide equivalent emissions, particularly electricity for the air warmer.

Inhalational anesthesia is known to have higher carbon dioxide equivalent emissions than total intravenous anesthesia.[35,36] For general anesthesia, the use of low flow (minimum 6 ml liquid sevoflurane/h) rather than total intravenous anesthesia increased the carbon dioxide equivalent emissions by 1.2 kg carbon dioxide equivalent emissions/h. There is, however, sparse evidence comparing the carbon footprint of general and spinal anesthesia.[13,37] Spinal anesthesia had a high carbon footprint, partially attributable to cleaning reusable equipment and compression of liquid oxygen, the carbon dioxide equivalent emissions for which were elevated due to the electricity mix of 75% brown coal for Melbourne, Australia. It is unclear internationally what standard oxygen administration is during spinal anesthesia, but flow rates of greater than 6 l/min may be atypical. For cleaning reusable equipment, we assumed worst case steam sterilizer efficiency,[25,27] recognizing that potential efficiency improvements[25,38] could reduce carbon dioxide equivalent emissions by 0.5 kg carbon dioxide equivalent emissions/h just for anesthesia alone. The modeled carbon dioxide equivalent emissions for cleaned reusables in Australia are similar to China, but double the United States, and quadruple Europe/United Kingdom, because of different energy mixes.[15]

Our small, single-center, prospective, nonrandomized, observational, unblinded study has limitations, which makes comparisons between the anesthetic groups and between countries uncertain. We did not prescribe anesthetic choice, and we limited our convenience sample to 30 patients having one operation type in Australia. We aimed to provide a life cycle assessment of three anesthetic approaches to a total knee replacement, but we caution comparison between the three groups. A prospective study powered appropriately would be a considerable undertaking and of limited benefit given the initial hypothesis posed by this study.

We acknowledge anesthetic practice variability, particularly choice of anesthetic gases with high global warming potential.[11] Use of desflurane and nitrous oxide in our small study could skew group results markedly (*e.g.*, greater than 100 kg carbon dioxide equivalent emissions for either nitrous oxide or desflurane use).[13] We chose to exclude the

one patient receiving nitrous oxide as the relative carbon dioxide equivalent emissions from using nitrous oxide compared with sevoflurane/total intravenous anesthesia/spinal anesthesia are very high, making intergroup comparison difficult.

Comparisons between the amount of equipment/drugs/gases are influenced by the duration of the operation. Many items have greater use in the first hour (induction, drug administration, spinal anesthesia) than for subsequent hours. Nevertheless, other environmental effects are more closely dependent upon duration (electricity for the air warmer and scavenging), carbon dioxide absorbent use, and oxygen use.

We excluded orthopedic surgery and all operating room heating/ventilation/air conditioning carbon dioxide equivalent emissions, focusing solely upon anesthesia. Anesthetic breathing circuits were changed weekly,[28,39] a practice common in Australia,[40] Germany,[41] and elsewhere. Reusable laryngoscope blades, handles, face masks, and surgical gowns were used.[15] We averaged the carbon dioxide equivalent emissions for all 20 drugs studied by Parvatker *et al.*,[31] using this average for unstudied drugs (cefazolin, paracetamol, and tranexamic acid).[31] Drugs given in relatively large quantities (cefazolin) dominated the pharmaceutical carbon dioxide equivalent emissions. Cardboard/paper was routinely separated preoperatively.

Avoiding the use of desflurane and nitrous oxide is only the beginning of actions that anesthetists can undertake to reduce their workplace carbon footprint. The fuel efficiency of the average U.S. car is 0.40 kg carbon dioxide equivalent emissions/mile, so in our study, the average anesthetic carbon contribution (17 kg carbon dioxide equivalent emissions) is like driving 42 miles (*without* desflurane or nitrous oxide). Several activities can safely reduce the anesthetist's carbon footprint. For spinal anesthesia, reducing O_2 flows from 10 l to 6 l/min reduces driving by 1 mile/h. For general anesthesia, reducing fresh gas flow with sevoflurane by 1 l/min saves 3 miles/h. Replacing 1 l/min fresh gas flow sevoflurane with total intravenous anesthesia saves another 3 miles/h. Using the minimum plastic and glass use will reduce the carbon dioxide equivalent emissions 1 kg carbon dioxide equivalent emissions/h, equaling saving 3 miles/h. Converting from Australia's electricity mix to Europe's for spinal procedures will save 2 kg carbon dioxide equivalent emissions, equaling 5 miles/h. When combining these mentioned carbon sparing activities, you have halved the miles driven for the 3-h anesthetic.

Decreasing the carbon footprint of some activities is challenging; a minimum of pharmaceuticals and equipment are required. Further, anesthesiologists cannot change the carbon intensity of electricity, although we can advocate.[13] The use of renewable energy decreases the carbon dioxide equivalent emissions associated with cleaning reusable equipment, with promising plans locally for Victorian electricity generation.[42] For the European Union/United Kingdom/U.S. anesthesiologist, moving from single-use to reusable anesthetic equipment right now will have financial and environmental benefits.[15] Our study quantifies carbon dioxide equivalent emissions of individual areas of anesthesia practice. We encourage cognizance of one's carbon footprint, emphasizing that instigating multiple, seemingly small changes in our workplace patterns is the best path to low carbon anesthesia.

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Competing Interests

The authors declare no competing interests.

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Appendix 1: Life Cycle Assessment Methods

For this appendix, we primarily draw upon past explanations about life cycle assessment generally,[43–45] and from several previous publications from our broader group.[4,13,17,18] Life cycle assessment is a scientific method to determine the entire "cradle to grave" environmental and financial effects of processes and products.[43,45] The Society for Environmental Toxicology and Chemistry (Pensacola, Florida) defined the components of a life cycle assessment in 1991: (1) raw material acquisition; (2) processing and manufacturing; (3) distribution and transportation; (4) use, reuse, and maintenance; (5) recycling; and (6) waste management.[1] Everything we use and do has an environmental footprint, whether this is for a tangible product or a service such as an admission to hospital. Life cycle assessments have a "system boundary," *i.e.*, a limit to which one examines the environmental effects of a product or process. This system boundary is defined by local Australian and international standards.[14,19] For example, if we are examining a plastic syringe, the system boundary could be defined to include the manufacture of the plastic and ongoing maintenance

of installed infrastructure, but not the actual manufacture of such installed infrastructures which are in turn used to make the syringe.

Environmental factors beyond carbon dioxide equivalent emissions, including water consumption; petrochemical use; air, water, and terrestrial pollution; and release of toxic byproducts, can be accounted for in life cycle assessment. We have focused upon carbon dioxide equivalent emissions as they are an important focus due to the increasing health concerns of climate change. In the late 1990s, standardization of how life cycle assessments should be conducted was achieved when the International Organization for Standardization released the ISO-14000 series.[20]

Functional Unit

Using the ISO-14040 standards,[20] we defined our study's *functional unit* as all anesthesia for a total knee replacement in a public hospital in Victoria, Australia. The ISO-14040 standards[14] life cycle assessment *system boundary* defines inclusions/exclusions. We did not include data for heating/ventilation/air conditioning, or any surgical equipment.

Importantly, once one has details about the components making up a process/procedure, their masses/amounts, and their origins, then one can then undertake a life cycle assessment with the relevant software and application. For example, for a general anesthetic, we obtained quantified data about (1) electricity used for cleaning/sterilizing reusable equipment, the patient air warmer, scavenging, and the anesthetic machine; (2) plastics, steel, cotton, and so forth; (3) pharmaceuticals; and (4) volatile anesthetics and oxygen use. Data related to the source/origin of the electricity, plastics, and so forth were also important. With these input data, we then turned to quantifying the outputs with life cycle inventories. We obtained the power rating for the patient air warmer (0.8 kilowatt-hours/h) from online data for Model 775, Bair Hugger, USA.[21] Anesthetic machine electricity use (0.08 kilowatt-hours/h) was obtained from Chakladar,[20] and anesthetic scavenging (0.4 kilowatt-hours/h) from Barwise.[23]

Life Cycle Inventories

Life cycle assessments make use of life cycle inventories. A life cycle inventory is a catalog of flows to and from nature, with *inputs* such as energy, water, and raw materials, and *outputs* (releases) to air, land, and water. There can be a large number of inventory flows numbering in the hundreds to thousands, in such a way that the life cycle inventory of even a simple plastic syringe requires multiple flows of petrochemical resource extraction, manufacture, transport, and use. To examine all of these details *de novo* every time a life cycle assessment is undertaken would be prohibitively exhaustive and expensive. It is ideal to obtain as much *primary/foreground* data (*e.g.*, measurement of electricity use for a hospital sterilizer) as possible in order to reduce the uncertainty of the data. Nevertheless, multiple *secondary/background* sources of information are usually required for life cycle assessments (*e.g.*, details of plastic manufacture).

Large national and international databases are the routine sources for such secondary data, such as EcoInvent[46] and the Australian Life Cycle Inventory,[47] which incorporate geographically specific average industry data. For example, the estimated carbon dioxide emission from burning coal from a defined region is obtained from such environmental databases. Such average industry data can have greater associated uncertainty than directly measured (primary) data.[27,44] Care must then be taken to ensure that the secondary data indicate the local conditions of the life cycle assessment in question (*e.g.*, local coal-fired electricity versus hydroelectric electricity used for the secondary data).

A process diagram/tree (fig. A1.1) is developed from all of the inputs that make up an output. We have included the process diagram for spinal anesthesia as an example. One can see that electricity forms a large part of the total carbon dioxide equivalent emissions as indicated by the wide red lines associated with electricity, with oxygen also being important on the right-hand side of the process diagram. Note that in this diagram, in order to be able to visualize some of the complexity of life cycle assessment methods, we have included a "cutoff" of only items that contribute greater than 1% of the final carbon dioxide equivalent emissions to general anesthesia. In reality, we included all inputs (at least several hundred) that contributed to the final carbon dioxide equivalent emissions.

Statistical Analyses: The Pedigree Matrix and Uncertainty

The life cycle inventory thus has inputs (such as electricity from coal) that are combined to form an output (*e.g.*, a plastic syringe). Every input in every process from secondary databases has a degree of uncertainty associated with it. This uncertainty routinely cannot be derived directly from the available information, so a standard procedure was developed to derive uncertainty factors from a qualitative assessment of the data, known as the Pedigree Matrix.[27] The Pedigree Matrix is a commonly used qualitative scoring system derived from the secondary data's reliability, completeness, temporal and geographical proximity to the process or item being assessed, and further technological factors,[27,44] with a score from 1 (good) to 5 (poor) for each factor. The Pedigree Matrix relies upon expert judgment. For example, if the secondary data for carbon dioxide equivalent emissions per kilowatt-hour of electricity produced was obtained recently from all local coal fired power stations, this would have better reliability, completeness, and temporal and geographical proximity than secondary data from an overseas-derived database that sampled one coal-fired power station a decade ago. As the Pedigree Matrix is based upon expert opinion, it is open to a perception of irregularities. The Pedigree Matrix has been updated to

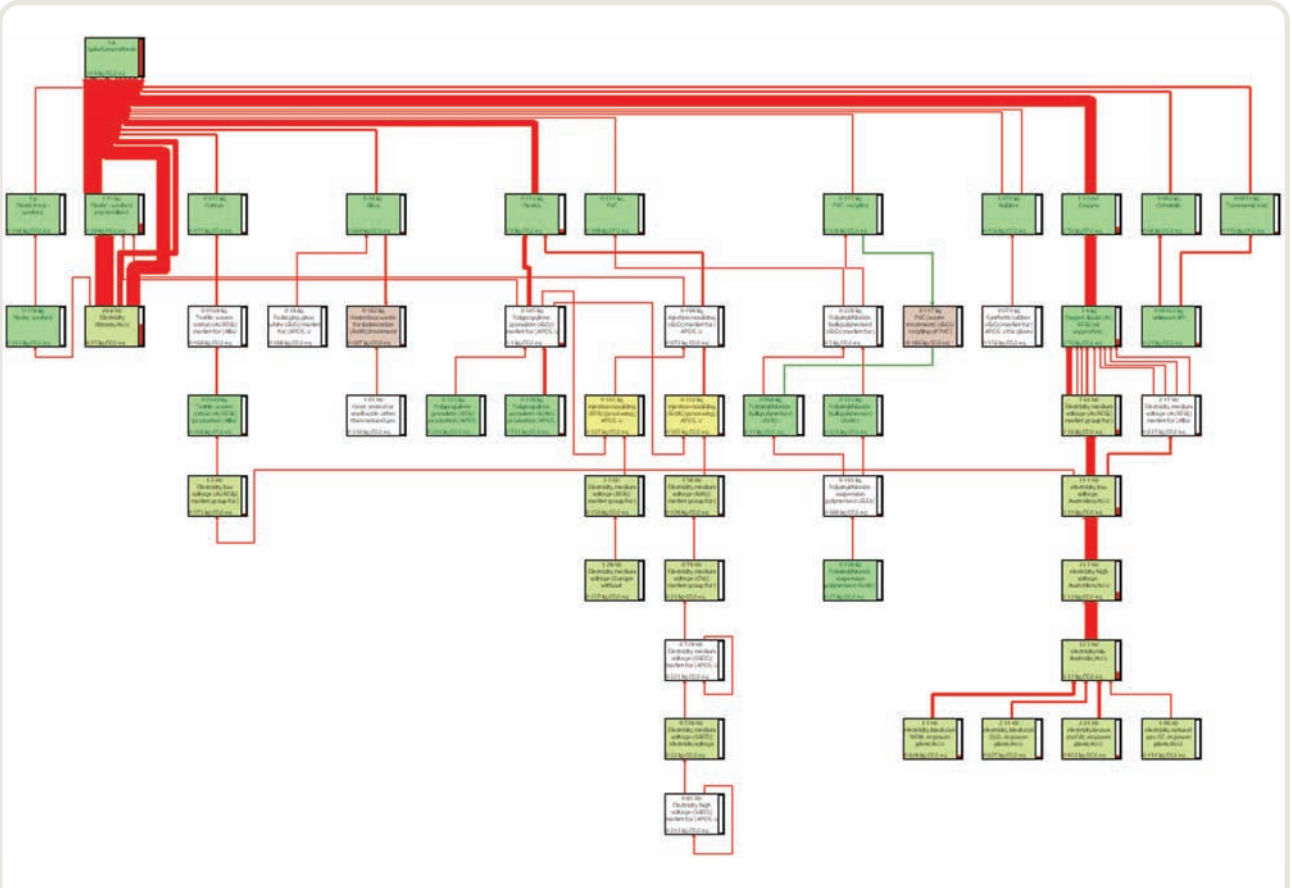

Figure A1.1. Process diagram for spinal anesthesia (as a sample).

incorporate some of these concerns with greater emphasis upon direct empirical values for each of the factors.[17,46]

There are also uncertainties associated with all life cycle assessment primary inputs that are directly measured. For example, the plastic syringes used by anesthesiologists in our study were transported from the Philippines to Australia. There is little uncertainty associated with the carbon dioxide emissions from such shipping as the distance traveled is known and the variability in fuel consumption of container ships is small. Similarly, the sterilization of the reusable plastic spinal trays in our study had little uncertainty as we had measured the sterilizer's electricity use more than 1,000 times[18] with different load types. If we had measured this sterilizer electricity use but once, the carbon dioxide equivalent emissions from such electricity use would have a greater associated uncertainty. As for secondary data from life cycle inventory databases, the Pedigree Matrix for primary input data is a qualitative scoring system.

To combine the values and frequency distributions of these hundreds of inputs to obtain outputs such as carbon dioxide equivalent emissions, we used Monte Carlo analyses (routine for life cycle assessment). Monte Carlo methods are a broad class of computational algorithms that rely on repeated random sampling to obtain numerical results. Monte Carlo methods are useful when there are large numbers of inputs and where it is impractical to obtain data for each of these inputs *de novo*.[27,44]

When there is a range of possible values for a result, there are a number of approaches to how to determine the best estimate and the frequency distribution with CIs around this result. Monte Carlo methods take data points from within the frequency distributions for all inputs to develop a final output result, frequency distribution, and the plausible range, including the central tendency of the frequency distribution.[27] The greater the number of "runs" by Monte Carlo analysis, the better the estimate of the most likely value and the associated frequency distribution. A final 95% CI for a process is achieved based on the random sampling anywhere within the 95% CIs for all inputs. A Monte Carlo analysis includes at least 1,000 "runs" of random samples to reduce the chance of unusual results—that is, taking input data from the extremes of the 95% CIs. The 95% CI of the mean/average (or any other result) indicates what the variability of the results could be if the study was performed a large number of times. The 95% CI of the mean/average from Monte Carlo analysis may not be closely aligned with the directly obtained minima/maxima results. The 95% CI may lie within or beyond the minimum/maximum. This is

Appendix 2: Energy Required to Wash and Sterilize Reusable Equipment

Reusable Items	General Anesthesia		Spinal		General Anesthesia + Spinal	
	Mass, kg	Energy, Kilowatt-Hour/ Megajoule	Mass, kg	Energy, Kilowatt-Hour/ Megajoule	Mass, kg	Energy, Kilowatt-Hour/ Megajoule
Plastics washed* (drug trays)	0.18 kg	0.08 kilowatt-hours + 0.2 megajoules	0.18	0.08 kilowatt-hours + 0.2 megajoules	0.18	0.08 kilowatt-hours + 0.2 megajoules
Anesthetic circuits washed weekly†		0.1		0		0.1
Items washed* and sterilized‡ (laryngeal mask, spinal tray, cotton hand towel, polypropylene surgical gown). No sterilization of items required for general anesthesia (drug trays and circuits).	0.014 kg	< 0.1 kilowatt-hours + 0.2 megajoules	1.59	0.6 kilowatt-hours + 1.8 megajoules + 2.8 kilowatt-hours = 3.4 kilowatt-hours + 1.8 megajoules	1.36	0.6 kilowatt-hours + 1.8 megajoules + 2.2 kilowatt-hours = 2.8 kilowatt-hours + 1.8 megajoules
Silicone washed* (face mask)	0.08 kg	0.05 kilowatt-hours + 0.1 megajoules	0	0.05 kilowatt-hours + 0.1 megajoules	0.08	0.05 kilowatt-hours + 0.2 megajoules
Stainless steel washed* and sterilized‡ (laryngoscope blade)	0.09 kg	< 0.1 kilowatt-hours + 0.2 megajoules + 0.2 kilowatt-hours = 0.3 kilowatt-hours	0	0	0.01	< 0.1 kilowatt-hours + 0.2 megajoules

*Data for electricity (kilowatt-hour) for washing/drying obtained from previous study by McGain *et al.*[43] Washer and dryer electricity was 5.7 kilowatt-hours and hot water from gas boiler 18 megajoules for a full load of 80 trays. Energy was kept separate for kilowatt-hour electricity and megajoule gas due to the differing carbon dioxide equivalent emissions per unit of energy. †Anesthetic circuits were washed weekly (single-use filters for all patients). Since approximately 25 operations per week were undertaken and six complete circuits could be washed in one load, the energy use per circuit per operation is approximately 10.7/(6 × 2 5) = 0.1 kilowatt-hours (*i.e.*, kilowatt-hour + megajoule, but shown as kilowatt-hour only as it was a minor contributor to carbon dioxide equivalent emissions). ‡Data for electricity (kilowatt-hour) for sterilization obtained from previous study by McGain *et al.*[44] Sterilization electricity use = 1.9 kilowatt-hours/kg items sterilized (including standby energy and so forth) For example, plastics washed and sterilized (reusable laryngeal mask, spinal tray, polypropylene surgical gown = 1.45 kg) will be equivalent to approximately 10 trays in the washer, and then add 1.9 kilowatt-hours/kg for sterilization. Sterilization was purely electric.

Appendix 3: Pharmaceutical Masses Used per Patient

Pharmaceuticals	General Anesthesia		Spinal Anesthesia		Combined General Anesthesia + Spinal	
	Average (mg/case)	Range (mg/case)	Average (mg/case)	Range (mg/case)	Average (mg/case)	Range (g/case)
Alfentanil	0.3	0–1	0	0	0	0
Atracurium	15	0–50	0	0	0	0
Atropine	0.12	0–1.2	0	0	0.12	0–1.2
Bupivacaine (heavy)	0	0	40	0–50	30	0–50
Bupivacaine (light)	0	0	20	0–100	45	0–100
Cefazolin*	1,800	0–2,000	2,000	0	2,000	0
Clindamycin	60	0–600	0	0	0	0
Dexamethasone	2.4	0–4	0	0	0.8	0–4
Droperidol	1	0–2.5	0.25	0–2.5	1	0–2.5
Ephedrine	25	0	2.5	0–25	11.0	0–50
Fentanyl	0.2	0–0.5	0.1	0–0.2	0.1	0–0.2
Glycopyrrolate	0.2	0.2–0.4	0	0	0.1	0–0.6
Hydralazine	2	0–20	0	0	0	0
Lignocaine	20	0–50	55	50	50	50
Metaraminol	1	0–10	3.5	0–10	5	0–10
Midazolam	1	0–5	3.5	0–5	2	0–5
Morphine	5.5	0–10	0	0	2.2	0–10
Neostigmine	1.3	0–2.5	0	0	0.3	0–2.5
Ondansetron	1.2	0–4	0	0	0.4	0–4
Paracetamol*	200	0–1,000	200	0–1,000	100	0–1,000
Parecoxib	20	0–40	0	0	20	0–20
Propofol*	300	200–1,000	610	200–1,100	600	200–1,400
Rocuronium	10	0–50	0	0	5	0–50
Ropivacaine	55	0–400	0	0	0	0
Tramadol	70	0–200	0	0	0	0
Tranexamic acid*	1,500	0	1,400	1,000–1,500	1,500	0
Vecuronium	2	0–10	0	0	1	0–10

Once a pharmaceutical was opened, it was assumed entirely used for that patient, even if some/most was discarded rather than actually given to the patient. Average masses were calculated over all the cases for each of the three groups, so if 1,000 mg of drug was given to two patients in a group (*e.g.*, paracetamol), the average mass across 10 patients would be 200 mg.

*Cefazolin, paracetamol, propofol, and tranexamic acid formed the largest masses of pharmaceuticals given. This was important because the carbon dioxide equivalent emissions for drugs were weight-based. From the Parvatker *et al.*[31] study, the average gram carbon dioxide equivalent/gram drug across the 20 drugs was 340 g carbon dioxide equivalent/g drug. Since Parvatker *et al.*[31] had not studied cefazolin, paracetamol, and tranexamic acid, we used this average 340 g carbon dioxide equivalent/g drug to calculate the actual carbon dioxide equivalent emissions for each drug.

because the 95% CI is reflective of the mean only; it is not immediately relevant to the other directly obtained results such as the minimum/maximum (range).

Modeling and the Final Results

As noted in the Materials and Methods section, we used two life cycle inventories (Ecoinvent[46] and the Australian Life Cycle Inventory[47]) to obtain carbon dioxide equivalent emissions associated with devices and processes. For all processes involving local electricity consumption (kilowatt-hours), we have used the Australian inventory.[47] This is particularly relevant to electricity for patient warming, anesthetic scavenging, cleaning/sterilizing, liquid oxygen compression, and waste management. Importantly, Australian[47] carbon dioxide equivalent emissions per kilowatt-hour are considerably higher than the European average due to coal-fired electricity sources of electricity in Australia.[46] For all devices (*e.g.*, manufacture of plastic endotracheal tubes), we used the Ecoinvent[46] inventory to obtain the associated carbon dioxide equivalent emissions. Because most common products (*e.g.*, plastics, steel, cotton) are traded on the international market, their origin can be varied and multiple, and it can be difficult to trace the precise origins of their makeup. Ecoinvent thus uses a "rest of the world" approach, averaging the associated carbon dioxide equivalent emissions. For example, if we know the carbon dioxide equivalent emissions/kilogram plastic polypropylene manufacture for 30 countries, we use the average carbon dioxide equivalent emissions per kilogram for that process.

Data were modeled in SimaPro-9 LCA (life cycle assessment) software (PRé Consultants). We developed an inventory that quantified materials and energy used, and modeled this using the Ecoinvent[46] (version 3.5) and Australian Life Cycle Inventory[47] databases. We used the International Reference Life Cycle Data System 2016 (European Commission) impact assessment method to translate the inventory into environmental impact scores, along with Monte Carlo software algorithms (SimaPro) to obtain results and 95% CIs. We divided our data on environmental impacts by an average Australian person's total daily environmental effects in order to compare the environmental impacts with peoples' routine activities.[14] To ascertain a global perspective, we modeled our results (carbon dioxide equivalent emissions) with Ecoinvent electricity data[46] with those for identical anesthetics being provided in China, the European Union, and the United States. Note that the aforementioned rest of the world average approach across at least 30 countries means that the carbon dioxide equivalent emissions arising from other items such as plastics manufacture will not vary between countries. Only variations in the carbon intensity of electricity generation will lead to inter-country variability in carbon dioxide equivalent emissions.

It is routine to provide 95% CIs in life cycle assessment around the summated data, but atypical to do so for all further modeled data. For example, figure 4 gives the carbon dioxide equivalent emissions for different countries for general, spinal, and combination anesthesia. There are 12 bars in this figure, so any 95% CI analysis would be prolonged. There are reasons though why such effort would be quite superficial. By definition, the same items/processes are being used in Australia and China/Europe/the United States (*e.g.*, electricity for multiple processes, single-use plastics, pharmaceuticals). Only the carbon dioxide equivalent emissions per kilowatt-hour or kilogram plastic will vary. The uncertainty associated with the carbon dioxide equivalent emissions for each of these common items/processes is thus proportional. For example, if 1 kg of carbon dioxide equivalent emissions is produced by 1 kilowatt-hour of electricity in Australia, but only 0.5 kg of carbon dioxide equivalent emissions in the United States, the 95% CI is approximately (not precisely, but near enough) half that in the United States compared with Australia. If a process is highly uncertain in Australia, then it will be highly uncertain elsewhere, just relatively so (according to the associated carbon dioxide equivalent emissions). The same model is being used to determine the carbon dioxide equivalent emissions and the uncertainty.

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ANESTHESIOLOGY

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

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- There are controversies about the value of processed electroencephalogram (*e.g.*, Bispectral Index [BIS]) guided anesthetic management for the prevention of postoperative delirium
- It is unclear whether reducing depth of anesthesia by the use of sedation with regional anesthesia decreases the risk of postoperative delirium compared to the use of general anesthesia

What This Article Tells Us That Is New

- This prospective single-center trial randomized patients undergoing spine surgery to spinal anesthesia with targeted sedation to BIS greater than 60 to 70 *versus* general anesthesia without BIS guidance
- There was no difference in the incidence of postoperative delirium between randomized groups in the trial
- Future studies are needed to determine whether these findings can be replicated at other centers and whether the results differ by cognitive status

ABSTRACT

Background: Reducing depth of anesthesia and anesthetic exposure may help prevent delirium, but trials have been conflicting. Most studies were conducted under general anesthesia or in cognitively impaired patients. It is unclear whether reducing depth of anesthesia beyond levels consistent with general anesthesia reduces delirium in cognitively intact patients. The authors' objective was to determine whether a bundled approach to reduce anesthetic agent exposure as determined by Bispectral Index (BIS) values (spinal anesthesia with targeted sedation based on BIS values) compared with general anesthesia (masked BIS) reduces delirium.

Methods: Important eligibility criteria for this parallel-arm randomized trial were patients 65 yr or greater undergoing lumbar spine fusion. The intervention group received spinal anesthesia with targeted sedation to BIS greater than 60 to 70. The control group received general anesthesia (masked BIS). The primary outcome was delirium using the Confusion Assessment Method daily through postoperative day 3, with blinded assessment.

Results: The median age of 217 patients in the analysis was 72 (interquartile range, 69 to 77). The median BIS value in the spinal anesthesia with targeted sedation based on BIS values group was 62 (interquartile range, 53 to 70) and in the general anesthesia with masked BIS values group was 45 (interquartile range, 41 to 50; $P < 0.001$). Incident delirium was not different in the spinal anesthesia with targeted sedation based on BIS values group (25.2% [28 of 111] *vs.* the general anesthesia with masked BIS values group (18.9% [20 of 106]; $P = 0.259$; relative risk, 1.22 [95% CI, 0.85 to 1.76]). In prespecified subgroup analyses, the effect of anesthetic strategy differed according to the Mini-Mental State Examination, but not the Charlson Comorbidity Index or age. Two strokes occurred among patients receiving spinal anesthesia and one death among patients receiving general anesthesia.

Conclusions: Spinal anesthesia with targeted sedation based on BIS values compared with general anesthesia with masked BIS values did not reduce delirium after lumbar fusion.

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Postoperative delirium is common in older adults after surgery, with estimates of 10 to 50% depending on the type of surgery.[1–3] Although previously thought to be transient with few long-term effects, it is now recognized that postoperative delirium is associated with important sequelae, including increased duration of hospitalization,[4,5] decreased functional status,[6,7] and cognitive decline.[8,9] Despite its significance, there are few effective treatment strategies, and so prevention of delirium is paramount.[3]

In the intensive care unit, reducing the level of sedation has been associated with less delirium.[10] However, in the operating room, it is unclear whether a parallel strategy to reduce depth of anesthesia and anesthetic exposure is effective, as the results of previous trials have been promising, but conflicting.[11–16] One limitation is that most previous studies were conducted in patients undergoing general anesthesia with the goal of limiting excessive depth of anesthesia and anesthetic exposure,[11–14] and the effectiveness of strategies

to avoid general anesthesia and target lighter sedation has not been well studied. Although two additional trials did examine the benefits of lighter sedation during hip fracture surgery under spinal anesthesia, the results may not be generalizable to most older adults undergoing surgery, since a substantial number of patients were cognitively impaired.[15,16]

Thus, there is a clear need to establish whether reducing depth of anesthesia and anesthetic exposure (beyond levels consistent with general anesthesia) can reduce delirium after surgery in a representative population of older adults. This question is highly applicable since many of the most common surgeries in older adults can be performed using neuraxial/regional approaches.[17] Lumbar spine fusion surgery is one such surgery that is among the top five most frequent surgeries in older adults,[17] with an estimated incidence of postoperative delirium of 10 to 30%.[18–20] Therefore, we conducted a randomized pragmatic trial in older patients undergoing lumbar spine surgery, with the hypothesis that a bundled approach to reduce anesthetic agent exposure as determined by Bispectral Index [BIS] values (spinal anesthesia with targeted light sedation based on BIS values) compared with general anesthesia with masked BIS values would reduce the incidence of postoperative delirium.

Materials and Methods

Study Design

The research protocol was approved by the Mercy Medical Center (Baltimore, Maryland) Institutional Review Board (No. 2015-45). The trial was registered at ClinicalTrials.gov (NCT03133845, Principal Investigator Charles Brown). The initial protocol was released by the investigators to ClinicalTrials.gov on October 23, 2015. Due to quality control issues (in particular, the specificity of some outcomes, most notably post-discharge secondary outcomes that are not reported in this manuscript), the protocol was not formally registered and released to the public until April 2017, so the formal registration was retrospective to the start of the trial. The primary aim and outcome as reported in this manuscript have been unchanged since the initial submission to ClinicalTrials.gov on October 23, 2015. However, the secondary delirium outcomes (delirium severity and number of days of delirium) were not formally added to the trial registration until April 2017, although these outcomes were collected since the start of the trial as part of the study protocol. Other changes in enrollment criteria and sample size calculation are described below. Participants provided written informed consent. The SHaping Anesthetic techniques to Reduce Postoperative delirium (SHARP) study was conducted as a single-center prospective randomized controlled superiority trial with two parallel groups. The protocol was published near the end of the trial to summarize the conduct of the trial and provide the final statistical plan.[21]

Participants

Patients were approached before scheduled surgery by a research coordinator to evaluate eligibility and obtain informed consent. Inclusion criteria were (1) age 65 yr or greater; (2) undergoing lumbar spine fusion; (3) expected surgery duration less than 3 h; (4) under the care of a participating surgeon; and (5) ability to understand and comply with study procedures. Exclusion criteria were (1) contraindications to spinal anesthesia (*e.g.*, severe aortic stenosis, anticoagulant therapy); (2) body mass index greater than 40 kg/m^2; (3) previous L2–L5 full lumbar fusion; (4) communication issues precluding baseline assessments; (5) baseline dementia or Mini-Mental State Examination less than 24; (6) psychiatric disease precluding cooperation with sedation; and (7) surgeon or anesthesiologist preference for either anesthetic approach for any reason due to clinical considerations. Delirium was not formally assessed, although all patients were assessed for capacity to consent. Patients were enrolled between September 2015 to May 2019. Eligibility criteria were expanded after the study began to allow slightly younger patients, a higher body mass index, and longer duration of surgery. The specific criteria that were changed were a decrease in the lower age limit from 70 yr to 65 yr, an increase in the upper limit of body mass index (from 35 kg/m^2 to 40 kg/m^2), and an increase in the upper limit of anticipated surgery duration (from 2 h to 3 h).

Randomization and Assignment of Intervention

A computer-generated simple randomization list with 1:1 allocation was created by a research nurse before the study. For allocation concealment, assignments were placed in sealed opaque envelopes, which were sequentially handed to clinicians after randomization, before entering the operating room.

Intervention and Control

The intervention group received spinal anesthesia with targeted depth of anesthesia based on BIS values. The BIS monitor is approved to monitor depth of anesthesia and displays a unitless number (0 to 100) derived from processed electroencephalogram waveforms. BIS values between 40 and 60 are consistent with general anesthesia.[22] In the

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intervention group, spinal anesthesia was obtained using intrathecal injection of bupivacaine (10 to 15 mg) or lidocaine. Patients received sedation with propofol (25 to 150 mcg · kg^{-1} · min^{-1}), targeted to a BIS greater than 60 to 70. However, the anesthesiologist was instructed to prioritize clinical concerns if depth of sedation needed to be increased.

In the control group, patients received general anesthesia with an endotracheal tube. Anesthesia induction was with propofol (1 to 2 mg/kg) or etomidate, maintenance with a volatile anesthetic, muscle relaxation with a nondepolarizing muscle relaxant, and analgesia with fentanyl (generally 2 to 5 mcg/kg titrated) or hydromorphone and/or morphine. Patients on baseline opioids could receive additional opioids based on clinical criteria. For patients under general anesthesia, the anesthetic provider was masked to BIS values unless there was a clinical need.

Masking

Delirium outcome assessors were masked to the intervention. Postoperative data were abstracted from the electronic medical record by staff masked to the intervention. Patients, surgeons, and anesthesiologists were not masked, because it is impossible for the anesthetic technique to be masked to treating physicians or patients. Statisticians and investigators involved in data analysis were masked.

Perioperative Management

Perioperative care was based on established clinical protocols. Patients could receive intrathecal morphine during spinal anesthesia at the discretion of the anesthesiologist, or by direct intraoperative injection at the discretion of the surgeon. Postoperative analgesia was with fentanyl or hydromorphone patient-controlled analgesia, with transition to oxycodone or other oral opioids as tolerated.

Outcomes and Other Covariates

Delirium was assessed once daily during the first 3 postoperative days in the hospital using the validated Confusion Assessment Method[23] (sensitivity, 94 to 100%; specificity, 90 to 95%). For purposes of missing data, daily in-hospital assessments were not considered missing if the patient was discharged from the hospital on that day and not available for assessment. The Confusion Assessment Method included formal tests of cognition (Mini-Mental State Examination,[24] Calendar Reverse Months, Shortened Digit Span Forward/Reverse, and Delayed Word Recall tests) as well as questions for nurses, clinicians, and family. Patients who refused an assessment and no delirium assessment could be made were considered to not have delirium for that assessment. The primary outcome was incident delirium as defined by any positive assessment during hospitalization. A chart review for delirium was also conducted using validated methods to supplement in-person assessments.[25] Secondary outcomes included delirium duration and severity (Delirium Rating Scale-Revised 98).[26] Covariate information was collected from baseline assessments, patient report, and the medical record. Instrumental activities of daily living were measured at baseline.[27] Number of surgical levels included the range of involved vertebrae.

Sample Size

At the start of the trial, we assumed a delirium incidence of 40% in the control group (general anesthesia with masked BIS values) and a 50% reduction in the intervention group, based on previous studies.[15,18] Further, we assumed a 4 to 6% dropout or crossover. With these assumptions, 190 patients would be needed to show a difference in incidence of delirium at a 0.05 significance level with a power of 0.8. After the first year of data collection, the delirium incidence was noted to be less than predicted, and so the sample size was increased to at least 218, based on a revised assumption of delirium incidence (40% to 35% in the control arm) and similar assumptions regarding 50% reduction in delirium in the intervention group and 4 to 6% dropout.

Statistical Analysis

The primary analysis was based on the intention to treat principle (patients included in the group to which randomized). For the primary outcome, incident delirium, both the absolute difference and relative change were computed. The chi-square test was used to compare proportions with the primary outcome between groups. Secondary outcomes were compared using Wilcoxon rank sum tests. Normally distributed variables are reported using mean ± SD, and nonnormally distributed variables are reported using mean and interquartile range. Adjusted analyses were conducted with multivariable logistic regression to account for potential confounding, first with prespecified adjustment for age, education, and cognitive score[28] and second with adjustment for additional variables associated with delirium in bivariate analyses. As-treated analyses were also conducted (patients included in the group to which they received treatment). Standard diagnostics, including goodness of fit, influence, and collinearity, were examined for all regression models. BIS data were downloaded from the monitor after surgery and were analyzed in several ways, including the mean ± SD and minutes below or above clinically relevant cutoffs (BIS less than 40 and BIS greater than 55), based on the methodology of previous studies.[11,16]

Prespecified subgroup analyses were conducted based on stratification by age (less than 75 *vs.* 75 yr old or greater), Charlson Comorbidity Index (0 *vs.* 1 or greater), and baseline cognition (Mini-Mental State Examination less than 27 *vs.* 27 or greater), with cutoffs chosen based on biologic relevance and/or to have anticipated sufficient number of patients in the subgroups.[16,29,30] *Post hoc*, we examined four subgroups identified based on differences in bivariate analyses. Relative risks were calculated within each subgroup, and 95% CIs were generated using the percentile method *via* a bootstrap procedure (5,000 bootstrap samples). The hypothesis that the intervention would have differential effect based on subgroups was formally tested using a *P* value for interaction, without adjustment for other covariates. SAS v9.4 (USA) was used. Formal interim analyses were to assess

recruitment, safety events, and dropout, but not efficacy, and a Data Safety and Monitoring Board monitored study conduct and safety. There were no prespecified stopping criteria, and enrollment ceased when the target sample size was obtained. In all analyses, $P < 0.05$ was considered significant, and all hypothesis testing was two-tailed.

Results

A patient flow diagram is shown in figure 1. Of 799 patients screened from September 8, 2015, to May 6, 2019, 111 patients were randomized to spinal anesthesia with targeted sedation based on BIS values, and 108 patients were randomized to general anesthesia with masked BIS values. Reasons that patients were not enrolled and randomized are listed in figure 1. Enrollment was stopped upon accrual of enrollment goals. Among patients randomized to spinal anesthesia with targeted sedation based on BIS values, an adequate level of spinal anesthesia could not be obtained in seven patients, and these patients crossed over to receive general anesthesia. Among patients randomized to general anesthesia with masked BIS values, two patients withdrew after randomization, and one patient crossed over to receive spinal anesthesia.

Baseline Patient Characteristics

The median age of patients in this study was 72 yr (interquartile range, 69 to 77), 38% were male, and the median Mini-Mental State Examination score was 29 (interquartile range, 27 to 29). Patients rated their average preoperative pain as a median of 7 (interquartile range, 5 to 8) and their current pain as a median of 3 (interquartile range, 1 to 6). Patient characteristics were generally similar in the two arms of the study (table 1). However, the Charlson Comorbidity Index was slightly higher and there were more patients with a previous myocardial infarction and atrial fibrillation in the spinal anesthesia with targeted sedation based on BIS values group.

Perioperative Characteristics and Separation in BIS Values

Intra- and postoperative characteristics are described in table 2 (intention to treat) and Supplemental Digital Content table 1 (http://links.lww.com/ALN/C700; as treated). Overall, the median length of surgery was 128 min (interquartile range, 106 to 159), the median number of spinal levels was 3 (interquartile range, 2 to 4), and the median estimated blood loss was 300 ml (interquartile range, 200 to 460). In the spinal anesthesia with targeted sedation based on BIS values group, the median dose of bupivacaine was 14 mg (interquartile range, 12.5 to 15), and the maximum propofol infusion rate was a median of 80 mcg · kg^{-1} · min^{-1} (interquartile range, 75 to 100). Among patients who received general anesthesia, desflurane was predominantly utilized. Patients in the general anesthesia with masked BIS values group received more fentanyl and less IV fluids.

The average BIS value in the spinal anesthesia with targeted sedation based on BIS values group was higher than in the general anesthesia with masked BIS values group (median of 62 [interquartile range, 53 to 70] *vs.* 45 [interquartile range, 41 to 50]; $P < 0.001$). The median duration of BIS less than 40 was substantially lower in the spinal anesthesia with targeted sedation based on BIS values group compared to the general anesthesia with masked BIS values group (3 min [interquartile range, 0 to 22] *vs.* 68 min [interquartile range, 22 to 102]; $P < 0.001$).

Effect of the Intervention on Postoperative Delirium and Other Outcomes

The overall incidence of delirium was 22% (48 of 217). Out of 544 opportunities for delirium assessments for nondischarged patients, 509 in-person assessments were completed, and 24 assessments were refused by patients. Two patients refused all assessments. In the intention to treat analysis, there was no significant difference in the incidence of delirium in the spinal anesthesia with targeted sedation based on BIS values group (25.2% [28 of 111]) compared with the general anesthesia with masked BIS values group (18.9% [20 of 106]; $P = 0.259$), absolute difference, 6.4% (95% CI, –4.6 to 17.4%), and relative risk, 1.22 (95% CI, 0.85 to 1.76). When a chart review delirium method was used to supplement the in-person assessments, there was no significant difference in the incidence of delirium in the spinal anesthesia with targeted sedation based on BIS values group (27.9% [31 of 111]) compared with the general anesthesia with masked BIS values group (23.6% [25 of 106]; $P = 0.465$). Similarly, there was no difference by group in the incidence of delirium for each individual postoperative day or in maximum delirium severity score (table 3 [intention to treat]; Supplemental Digital Content table 2, [http://links.lww.com/ALN/C700; as treated]). The incidence of delirium was also not different between groups when adjusted for variables associated with delirium in bivariate analyses (Supplemental Digital Content table 3, http://links.lww.com/ALN/C700).

Duration of recovery in the postanesthesia care unit was similar between the two groups, but pain at postanesthesia care unit discharge was lower in the spinal anesthesia with targeted sedation based on BIS values group compared with the general anesthesia with masked BIS values group (median, 4 [interquartile range, 1 to 5] *vs.* median, 5 [interquartile range, 3 to 7]; $P = 0.004$). There were two strokes in the spinal anesthesia with targeted sedation based on BIS values group, and there was one death in the general anesthesia with masked BIS values group. Other complications by randomization group are listed in table 2 (intention to treat) and Supplemental Digital Content table 1 (http://links.lww.com/ALN/C700; as treated).

Prespecified Subgroup Analyses

There were three prespecified subgroup analyses, based on cutoffs of the Mini-Mental State Examination, the Charlson Comorbidity Index, and age, with forest plot results by the primary intention to treat analysis shown in figure 2. (The forest plot for the as treated analysis, as well as an expanded description of the numbers of events in each subgroup, are shown in Supplemental Digital Content figure 1 and Supplemental Digital Content table 4, respectively, http://

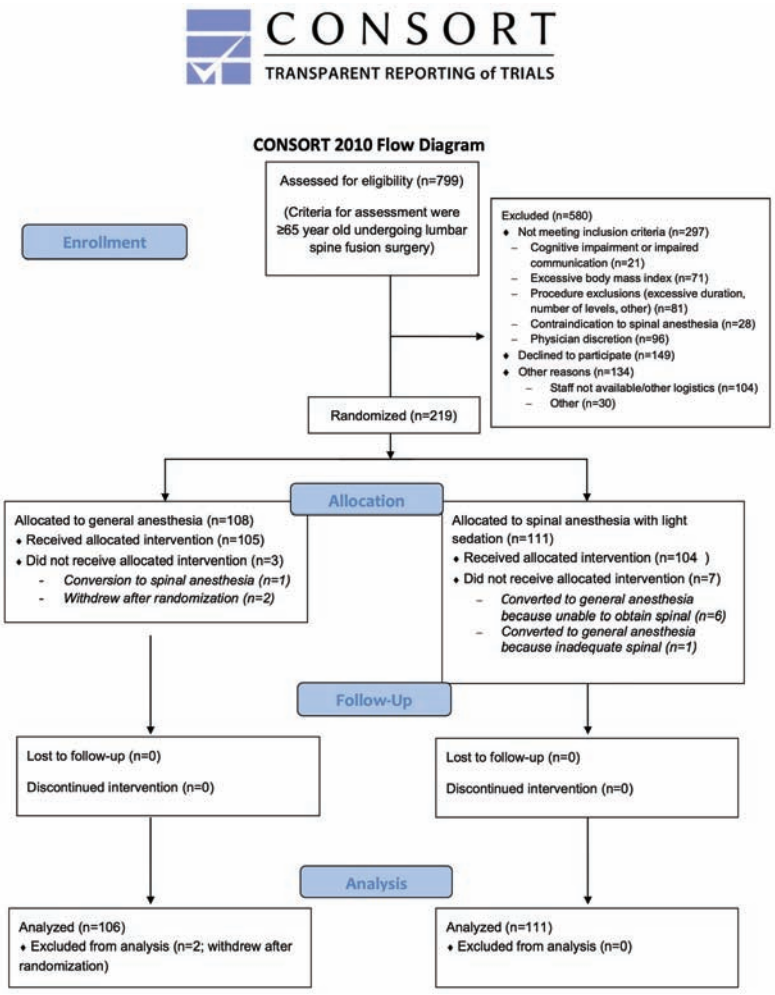

Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) diagram. A patient flow diagram is shown.

links.lww.com/ALN/C700). Baseline Mini-Mental State Examination did moderate the effect of the intervention (P interaction = 0.009). Specifically, for patients with Mini-Mental State Examination less than 27, the incidence of delirium was less in the spinal anesthesia with targeted sedation based on BIS values group compared to the general anesthesia with masked BIS values group (17.7% [3 of 17] *vs.* 43.5% [10 of 23]). On the other hand, for patients with Mini-Mental State Examination 27 or greater, the incidence of delirium was greater in the spinal anesthesia with targeted sedation based on BIS values group *versus* the general anesthesia with masked BIS values group (26.6% [25 of 94] *vs.* 12.1% [10 of 83]). There was no difference in the effect of the intervention (*i.e.*, no interaction) based on the other prespecified subgroups of age strata (less than 75 *vs.* 75 yr old or greater) or Charlson Comorbidity Index (0 *vs.* 1 or greater). Several other subgroup analyses were chosen *post hoc* (sex, education, use of short-acting opioids at baseline, and administration of intrathecal morphine during surgery; fig. 2). Intrathecal morphine did modify the effect of the intervention in the intention to treat analysis (P interaction = 0.029) but not in the as treated analysis (P interaction = 0.088). Specifically, for patients who did not receive intrathecal morphine, the incidence of delirium in the intention to treat analysis was less in the spinal anesthesia with targeted sedation based on BIS values group compared to the general anesthesia with masked BIS values group (8.8% [3 of 34] *vs.* 20.4% [10 of 49]). On the other hand, for patients who did receive intrathecal morphine, the incidence of delirium was greater in the spinal anesthesia with targeted sedation based on BIS values group *versus* the general anesthesia with masked BIS values group (32.5% [25 of 77] *vs.* 17.5% [10 of 57]).

Risk Factors for Delirium

In bivariate analyses, male sex, lower Mini-Mental State Examination score, higher Charlson Comorbidity Index, preoperative short-acting opioid medication, longer surgery, and increased postoperative pain were among the variables associated with delirium (Supplemental Digital

Table 1. Baseline Patient Characteristics

	Total (n = 217)*	General Anesthesia with Masked BIS Values (n = 106)	Spinal Anesthesia with Targeted Sedation Based on BIS Values (n = 111)
Age (yr), median (interquartile range)	72 (69–77)	72 (69–76)	73 (69–78)
Male, n (%)	83 (38.2)	35 (33.0)	48 (43.2)
Race, n (%)			
White	197 (90.8)	93 (87.7)	104 (93.7)
Black	20 (9.2)	13 (12.3)	7 (6.3)
Education college or higher, n (%)	104 (47.9)	49 (46.2)	55 (49.5)
Living arrangement, at home, n (%)	203 (94.4)	95 (91.3)	108 (97.3)
Mini-Mental State Examination,† median (interquartile range)	29 (27–29)	28 (27–29)	29 (27–29)
Instrumental Activities of Daily Living,‡ median (interquartile range)	13 (12–14)	13 (12–14)	13 (12–14)
Comorbidities, n (%)			
Previous stroke	3 (1.4)	2 (1.9)	1 (0.9)
Hypertension	157 (72.4)	74 (69.8)	83 (74.8)
Atrial fibrillation	12 (5.5)	2 (1.9)	10 (9.0)
Congestive heart failure	1 (0.5)	0 (0)	1 (0.9)
Myocardial infarction	20 (9.2)	5 (4.7)	15 (13.5)
Peripheral vascular disease	9 (4.1)	1 (0.9)	8 (7.2)
Chronic obstructive pulmonary disease	22 (10.1)	10 (9.4)	12 (10.8)
Tobacco (previous)	73 (33.6)	33 (31.1)	40 (36)
Diabetes	54 (24.9)	25 (23.6)	29 (26.1)
Chronic kidney disease	38 (17.5)	15 (14.2)	23 (20.7)
ASA Status,§ median (interquartile range)	II (II–III)	II (II–III)	II (II–III)
Charlson Comorbidity Index,‖ median (interquartile range)	1 (0–1)	0 (0–1)	1 (0–1)
Hemoglobin (g/dl), mean ± SD	13.5 ± 1.3	13.6 ± 1.2	13.5 ± 1.4
Baseline medications			
Aspirin, n (%)	21 (9.8)	12 (11.5)	9 (8.1)
β-Blockers, n (%)	56 (26)	21 (20.2)	35 (31.5)
Calcium channel blockers, n (%)	51 (23.7)	22 (21.2)	29 (26.1)
Angiotensin-converting enzyme inhibitors, n (%)	43 (20)	17 (16.3)	26 (23.4)
Angiotensin II-receptor blockers, n (%)	49 (22.8)	26 (25)	23 (20.7)
Statin, n (%)	109 (50.7)	55 (52.9)	54 (48.6)
Selective serotonin reuptake inhibitors or serotonin and norepinephrine reuptake inhibitors, n (%)	39 (18.1)	20 (19.2)	19 (17.1)
Other psychotropic medication, n (%)	23 (10.7)	9 (8.7)	14 (12.6)
Short-acting opioids, n (%)	106 (49.3)	44 (42.3)	62 (55.9)
Current pain,# median (interquartile range)	3 (1–6)	3 (1–7)	3 (0–5)
Average pain,# median (interquartile range)	7 (5–8)	7 (5–8)	8 (5–8)

*All variables were complete (n = 217) except the following: Instrument Activities of Daily Living, ASA score (n = 211), current and average pain (n = 212), living status (n = 203), all baseline medications (n = 215), hemoglobin (n = 216). †Mini-Mental State Examination scores range from 0 to 30, with higher scores indicating better performance. ‡Instrumental Activities of Daily Living scores range from 0 to 14 with higher scores indicating better functional status. §For non–brain dead surgical patients, ASA scores range from I to V with higher scores indicating greater comorbidities. ‖The Charlson Comorbidity Index ranges from 0 to 33, with higher scores indicating greater risk of long-term mortality. #Pain is rated on a scale of 0 to 10, with higher scores indicating more pain.

ASA, American Society of Anesthesiologists; BIS, Bispectral Index.

Content tables 5 and 6, http://links.lww.com/ALN/C700). In adjusted models (Supplemental Digital Content table 3, http://links.lww.com/ALN/C700), only lower Mini-Mental State Examination score remained independently associated with delirium. The administration of intrathecal morphine was also associated with delirium in the adjusted model, but not in the bivariate comparison.

Discussion

The results of this trial demonstrate that spinal anesthesia with targeted sedation based on BIS values compared with general anesthesia with masked BIS values does not reduce the incidence of delirium in lumbar spine surgery patients.

The results of this study add to several studies examining whether titrating depth of anesthesia and anesthetic exposure compared with usual care can reduce delirium. Early trials in general anesthesia patients suggested that a strategy to reduce anesthetic exposure based on BIS values could reduce delirium.[11,12] Based on these and other studies, delirium guidelines have recommended depth of anesthesia monitoring may be considered.[1] However, the recent large trial reported no difference in delirium in patients randomized to a strategy of avoiding excessive anesthetic exposure and burst suppression on the electroencephalogram.[14] Similarly, the results of the current study demonstrate that a bundled approach to reduce anesthetic agent exposure as determined by BIS values does not reduce the

Table 2. Perioperative and Postoperative Characteristics by Randomization Group

	Overall (n = 217)*	General Anesthesia with Masked BIS Values (n = 106)	Spinal Anesthesia with Targeted Sedation Based on BIS Values (n = 111)	*P* Value
Intraoperative				
Duration of surgery (min), median (interquartile range)	128 (106–159)	130 (110–163)	123 (102–154)	0.262
Number of levels, median (interquartile range)	3 (2–4)	3 (2–3)	3 (2–4)	0.425
Anesthetic management				
Spinal anesthesia arm				
Bupivacaine dose (mg), median (interquartile range)	14 (12.5–15)	Not applicable	14 (12.5–15)	Not applicable
Maximum propofol infusion (mcg · kg^{-1} · min^{-1}), median (interquartile range)	80 (75–100)	Not applicable	80 (75–100)	Not applicable
General anesthesia arm				
Desflurane, n (%)	82 (37.8)	77 (72.6)	Not applicable	Not applicable
Intrathecal morphine, n (%)	134 (61.8)	57 (53.8)	77 (69.4)	0.018
Intrathecal morphine (mg), median (interquartile range)	0.2 (0.2–0.2)	0.2 (0.2–0.2)	0.2 (0.2–0.2)	0.019
Fentanyl, n (%)	203 (93.5)	100 (94.3)	103 (92.8)	0.643
Fentanyl (mcg), median (interquartile range)	150 (100–250)	200 (150–250)	100 (100–100)	< 0.001
Hydromorphone, n (%)	43 (19.8)	40 (37.7)	3 (2.7)	< 0.001
Hydromorphone (mg), median (interquartile range)	1.5 (1–2)	1.3 (1–2)	2 (1–2)	0.449
Midazolam, n (%)	69 (31.8)	33 (31.1)	36 (32.4)	0.837
Midazolam (mg), median (interquartile range)	2 (2–2)	2 (2–2)	2 (2–2)	0.554
Phenylephrine, n (%)	50 (23.0)	23 (21.7)	27 (24.3)	0.646
Phenylephrine (mcg), median (interquartile range)	300 (200–650)	300 (50–450)	250 (150–750)	0.611
Ephedrine, n (%)	140 (64.5)	68 (64.2)	72 (64.9)	0.913
Ephedrine (mg), median (interquartile range)	20 (10–33)	25 (13–40)	20 (10–30)	0.055
Fluids administered (ml), median (interquartile range)	2,000 (1,700–2,700)	2,000 (1,400–2,600)	2,050 (1,900–2,950)	0.006
Estimated blood loss (ml), median (interquartile range)	300 (200–460)	300 (200–500)	300 (200–400)	0.648
Packed erythrocyte transfusion, n (%)	4 (1.8)	1 (0.9)	3 (2.7)	0.622
Lowest MAP (mm Hg), median (interquartile range)	59 (52–64)	59 (51–64)	60 (52–64)	0.672
Average BIS, median (interquartile range)	51 (44–63)	45 (41–50)	62 (53–70)	< 0.001
Duration of BIS < 40 (min), median (interquartile range)	22 (1–76)	68 (22–102)	3 (0–22)	< 0.001
Duration of BIS > 55 (min), median (interquartile range)	31 (16–92)	20 (13–30)	87 (34–110)	< 0.001
Duration of PACU (min), median (interquartile range)	119 (75–164)	119 (75–169)	118 (75–160)	0.530
Pain score at PACU discharge, median (interquartile range)	4 (2–6)	5 (3–7)	4 (1–5)	0.004
Postoperative				
ICU admission, n (%)	4 (1.8)	0 (0)	4 (3.6)	0.122
Duration of hospitalization (days), median (interquartile range)	3 (2–3)	3 (2–3)	3 (2–3)	0.087
Maximum pain on postoperative day 1 (0–10), median (interquartile range)	8 (7–10)	8 (7–10)	8 (7–10)	0.413
Complications,† n (%)				
Stroke	2 (0.9)	0 (0)	2 (1.8)	0.498
Atrial fibrillation	1 (0.5)	0 (0)	1 (0.9)	1.000
Congestive heart failure	0 (0)	0 (0)	0 (0)	Not applicable
Myocardial infarction	1 (0.5)	0 (0)	1 (0.9)	1.000
Sepsis	0 (0)	0 (0)	0 (0)	Not applicable
Pneumonia	2 (0.9)	0 (0)	2 (1.8)	0.498
Urinary tract infection	18 (8.3)	9 (8.5)	9 (8.1)	0.919
Pulmonary embolism or deep venous thrombosis	2 (0.9)	1 (0.9)	1 (0.9)	1.000
Acute kidney injury	1 (0.5)	0 (0)	1 (0.9)	1.000
Fall	0 (0)	0 (0)	0 (0)	Not applicable
Reoperation	1 (0.5)	0 (0)	1 (0.9)	1.000
In-hospital death	1 (0.5)	1 (0.9)	0 (0)	0.488

*All variables were complete except bupivacaine and propofol dose in the spinal anesthesia group (n = 101), BIS values (n = 192), and postoperative day 1 pain (n = 216). †Some patients experienced multiple complications, apart from urinary tract infections. One patient in the general anesthesia group had a pulmonary embolism and died. One patient in the spinal anesthesia group had a stroke, myocardial infarction, and pneumonia.

BIS, Bispectral Index; ICU, intensive care unit; MAP, mean arterial pressure; PACU, postanesthesia care unit.

incidence of delirium in older adults undergoing lumbar spine fusion surgery.

An important consideration in interpreting previous studies is that in most trials, all patients received general anesthesia. The pertinent comparisons were general anesthesia *versus* deeper general anesthesia, and the benefits of lighter anesthesia could not be examined. This is an important gap since critical care guidelines recommend that mechanically ventilated patients in the intensive care unit benefit from light sedation,[31] a level of consciousness that is substantially more alert than general anesthesia. Two trials in hip fracture surgery patients under spinal anesthesia examined benefits

Table 3. Effect of the Intervention on Postoperative Delirium

	General Anesthesia with Masked BIS Values (n = 106)	Spinal Anesthesia with Targeted Sedation Based on BIS Values (n = 111)	*P* Value
Any delirium, n (%)*	20 (18.9)	28 (25.2)	0.259
Number of days of delirium, among delirious patients, median (interquartile range)	1 (1–3)	1 (1–2)	0.224
Delirium by postoperative day*			
Day 1, n (%)	7 (6.6)	15 (13.5)	0.092
Day 2, n (%)	15 (14.2)	22 (19.8)	0.267
Day 3, n (%)	11 (10.4)	14 (12.6)	0.606
Maximum delirium severity score as measured by Delirium Rating Scale–Revised-98,† median (interquartile range)*	4 (3–6)	5 (3–8)	0.276
Maximum delirium severity score as measured by Delirium Rating Scale–Revised-98 by postoperative day*			
Day 1, median (interquartile range)	3 (2–6)	4 (3–7)	0.088
Day 2, median (interquartile range)	3 (1.5–5)	3 (2–6)	0.354
Day 3, median (interquartile range)	3 (1–5)	3 (1–6)	0.960

*Out of 544 opportunities for delirium assessments for nondischarged patients at assessment, 509 in-person assessments were completed, and 24 assessments were refused by patients. A total of 215 patients had a postoperative assessment with the Confusion Assessment Method and Delirium Rating Scale-Revised-98 (two patients refused all assessments and were considered to not have delirium). For each postoperative day, the number of patients with a Confusion Assessment Method and Delirium Rating Scale-Revised-98 evaluation among the number of nondischarged patients at assessment was 199/217 (postoperative day 1), 190/198 (postoperative day 2), and 120/129 (postoperative day 3).

†Delirium Rating Scale–Revised-98 severity scores range from 0 to 39, with higher scores indicating greater severity of delirium.

of intraoperative "light" sedation.[15,16] However, the results of these two studies were conflicting, and moreover, the elderly, frail, and cognitively impaired populations may not be generalizable to most older adults undergoing surgery. Thus, there has been a clear need to determine whether reducing depth of anesthesia beyond general anesthesia could reduce delirium in a generalizable population of older adults. This question is highly relevant since many surgeries can be performed with neuraxial or regional approaches. The SHARP study addressed this question in a pragmatic manner and demonstrated no delirium reduction in patients treated with spinal anesthesia with targeted sedation based on BIS values compared with general anesthesia with masked BIS values.

One of three preplanned subgroup analyses showed different effects of the intervention according to baseline cognition. Specifically, for patients with Mini-Mental State

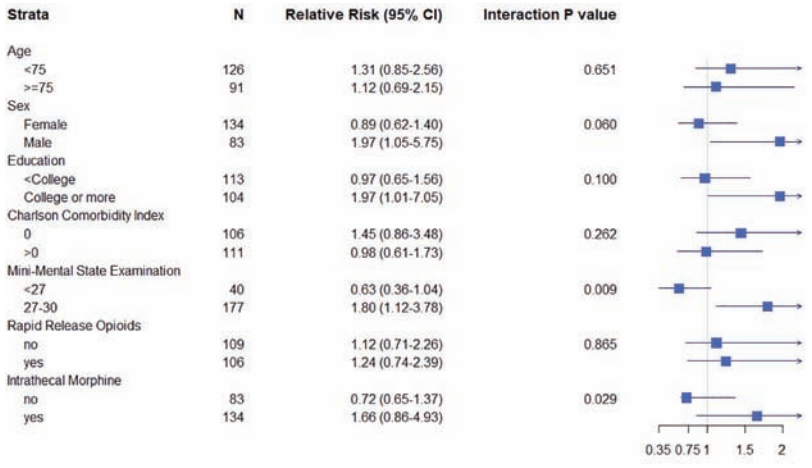

Fig. 2. Subgroup analyses of the primary outcome of incident delirium. Subgroup analyses based on intention to treat analyses with the primary outcome of incident delirium. Prespecified subgroup analyses were conducted based on stratification by age, Charlson Comorbidity Index, and baseline cognition. *Post hoc*, four subgroups were identified based on differences in bivariate analyses. The effect of anesthetic approach (relative risk [95% CI]) is presented separately in each subgroup to define the effect of the intervention in that particular subgroup. The interaction term is a test of significance for whether the effect of anesthetic approach is statistically different between subgroups. Rapid release opioids refer to baseline opioids. Relative risk less than 1 favors spinal anesthesia with targeted sedation based on Bispectral Index values. Relative risk greater than 1 favors general anesthesia with masked Bispectral Index values.

Examination less than 27, there was less delirium in the spinal anesthesia with targeted sedation based on BIS values group, while for patients with Mini-Mental State Examination 27 or greater, there was less delirium in the general anesthesia with masked BIS values group. The results of this subgroup analysis are qualitatively similar to a subgroup analysis reported in a trial of depth of sedation in hip fracture surgery patients.[16] In this trial in which the median Mini-Mental State Examination score was 24, the subgroup of healthy patients with a Charlson Comorbidity Index score of 0 to 1 (but not higher) had less delirium with a light *versus* deep sedation strategy. Thus, in both the hip fracture trial and the current trial, patients who were relatively healthy but with impaired cognition derived benefit from lighter sedation. These results need to be considered hypothesis-generating since they were subgroup analyses. One potential explanation is that cognitively impaired patients are more sensitive to anesthetic depth, perhaps due to underlying neurodegenerative disease.[32–35] On the other hand, it is not entirely clear why cognitively intact patients benefited from general anesthesia with masked BIS values. The overall risk of delirium was less in these patients, as would be expected. Future studies should examine anesthetic strategies to reduce depth of anesthesia in cognitively impaired older adults, although the logistics of enrolling a sufficient number of eligible patients would be challenging. A *post hoc* analysis also showed that the administration of intrathecal morphine was independently associated with delirium and modified the effects of the intervention such that in patients who received intrathecal morphine, there was less delirium in the general anesthesia with masked BIS values group. Previous work has suggested that intrathecal morphine was associated with less postoperative delirium,[36] while in our study, patients who received intrathecal morphine had more delirium, and the finding of this *post hoc* analysis should also be considered exploratory.

In the current study, the strongest and most consistent delirium risk factor was lower Mini-Mental State Examination score. These results are consistent with other studies examining risk factors for delirium[3] and highlight the importance of cognitive testing for risk stratification. Overall, pain and pain treatment were important, with baseline short-acting opioids and maximum postoperative pain being associated with delirium. These results highlight the balance of treating pain while minimizing deliriogenic opioid medication.[3,37]

There are several strengths of this study. The SHARP trial used a unique study design to compare spinal anesthesia with targeted sedation based on BIS values *versus* general anesthesia with masked BIS values in cognitively intact older adults. The intervention was pragmatic, conducted at a community-based hospital, and achieved a separation in BIS values. The research group is experienced in assessing postoperative delirium. Although the study sample was older adults undergoing spine surgery, results are likely generalizable to a number of surgeries for which general or neuraxial/regional anesthesia is appropriate.

There are several limitations. The intervention was bundled, and it is unclear which aspect (light sedation, spinal anesthesia, or propofol) was most responsible for the subgroup effect. The doses of propofol that were used were relatively high, the sedation protocol was pragmatic, and a formal observer assessment of sedation was not used. Thus, a number of patients in the spinal anesthesia with targeted sedation based on BIS values group had BIS values below the target of 60 to 70, and this may have biased the results toward the null. Additionally, BIS may not be an accurate measure of depth of anesthesia in older adults. However, the majority of patients had BIS values that exceeded the upper limit of 55 that has been advocated to prevent awareness during general anesthesia.[38,39] The bundled approach also did not permit the use of other sedative agents, such as dexmedetomidine, and future studies are needed to examine potentially beneficial effects of dexmedetomidine in this population. The study was powered for a large effect size, based on a previous study,[15] and we revised the estimate of delirium incidence due to a lower incidence than originally expected. However, the overall incidence of delirium was still below the expected incidence in the power calculation, and so the study was underpowered. Nevertheless, given the observed effect, it is unlikely that a larger study would demonstrate a benefit in the intervention group. We assessed delirium only once daily, and some cases may have been missed. Thus, imprecision of the outcome assessment and/or misclassification may have biased the results. Patients in the spinal anesthesia with targeted sedation based on BIS values had more cardiac and vascular disease at baseline, although the baseline Mini-Mental State Examination was slightly higher than the general anesthesia with masked BIS values group. Perioperative management aside from the intervention was based on established protocols, and this introduced heterogeneity into the study. There was crossover between study arms in eight patients, largely due to obtaining adequate spinal anesthesia in patients with degenerative spine disease, and this is a source of bias. However, results were similar in intention to treat and as treated analyses. The Mini-Mental State Examination is a general screen of cognition and is limited by ceiling effect and educational biases.[40] Further, the distinction between a Mini-Mental State Examination score above and less than 27 may not be clinically meaningful, and so the results of the subgroup analyses should be considered hypothesis-generating. Finally, the trial was not formally registered in ClinicalTrials.gov until 2017 due to quality control issues, although the initial protocol with the aim and primary outcome of this manuscript was submitted in October 2015.

In conclusion, the results of the SHARP study demonstrate that spinal anesthesia with targeted sedation based on BIS values does not reduce delirium in older adults undergoing lumbar spine surgery. Further studies are needed to examine optimal anesthetic strategies in cognitively impaired patients, who are at high risk for delirium.

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Competing Interests

Dr. Brown has consulted for and received grant funding from Medtronic Inc. (Minneapolis, Minnesota). Dr. Neufeld has received grant funding from Hitachi Inc. (Tokyo, Japan) and consulted for Merck Inc. (Kenilworth, New Jersey). Dr. Hogue has received payment for advisory board membership from Medtronic Inc. and Edwards Lifesciences (Irvine, California). He serves on a data safety monitoring committee for Merck Inc. Dr. Cha has consulted for Avania LLC (Marlborough, Massachusetts) and MC3 Corp (Dexter, Michigan). The other authors declare no competing interests.

Reproducible Science

Full protocol available at: cbrownv@jhmi.edu. Raw data may be available with the appropriate institutional agreements at: cbrownv@jhmi.edu.

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Dr. Alan Van Poznak Slides the Musical into the Medical Syringe!

Gentleman, scholar, and lifelong Cornellian, Alan Van Poznak, M.D. (hugging Dr. Kathryn McGoldrick, *upper left*), famously developed methoxyflurane in the 1960s with longtime colleague Joseph Artusio, M.D. Proving his inventive mind was not limited to the lab bench, he combined pieces from two precisely cut syringes and created a musical masterpiece—the syringe slide whistle (*right)*! Once again, fortune favored the prepared mind. Apprenticed to a pipe-organ builder in his teens, Dr. Van Poznak was able to recognize the instrumental potential in the cylindrical syringe. While serenading pediatric patients at the New York Hospital, he taught anesthesia residents both Bernoulli and Venturi principles just before closing lectures with Cornell's school song (*bottom*). To learn how this little whistle sang its way into the hearts of the Big Apple Circus and Late Night TV hosts, watch the full interview of Dr. Van Poznak by former student Kathryn McGoldrick, M.D. (hugging Dr. Van Poznak, *upper left*), in the Wood Library-Museum's John W. Pender Collection of the Living History of Anesthesia (https://www.woodlibrarymuseum.org/library/living-history).

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ANESTHESIOLOGY

Pressure Support *versus* Spontaneous Ventilation during Anesthetic Emergence—Effect on Postoperative Atelectasis: A Randomized Controlled Trial

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Pressure support ventilation modalities are now standard on newer anesthesia machines and are commonly used during emergence from anesthesia
- Their benefits in preventing postoperative atelectasis have not been well studied

What This Article Tells Us That Is New

- A randomized trial in patients undergoing laparoscopic colectomy or robot-assisted prostatectomy compared pressure support ventilation to spontaneous ventilation with intermittent manual assistance during anesthetic emergence
- The outcome was atelectasis in the postanesthesia recovery unit, using lung ultrasound
- The incidence of atelectasis was significantly lower and the Pa_{O_2} was significantly higher with pressure support ventilation; however, in the 48-h postoperative observation period, the incidence of oxygen saturation measured by pulse oximetry less than 92% was not different between groups

ABSTRACT

Background: Despite previous reports suggesting that pressure support ventilation facilitates weaning from mechanical ventilation in the intensive care unit, few studies have assessed its effects on recovery from anesthesia. The authors hypothesized that pressure support ventilation during emergence from anesthesia reduces postoperative atelectasis in patients undergoing laparoscopic surgery using the Trendelenburg position.

Methods: In this randomized controlled double-blinded trial, adult patients undergoing laparoscopic colectomy or robot-assisted prostatectomy were assigned to either the pressure support (n = 50) or the control group (n = 50). During emergence (from the end of surgery to extubation), pressure support ventilation was used in the pressure support group *versus* intermittent manual assistance in the control group. The primary outcome was the incidence of atelectasis diagnosed by lung ultrasonography at the postanesthesia care unit (PACU). The secondary outcomes were Pa_{O_2} at PACU and oxygen saturation measured by pulse oximetry less than 92% during 48 h postoperatively.

Results: Ninety-seven patients were included in the analysis. The duration of emergence was 9 min and 8 min in the pressure support and control groups, respectively. The incidence of atelectasis at PACU was lower in the pressure support group compared to that in the control group (pressure support *vs.* control, 16 of 48 [33%] *vs.* 28 of 49 [57%]; risk ratio, 0.58; 95% CI, 0.35 to 0.91; $P = 0.024$). In the PACU, Pa_{O_2} in the pressure support group was higher than that in the control group (92 ± 26 mmHg *vs.* 83 ± 13 mmHg; $P = 0.034$). The incidence of oxygen saturation measured by pulse oximetry less than 92% during 48 h postoperatively was not different between the groups (9 of 48 [19%] *vs.* 11 of 49 [22%]; $P = 0.653$). There were no adverse events related to the study protocol.

Conclusions: The incidence of postoperative atelectasis was lower in patients undergoing either laparoscopic colectomy or robot-assisted prostatectomy who received pressure support ventilation during emergence from general anesthesia compared to those receiving intermittent manual assistance.

(ANESTHESIOLOGY 2021; 135:1004–14)

Although there have been many studies regarding ventilatory techniques to reduce postoperative pulmonary complications,[1–4] only a few studies have focused on the period of recovery from anesthesia. The benefits obtained from the protective ventilation techniques may be lost during this emergence process. Whalen *et al.*[5] found that recruitment maneuver and the application of positive end-expiratory pressure (PEEP) improved intraoperative oxygenation, but the effect dissipated promptly after extubation. Many studies have observed the development of

This article is featured in "This Month in Anesthesiology," page A1. This article is accompanied by an editorial on p. 943. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). This article has a visual abstract available in the online version.

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atelectasis during the emergence period.[6,7] Furthermore, it is estimated that the emergence period contributes to approximately 39% of the total amount of postoperative atelectasis.[7]

Currently, we allow patients to breathe spontaneously and assist their respiration intermittently during the transition from controlled ventilation to spontaneous respiration while assessing whether the patients have enough power to breathe without assistance. However, patients who are spontaneously breathing remain under the influence of residual anesthetic agents and neuromuscular blockers and may not have restored their functional residual capacity,[8,9] subsequently developing atelectasis.[10] In addition, pain-induced respiratory restriction or respiratory muscle fatigue during spontaneous respiration may increase the risk of atelectasis. Postoperative atelectasis is one of the most common pulmonary complications noted in surgical patients,[10,11] and a fair majority of studies have suggested that postoperative atelectasis is harmful. It increases the risk of hypoxemia and forms the pathophysiologic basis for other postoperative pulmonary complications.[12–14] Atelectasis can last for several days after surgery,[15] impairing respiratory function, and ultimately delaying patient discharge.[16,17]

Pressure support ventilation is widely used for weaning from the ventilator in the intensive care unit (ICU) and is recently available in anesthesia machines. Pressure support ventilation applies a fixed amount of pressure the physician selects to the patients throughout each breath to augment their own respiration and is one of the most comfortable ventilation modes for patients. In these aspects, pressure support ventilation during recovery from anesthesia may reduce postoperative atelectasis compared to spontaneous respiration with intermittent manual assistance. To date, few studies have assessed the effect of pressure support ventilation on postoperative atelectasis.

Therefore, we compared the incidence of postoperative atelectasis in patients who received pressure support ventilation with that in patients who received spontaneous respiration with intermittent manual assistance, postlaparoscopic colectomy, or robot-assisted laparoscopic prostatectomy. In recent times, laparoscopic colectomy and robot-assisted laparoscopic prostatectomy have gained wide acceptance for their better or noninferior outcomes and more enhanced recovery compared to open surgery. However, these procedures are associated with a higher risk of postoperative atelectasis due to the high intra-abdominal pressure and Trendelenburg position, which pushes the diaphragm upward and subsequently results in the collapse of the alveoli.[9,18]

We hypothesized that pressure support ventilation reduces the incidence of postoperative atelectasis compared to spontaneous respiration with intermittent manual assistance in patients undergoing laparoscopic colectomy or robot-assisted laparoscopic prostatectomy.

Materials and Methods

Study Design

This was a single-center, randomized, controlled, patient- and evaluator-blinded trial with a two-arm parallel design to assess the possible superiority of pressure support ventilation. The study protocol was approved by the Samsung Medical Center (Seoul, Korea) Institutional Review Board (approval No. SMC 2020-02-117-002; date of approval, April 16, 2020). It was prospectively registered with the Korean Clinical Research Information Service (registration No. KCT0004944; principal investigator, Hyun Joo Ahn; date of registration, April 20, 2020; https://cris.nih.go.kr). Our study was conducted in accordance with the ethical principles of the 1964 Declaration of Helsinki and its later amendments and was performed at Samsung Medical Center. The trial was conducted in accordance with the original protocol. Written informed consent was obtained from all participants.

Participants

Between April 2020 and September 2020, 108 patients scheduled for elective laparoscopic colectomy or robot-assisted laparoscopic prostatectomy were screened for inclusion and contacted by primary investigators a day before the surgery to obtain written informed consent.

The inclusion criteria were age 20 yr or greater and American Society of Anesthesiologists (ASA; Schaumburg, Illinois) Physical Status I to III. The exclusion criteria were a body mass index 30 kg/m^2 or greater, pregnancy, underlying lung disease, moderate or severe obstruction observed on pulmonary function test, previous lung surgery, pneumothorax, pulmonary tuberculosis, pleural effusion, expectation of difficult intubation, and patient's refusal. The dropout criteria included the withdrawal of consent, change of surgical plan to open surgery, intraoperative blood loss greater than 400 ml, or unstable hemodynamics, which is defined as vital signs not maintained within the target range (20% of the baseline values) despite administration of fluid and vasopressors.

Randomization

Randomization was performed using a computer-generated random numbers table with a fixed block size of four and a 1:1 ratio. Allocation was sequentially numbered and sealed in opaque envelopes by the corresponding author. The attending anesthesiologists opened the envelopes 10 min before commencing the emergence procedure.

Blinding Method

This was a randomized, controlled, patient- and evaluator-blinded trial. The patients, surgeons, sonographers, and staff of the postanesthesia care unit (PACU) were blinded to patient

group allocation. Attending anesthesiologists were not blinded to the group allocation. However, they were not aware of the aim of the study. Attending anesthesiologists were not involved in lung ultrasound examination or data analysis.

Anesthesia and Monitoring

A chest x-ray was performed 1 day before operation to exclude preexisting lung pathologies including atelectasis. No patient received sedating premedication. The induction and maintenance of anesthesia were standardized and identical for all patients. After standard monitoring, IV propofol (2.0 to 2.5 mg/kg) and rocuronium (1.0 mg/kg) were administered for induction, and maintenance was achieved using 1.0 to 2.0 minimum alveolar concentration of sevoflurane and IV remifentanil (0.05 to 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Rocuronium was continuously infused at a rate of 0.3 to 0.8 $mg \cdot kg^{-1} \cdot h^{-1}$ under train-of-four monitoring (target train-of-four count, 1/4) and stopped approximately 40 min before the end of surgery. An additional bolus was allowed if necessary.

Preoxygenation was performed for 2 min (O_2 4 l/min) in the supine position. After the loss of spontaneous breathing, the patients were bag mask–ventilated with a fraction of inspired oxygen (F_{IO_2}) of 0.8. Endotracheal intubation was performed 4 min after the start of preoxygenation. After intubation, an arterial catheter was placed in the radial artery for blood gas sampling and invasive blood pressure monitoring.

Mechanical ventilation was maintained using an anesthesia machine (Carestation 650; Datex-Ohmeda, Inc.; USA) in a volume-controlled mode. The ventilatory settings in both groups were F_{IO_2}, 0.4; tidal volume (V_T), 8 ml/kg of predicted body weight; inspiratory to expiratory ratio, 1:2; and PEEP, 5 cm H_2O. The respiratory rate (RR) was set to 12 breaths/min and further adjusted to maintain end-tidal carbon dioxide pressure between 33 and 45 mmHg. The recruitment maneuver was not used.

The patients were placed in the lithotomy with Trendelenburg positioning during surgery (approximately 30 degrees head-down position in both laparoscopic colectomy and robot-assisted laparoscopic prostatectomy). Pneumoperitoneum was established with carbon dioxide, and intra-abdominal pressure in all patients was maintained between 12 and 15 mmHg during abdominal insufflation.

Blood pressure was maintained within 20% of the baseline values. Phenylephrine, ephedrine, or nicardipine was administered as required to maintain mean arterial blood pressure within this range. If the heart rate was less than 40/min, IV atropine 0.5 mg was administered. Lactated Ringer's solution was used as maintenance fluid and infused at a rate of 4 to 6 $ml \cdot kg^{-1} \cdot h^{-1}$. If intraoperative bleeding occurred, crystalloid solution was administered to replace blood loss. IV hydromorphone 0.01 mg/kg and paracetamol 1 g were administered 5 min before the end of surgery, and IV patient-controlled analgesia was applied to all patients (bolus dose, fentanyl 10 μg; basal infusion dose, fentanyl 10 μg/h). In the PACU, patients who complained of moderate pain greater than 4, measured using a numeric rating scale (0 = no pain, 10 = worst pain), received rescue opioids (IV hydromorphone 0.01 mg/kg) until the numeric rating scale was 4 or lower.

Study Protocol

The duration of anesthesia emergence was the duration from the end of surgery to extubation. The designated ventilatory support method was maintained during emergence in both groups. At the end of surgery, sevoflurane was ceased, and the attending anesthesiologist began the recovery protocol; the pressure support group received pressure support ventilation. The initial pressure support ventilation setting was a driving pressure of 5 cm H_2O, PEEP of 5 cm H_2O, and safety backup ventilation of 12 breaths/min (safety backup ventilation setting, V_T, 8 ml/kg of predicted body weight; and PEEP, 5 cm H_2O). The flow trigger and end of breath were set at 2 l/min and 30% of peak flow, respectively. Support amount and safety backup ventilation were adjusted according to the patient's response to meet the target V_T of 7 to 8 ml/kg and RR of 10 to16 breaths/min and decreased gradually as the patient restored his or her own V_T and RR. Ventilatory support was stopped when the patient showed adequate V_T (greater than 6 ml/kg) and RR (10 breaths/min or greater) without ventilatory support. However, PEEP (5 cm H_2O) was maintained until extubation in the pressure support group. In the control group, the emergence process was led by the discretion of the attending anesthesiologist. The basic strategy was to allow the patient to breathe spontaneously and only help respiration if necessary, with intermittent manual assistance. Both groups received fresh gas flow at 4 l/min and F_{IO_2} of 0.4 during emergence from anesthesia. In patients who developed oxygen saturation measured by pulse oximetry (S_{PO_2}) less than 90% after extubation, rescue mask ventilation was applied with F_{IO_2} of 1.0.

A train-of-four of peripheral nerve stimulator was monitored using the ulnar nerve throughout recovery, and neuromuscular blockade was reversed with 0.2 mg/kg pyridostigmine and 0.008 mg/kg glycopyrrolate IV when the train-of-four counts were 3 or greater or sugammadex 2 to 4 mg/kg IV when the train-of-four counts were 2 or less. In both groups, extubation was performed when the patient met the following criteria: obeys commands such as eye-opening or hand-grip, V_T greater than 250 ml, end-tidal carbon dioxide less than 45 mmHg, RR 10 to 20 breaths/min, and a train-of-four ratio greater than 0.9. After extubation, all patients were transferred to the PACU without oxygen supplementation.

Lung Ultrasonography and Scoring System

All patients were evaluated using lung ultrasonography 30 min after their PACU arrival. Lung ultrasonography was

performed using a Vivid S70N (GE Vingmed Ultrasound AS; Norway) with an 11-MHz linear transducer and real-time B-mode. Inspection of each lung was performed at 12 lung sections (each hemithorax was divided into six sections), determined by parasternal, anterior, and posterior axillary lines (vertically) and by nipple and diaphragm lines (horizontally) as landmarks in the supine position, similar to previous studies.[19,20] The 12 lung sections were scanned sequentially from right to left, cranial to caudal, and anterior to posterior. Posterior fields were examined while an assistant held the patient in the 45-degree lateral position. The examination was carried out longitudinally on the acoustic windows of the intercostal spaces, and the ultrasound probe was applied perpendicular to the pleura, with a conventional gel between the transducer and skin. The following signs were assessed: the lung "sliding" sign, A-lines, B-lines, lung pulse, and air bronchograms. Postoperative atelectasis was scored between 0 and 4, according to the degree of de-aeration: score 0: normal lung, or one or two well-spaced vertical lines per intercostal space; score 1: three or more well-spaced vertical lines per intercostal space (B-lines) or juxtapleural consolidation with normal pleural line; score 2: loss of A-line with multiple juxtapleural consolidations and irregular pleural lines; score 3: loss of lung sliding and appearance of lung pulse; score 4: consolidation exceeding 1 cm × 2 cm with or without air bronchogram (fig. 1; Supplemental Digital Content 1, http://links.lww.com/ALN/C690).[21] Vertical lines originating from the consolidation were not scored as 1. Transient loss of A-line by B-lines was not scored as 2. The atelectasis score was calculated by adding up the scores of the 12 sections, and a higher score indicated a more severe loss of aeration. We defined anesthesia-induced atelectasis to be clinically significant if more than three sections (approximately 25% of total lung surface) showed any sign of atelectasis (atelectasis score 1 or greater). Ultrasonography was performed by two anesthesiologists (P. Tanatporn and H. Yeo) with more than 1 yr of experience, and they had performed more than 100 cases. They were blinded to the group assignment. All measurements were conducted during deep spontaneous respiration. All clips were stored and interpreted by the consensus read of the two sonographers.

Arterial Blood Gases and Oxygenation

Arterial blood gas analysis was performed immediately after arrival at the PACU without oxygen supplementation. In both groups, patients were encouraged to breathe deeply without oxygen during the PACU and ward stay. Oxygen *via* nasal prong at 3 l/min was provided to patients when Spo_2 could not be maintained at 92% or greater.

Study Outcomes and Measurements

The primary outcome was the incidence of postoperative atelectasis diagnosed by lung ultrasonography at PACU. The secondary endpoints were Pao_2 at PACU and incidence of Spo_2 less than 92% during 48 h postoperatively.

We recorded the patients who needed supplemental oxygen or mechanical ventilatory support during 48 h postoperatively. The patient's vital signs, temperature, and respiratory symptoms (cough, sputum, and sore throat) were evaluated every 8 h during 48 h postoperatively. Pulmonary complications, adverse cardiac events, postoperative acute kidney injury, delirium until discharge, and postoperative transfusion were also recorded. The definitions of each complication are presented in Supplemental Digital Content 2 (http://links.lww.com/ALN/C691).

Statistical Analysis

The incidence of postoperative atelectasis was assumed to be 53% based on previous studies.[10,22] Our hypothesis was that pressure support ventilation reduces the incidence of postoperative atelectasis by 30%. Thus, we expected an incidence of postoperative atelectasis of 37% in the pressure support group. With a significance level of 0.05 (two-tailed) and a power of 80%, 88 study subjects were required. Considering a dropout rate of 15%, we included 100 patients in this study. Continuous variables are presented as the mean ± SD or median (interquartile range). Categorical variables are described as counts (%). The normal distribution of data was evaluated using the Shapiro–Wilk test. CIs for nonnormally distributed variables were calculated using the Hodges–Lehmann estimator.

The primary outcome (incidence of atelectasis) was analyzed using the chi-square test. The secondary outcomes (Pao_2, event of Spo_2 less than 92%) were evaluated using an independent *t* test and chi-square test. Effect sizes were also evaluated by computing risk ratio with 95% CIs for binary outcomes and calculating Cohen's *d* with pooled SD with 95% CIs for continuous outcomes. As a *post hoc* sensitivity analysis, we used a logistic regression model with a simultaneous entering of age, body mass index, cardiovascular disease, ASA Physical Status, and operation duration. All *P* values were two-sided, and $P < 0.05$ was considered significant. All data were analyzed using MedCalc 14.12.0 (MedCalc Software Ltd., Belgium).

Results

Enrollment ceased when the target sample size was obtained. In total, 108 patients were assessed for eligibility between April 2020 and September 2020. Eight patients were excluded due to their refusal (n = 7) or cancelation of surgery (n = 1). The remaining 100 patients were randomized and received their allocated treatment. However, three patients dropped out. One in the control group dropped out due to a technical problem with the ultrasound machine. Two in the pressure support group dropped out due to postoperative pneumothorax and open conversion. (Postoperative pneumothorax in the pressure

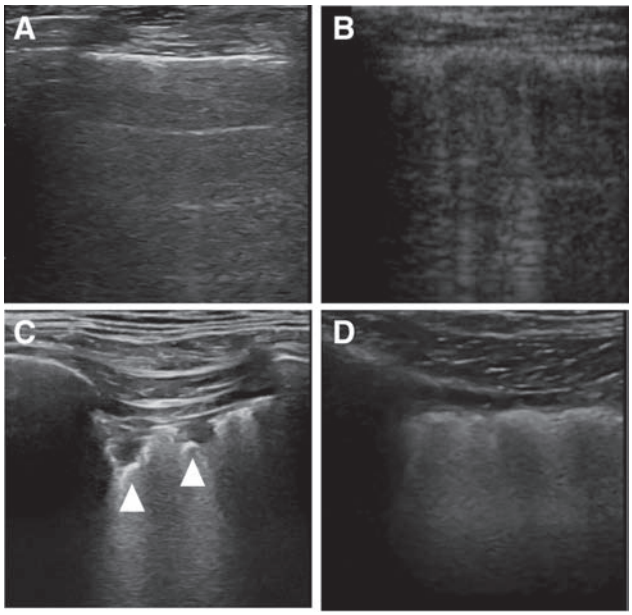

Fig. 1. Lung sonographic signs associated with atelectasis. (*A*) Score 0: normal lung. Pleura is thin and A-lines are apparent. One or two well-spaced lines per intercostal space are allowed. (*B*) Score 1: more than three well-spaced vertical lines per intercostal space (B-lines). (*C*) Score 1: juxtapleural consolidation (*arrows*) with normal pleural line. Juxtapleural consolidation is caused by a loss of lung aeration. It commonly arises from the pleural line. (*D*) Score 2: loss of A-line with multiple juxtapleural consolidations and irregular pleural lines are seen. Score 3 (loss of lung sliding and appearance of lung pulse; Supplemental Digital Content 1, http://links.lww.com/ALN/C690) and score 4 (large consolidation, no occurrence in our study) are not presented here.

support group was developed from peritoneal carbon dioxide insufflation during surgery. The peritoneal gas traveled to the mediastinum and then pleura through the esophageal hiatus. The amount of pleural air was minimal, but the ultrasonographic diagnosis was impaired.) Finally, 49 and 48 patients in the control and pressure support groups, respectively, were analyzed (fig. 2). There were no missing data for these 97 patients for subsequent analyses. There were no adverse events related to study protocol, including immediate postextubation respiratory failure, in both groups.

The baseline characteristics of the participants, operative, and ventilatory data between the two groups are presented in table 1. The mean duration of emergence (from the end of surgery to extubation) was 8 ± 3 min and 9 ± 4 min in the control and pressure support groups, respectively. We defined anesthesia-induced atelectasis to be clinically significant if more than three sections (approximately 25% of total lung surface) showed any sign of atelectasis. Based on this definition, the incidence of postoperative atelectasis diagnosed by lung ultrasonography was 28 of 49 (57%) and 16 of 48 (33%) in the control and pressure support groups, respectively (risk ratio, 0.58; 95% CI, 0.35 to 0.91; $P = 0.024$). The area of atelectasis is shown in figure 3 and Supplemental Digital Content 3 (http://links.lww.com/ALN/C692). Atelectasis was most common in the dependent area in both lungs, and the left lower lobe showed the highest incidence.

Various phenotypes of atelectasis are shown in table 2. The most common atelectasis findings were loss of A-lines with multiple juxtapleural consolidations and irregular pleural lines (score 2, n = 64), followed by multiple B-lines (score 1, n = 51), juxtapleural consolidation with normal pleural line (score 1, n = 19), and loss of sliding and appearance of lung pulse (score 3, n = 2). No patient showed score 4 consolidation. The sum of score was 5 (2 to 8) and 3 (1 to 6) in the control and pressure support groups, respectively (median [interquartile range]; $P = 0.093$).

Spo_2 at extubation was 100 (100 to 100) *vs.* 100 (100 to 100) in the control and pressure support groups, respectively (median [interquartile range]; $P = 0.715$). The duration of PACU stay was 65 (56 to 79) min *vs.* 68 (60 to 75) min in the control and pressure support groups, respectively (median [interquartile range]; $P = 0.318$).

The percentage of patients who showed Spo_2 less than 92% during the PACU stay was 26% and 23% ($P = 0.680$) in the control and pressure support groups, respectively. Pao_2 at PACU was higher in the pressure support group (83 ± 13 mmHg *vs.* 92 ± 26 mmHg; $P = 0.034$).

After transfer to the ward, the incidence of Spo_2 less than 92% during the postoperative 48 h was 22% and 19% in the control and pressure support groups, respectively

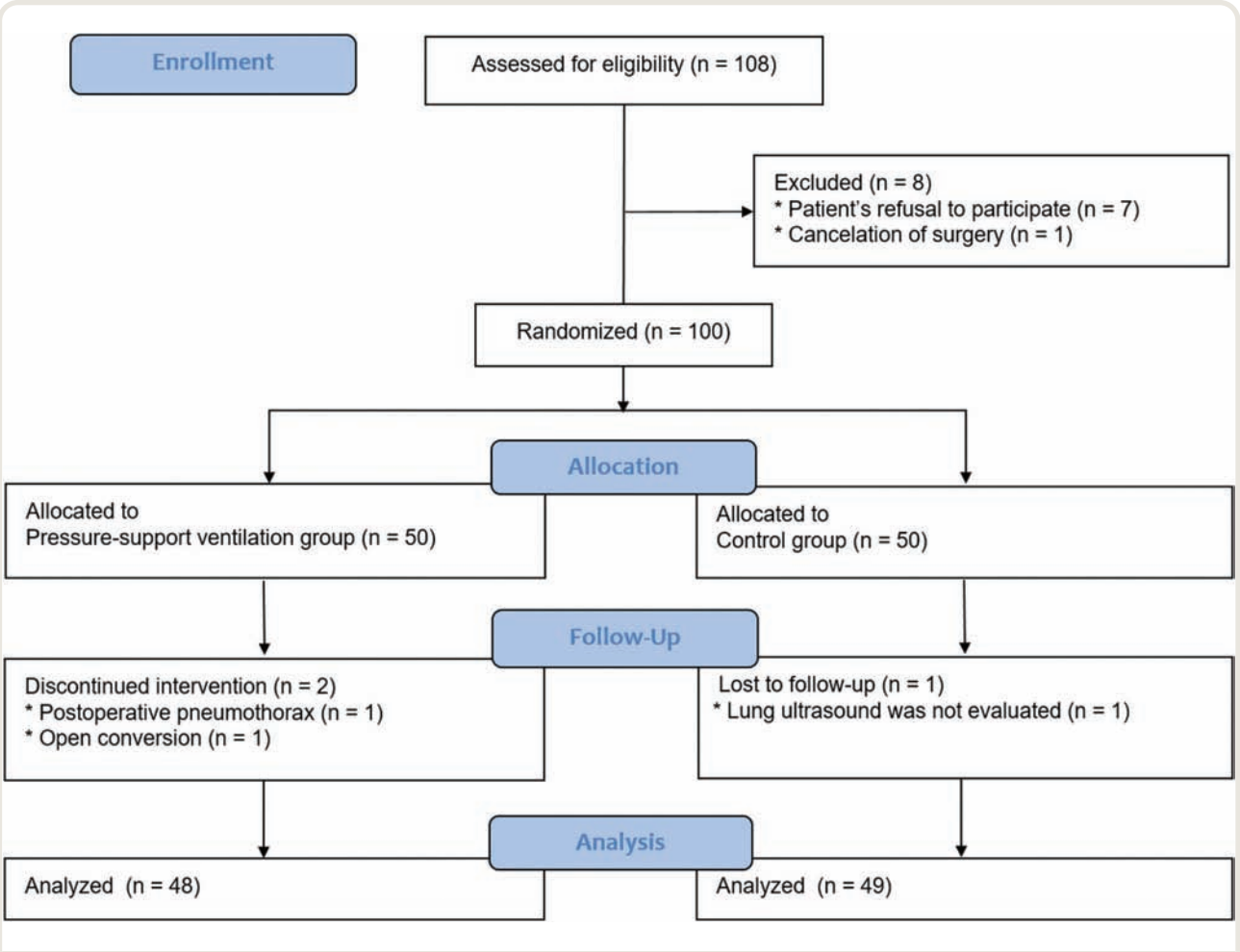

Fig. 2. Consolidated Standards of Reporting Trials flow diagram of the study.

(P = 0.653; table 3). Twenty patients (22% *vs.* 19%, control group *vs.* pressure support group; P = 0.653) received supplemental oxygen therapy to maintain Spo_2 of 92% or greater. However, none received ventilatory support during the postoperative 48 h. Other major postoperative complications did not differ between the groups (Supplemental Digital Content 2, http://links.lww.com/ALN/C691).

The beneficial effect of pressure support ventilation on postoperative atelectasis diagnosed by lung ultrasonography was not changed after *post hoc* sensitivity analysis using variables that may influence postoperative atelectasis (age, body mass index, cardiovascular disease, ASA Physical Status, and operation duration; table 4).

Discussion

In the current study, the pressure support group showed a lower incidence of postoperative atelectasis and higher oxygenation compared to the control group in laparoscopic colectomy and robot-assisted laparoscopic prostatectomy.

Pressure support ventilation is widely utilized in ventilator weaning of patients in the ICU,[23–26] and the latest American Thoracic Society (New York, New York) guideline recommends pressure support ventilation for successful weaning.[27] However, few studies evaluated it as a ventilatory mode of emergence from anesthesia.

Due to the lack of reports in surgical patients, anesthesiologists may be concerned that some patients who breathe comfortably with pressure support ventilation could develop respiratory failure immediately after extubation, or others may argue that we need to watch our patients' spontaneous breathing to predict the patients' physiologic conditions after extubation.[25] Pellegrini *et al.*[28] demonstrated that high continuous positive airway pressure reduced respiratory drive and the contractile activity of the diaphragm in patients in the ICU. In our study, pressure support ventilation was not associated with postextubation hypoxia or extubation failure; rather, it contributed to the lower incidence of postoperative atelectasis and higher oxygenation. Pressure support ventilation reduced the risk

Table 1. Baseline Characteristics, Operative Data, and Ventilatory Data of Participants

Variables	Control (n = 49)	Pressure Support (n = 48)
Age, yr	64 ± 9	62 ± 10
Sex, male	38 (78)	31 (65)
Body mass index, kg/m^2	25 ± 3	24 ± 3
ASA Physical Status ≥ III	5 (10)	4 (8)
Smoking*	2 (4)	2 (4)
Comorbid condition		
Hypertension	23 (47)	17 (35)
Diabetes mellitus	11 (22)	10 (21)
Cardiovascular diseases†	4 (8)	3 (6)
Difficult intubation‡	6 (12)	3 (6)
Duration of surgery, min	157 ± 40	172 ± 54
Type of surgery		
Laparoscopic colectomy	22 (45)	29 (60)
Robot-assisted laparoscopic prostatectomy	27 (55)	19 (40)
Intraoperative fluid infusion, ml/min	4.5 ± 1.2	4.9 ± 2.1
Estimated blood loss, ml	118 ± 92	134 ± 111
Mean arterial pressure, mmHg	85 ± 8	88 ± 12
Heart rate, beats/min	66 ± 11	67 ± 10
Peak airway pressure,§ cm H_2O	25 [23–27]	24 [22–26]
Plateau airway pressure,§ cm H_2O	20 [18–22]	19 [17–21]
Driving pressure,§ cm H_2O	15 [13–17]	14 [12–16]
Tidal volume per predicted body weight,§ ml/kg	6 [6–7]	7 [6–8]
Respiratory rate,§ breaths/min	13 [12–14]	13 [12–14]
Static compliance,§ ml/cm H_2O	29 [25–34]	35 [31–42]
End-tidal carbon dioxide pressure,§ mmHg	36 ± 2	37 ± 2
Intraoperative Pao_2,§ mmHg	255 ± 113	222 ± 98
Use of sugammadex before extubation	22 (45)	16 (33)
Event of Spo_2 < 92% during operation	3 (6)	2 (4)
Duration of emergence, min	8 ± 3	9 ± 4
Opioid consumption during the PACU stay, fentanyl equivalent, μg	20 [0–35]	20 [0–30]

Data are presented as n (%), mean ± SD, or median [interquartile range].

*Smoking included current smokers and ex-smokers within 1 month. †Cardiovascular diseases included angina pectoris and myocardial infarction. ‡Difficult intubation included more than two attempts of intubation with direct laryngoscope or cases were needed video-assisted intubation devices. §Respiratory values were measured during 30-degree Trendelenburg position and abdominal insufflation.

ASA, American Society of Anesthesiologists; PACU, postanesthesia care unit, Spo_2, oxygen saturation measured by pulse oximetry.

of postoperative atelectasis diagnosed by current method ultrasonography regardless of patient's age, body mass index, cardiovascular disease, ASA Physical Status, or operation duration (table 4). There is no evidence that a short duration of pressure support ventilation would have a significant impact on respiratory muscle dysfunction.

The possible mechanisms for how pressure support ventilation shows a lower incidence of postoperative atelectasis are as follows. First, in inspiratory pressure support, driving pressure helps lung expansion during inspiration with reduced work of breathing by as much as 30 to 40%.[25,29,30] Second, PEEP increases the end-expiratory lung volume and counteracts airway closure with a dominant effect in the dependent lung region, which is sufficient to prevent or reverse atelectasis in healthy patients undergoing surgery.[31]

To date, the use of low FIO_2 has been the most commonly suggested technique to decrease atelectasis during recovery from anesthesia.[6,7,32–36] An FIO_2 of 0.3 to 0.4 before extubation resulted in reduced incidence of postoperative atelectasis compared to an FIO_2 of 1.0,[6] and the same was observed in patients with chronic obstructive pulmonary disease (COPD)[35] and obese patients undergoing laparoscopic surgery.[34] However, some studies were unable to show the protective effect of low FIO_2 against atelectasis.[33] In the current study, the incidence of postoperative atelectasis was as high as 57% in laparoscopic surgery, even though low FIO_2 (0.4) was administered. Pressure support ventilation reduced the incidence of atelectasis by 42% in these patients. Our finding suggests that pressure support ventilation is another armamentarium against postoperative atelectasis.

Most of the previous studies which compared ventilatory techniques used computed tomography to diagnose immediate postoperative atelectasis.[6,7,33,37] In most studies, a single-sliced transverse scan was performed approximately 5 mm above the right dome of diaphragm 15 to 60 min postoperatively.[7] The approximate measurement time was similar to that in our study, but a single cut scan may not reflect the lesions in other lung areas. Lung ultrasonography is a fast, simple, noninvasive, and radiation-free technique in which the entire lung area and dynamic changes during respiration can be examined.[38–40] The quantitative association between lung ultrasonography scores of aeration and the volumetric data of atelectasis observed on thoracic computed tomography showed that lung ultrasonography had reliable performance in the diagnosis of postoperative atelectasis, with a sensitivity of 88%, a specificity of 92%, and a diagnostic accuracy of 91%.[41] A recent meta-analysis demonstrated that lung ultrasonography had a higher diagnostic ability compared to chest x-ray film for lung consolidation/collapse (lung ultrasonography: sensitivity of 92% and specificity of 92%; x-ray film: sensitivity of 53% and specificity of 78%).[42]

However, the atelectasis scoring system using ultrasonography has not yet been standardized.[20,21,43,44] Originally, lung ultrasound score was developed for ICU patients to assess the severity of pulmonary disease, including B-lines 3 or greater (score 1), multiple coalescent B-lines (score 2), and consolidation (score 3).[45] Several studies have adopted the same system to assess postoperative atelectasis.[46] B-lines are hyperechoic lines produced by the interaction between alveolar air and interstitial fluid and can be seen in histologically normal lungs which are deflated to a critical level of density (greater than 0.45 g/ml).[43] However, coalescent B-lines, which are common in pulmonary edema and acute respiratory distress syndrome, were not observed in our study, and they were probably not in previous studies either, according to lung ultrasound photos presented.[43,44] We found that B-lines in postoperative atelectasis were mostly pseudo B-lines. They were not long enough to reach 8 to

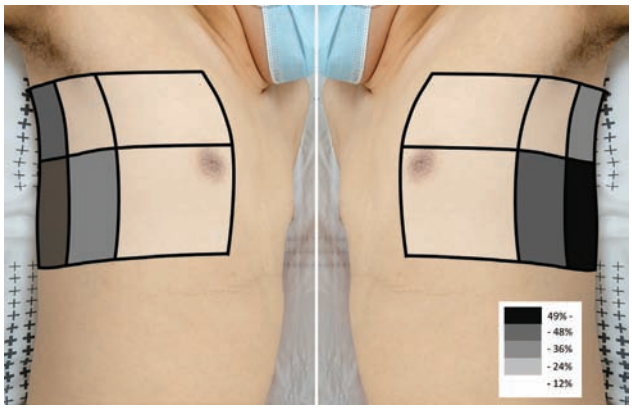

Fig. 3. The regional distribution of atelectasis. *Darker colors* indicate higher incidence. Most atelectasis occurred in the dependent area. The left lower lobe showed the highest incidence.

Table 2. Postoperative Atelectasis Outcomes in the Postanesthesia Care Unit

Variables	Control (n = 49)	Pressure Support (n = 48)	Effect Estimate (95% CI)	*P* Value
Atelectasis diagnosed by lung ultrasonography	28 (57)	16 (33)	0.58 (0.35 to 0.91)*	0.024
Atelectasis score	5 [2 to 8]	3 [1 to 6]	0.35 (–0.06 to 0.72)†	0.093
Major findings of atelectasis				
B-lines ≥ 3	25 (51)	26 (54)	1.06 (0.72 to 1.57)*	0.756
Juxtapleural consolidation with normal pleural line	12 (25)	7 (15)	0.60 (0.24 to 1.35)*	0.228
Loss of A-line with multiple juxtapleural consolidations and irregular pleural lines	35 (71)	29 (60)	0.85 (0.62 to 1.13)*	0.257
Loss of lung sliding and appearance of lung pulse	0 (0)	2 (4)	Not reported‡	0.149
Tissue-like change with or without airbronchogram	0	0		

Data are presented as n (%) or median [interquartile range].

*Effect estimate is risk ratio (two-sided 95% CI) by Wald likelihood ratio approximation test and chi-square hypothesis tests. †Effect estimate is calculated by Cohen's *d* with pooled SD. ‡Not reported because there were no patients in the control group.

Table 3. Secondary and Other Outcomes of Participants

Variables	Control (n = 49)	Pressure Support (n = 48)	*P* Value
Pa_{O_2} measured in the PACU, mmHg	83 ± 13	92 ± 26	0.034
Events of Sp_{O_2} < 92% during the PACU stay	13 (26)	11(23)	0.680
After discharge to ward			
Events of Sp_{O_2} < 92% 48 h postoperatively	11 (22)	9 (19)	0.653
Patients who needed supplemental oxygen 48 h postoperatively	11 (22)	9 (19)	0.653
Patients who needed mechanical ventilation support	0	0	
Fever (≥ 37.5°C) 48 h postoperatively	6 (12)	9 (19)	0.376
Postoperative hospital stay, day	7 [6–8]	7 [6–8]	0.515

Data are presented as mean ± SD, n (%), or median [interquartile range].

PACU, postanesthesia care unit; Sp_{O_2}, oxygen saturation measured by pulse oximetry.

10 cm in length and usually occur below the subpleural consolidation, not below the pleura.[44] Acosta *et al.*,[20] who first examined the capability of lung ultrasound to diagnose postoperative atelectasis, and others[41] also reported findings similar to ours. Therefore, Monastesse *et al.*[21] proposed modified lung ultrasound scores that emphasize subpleural consolidation for postoperative atelectasis. Other researchers combined B-lines (score 0 to 3) and subpleural

Table 4. *Post Hoc* Sensitivity Analysis Using Multiple Logistic Regression

Variable	Odds Ratio	95% CI	*P* Value
Sensitivity analysis using multiple logistic regression model			
Pressure support ventilation	0.381	0.159–0.91	0.030
Age, per yr	1.03	0.98–1.08	0.232
Body mass index ≥ 25 kg/m^2	0.70	0.274–1.79	0.459
Cardiovascular diseases*	2.16	0.171–27.4	0.552
ASA Physical Status ≥ III	1.28	0.132–12.3	0.833
Duration of surgery, per min	1.00	0.99–1.00	0.504

Multiple logistic regression with a simultaneous entering of variables associated with postoperative atelectasis was conducted for *post hoc* sensitivity analysis.

*Cardiovascular diseases included angina pectoris and myocardial infarction.

ASA, American Society of Anesthesiologists.

consolidation (score 0 to 3)[1,19] in the assessment of postoperative atelectasis. Our scoring system is similar to that in the proposal by Monastesse *et al.*,[21] but we replaced "coalescent B-lines" with "loss of A-line with multiple juxtapleural consolidations and irregular pleural lines" (score 2, the most common finding), and added loss of lung sliding and appearance of lung pulse, which indicate noninflating lungs (score 3).[20,44] Of note, A-lines, the reverberation artifacts of the pleura, were lost when the lung parenchyma became inhomogeneous with de-aeration.[44] We did not observe large consolidation (score 4) in anesthesia-induced atelectasis, which is in line with several pediatric cases.[19,20]

This study has some limitations. First, lung ultrasonography depends on the sonographer's skill, and requires patient cooperation. Both greatly influence the diagnostic accuracy of lung ultrasonography. Second, the median lung ultrasound score (5 and 3) and the incidence of hypoxia (22% and 19%) during 48 h postoperatively were not different between the two groups. This may be because these outcomes were not powered to see differences, but it may be because the atelectasis occurring postoperatively is low-grade, and the antiatelectasis effect of pressure support ventilation is transient. However, we regard that small bits of improvement collectively contribute to a better outcome. Therefore, lower incidence of immediate postoperative atelectasis with the use of pressure support ventilation will have an important role in a multimodal approach. Third, atelectasis was diagnosed by consensus reading of two sonographers. It is known that inter- or intrarater variability exists. Thus, independent diagnosis by two sonographers and a statistical test for the degree of the agreement would be a more reliable assessment than consensus reading of two sonographers.[20] Fourth, in this study, low F_{IO_2} (0.4) was maintained during emergence, and patients did not receive oxygen at PACU to avoid absorption atelectasis in both groups. Usually, higher F_{IO_2} is used to prevent hypoxemia in these periods.[35] Therefore, the baseline incidence of atelectasis and outcomes may be different when higher F_{IO_2} is used. Fifth, there were nine patients with unexpected difficult intubation. Attending anesthesiologists proceeded with the protocol because mask ventilation was adequate and intubation was successful with video-laryngoscope in these patients. However, using low F_{IO_2} can be risky in patients with the previous difficult intubation. Finally, this study was performed in patients with a relatively low risk of postoperative atelectasis. Thus, the effect of pressure support ventilation is not known in patients with COPD, obesity, or other significant comorbidities.

In conclusion, pressure support ventilation during emergence from general anesthesia showed a lower incidence of postoperative atelectasis compared to the patient's spontaneous respiration with intermittent manual assistance in laparoscopic colectomy and robot-assisted laparoscopic prostatectomy. Because this result was derived from the low-risk patients of postoperative atelectasis, subsequent validation studies for high-risk patients such as obesity and COPD are required.

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Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available at: hyunjooahn@skku.edu. Raw data available at: hyunjooahn@skku.edu.

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ANESTHESIOLOGY

Preoperative Opioid Utilization Patterns and Postoperative Opioid Utilization: A Retrospective Cohort Study

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Many patients undergoing surgery are chronic preoperative opioid users
- It is unclear how preoperative changes in opioid use among chronic opioid users may affect postoperative opioid utilization (prescriptions filled)

What This Article Tells Us That Is New

- In a national claims database of 57,000 chronic opioid users undergoing common surgical procedures, 41, 22, and 37%, respectively, had stable, decreasing, or increasing preoperative opioid utilization (more than 20% change)
- After adjustment for potential confounders, 96, 89, and 94% of patients with stable, decreasing, or increasing preoperative opioid use utilized opioids (prescriptions filled) between postoperative days 91 and 365
- All three groups had similar average daily oral morphine milligram equivalent utilization
- Changes in preoperative opioid utilization were not associated with clinically significant differences in postoperative opioid utilization

ABSTRACT

Background: Among chronic opioid users, the association between decreasing or increasing preoperative opioid utilization and postoperative outcomes is unknown. The authors hypothesized that decreasing utilization would be associated with improved outcomes and increasing utilization with worsened outcomes.

Methods: Using commercial insurance claims, the authors identified 57,019 chronic opioid users (10 or more prescriptions or 120 or more days supplied during the preoperative year), age 18 to 89 yr, undergoing one of 10 surgeries between 2004 and 2018. Patients with a 20% or greater decrease or increase in opioid utilization between preoperative days 7 to 90 and 91 to 365 were compared to patients with less than 20% change (stable utilization). The primary outcome was opioid utilization during postoperative days 91 to 365. Secondary outcomes included alternative measures of postoperative opioid utilization (filling a minimum number of prescriptions during this period), postoperative adverse events, and healthcare utilization.

Results: The average age was 63 ± 13 yr, with 38,045 (66.7%) female patients. Preoperative opioid utilization was decreasing for 12,347 (21.7%) patients, increasing for 21,330 (37.4%) patients, and stable for 23,342 (40.9%) patients. Patients with decreasing utilization were slightly less likely to fill an opioid prescription during postoperative days 91 to 365 compared to stable patients (89.2% *vs.* 96.4%; odds ratio, 0.323; 95% CI, 0.296 to 0.352; $P < 0.001$), though the average daily doses were similar among patients who continued to utilize opioids during this timeframe (46.7 *vs.* 46.5 morphine milligram equivalents; difference, 0.2; 95% CI, –0.8 to 1.2; $P = 0.684$). Of patients with increasing utilization, 93.6% filled opioid prescriptions during this period (odds ratio, 0.57; 95% CI, 0.52 to 0.62; $P < 0.001$), with slightly lower average daily doses (44.3 morphine milligram equivalents; difference, –2.2; 95% CI, –3.1 to –1.3; $P < 0.001$). Except for alternative measures of persistent postoperative opioid utilization, there were no clinically significant differences for the secondary outcomes.

Conclusions: Changes in preoperative opioid utilization were not associated with clinically significant differences for several postoperative outcomes including postoperative opioid utilization.

(ANESTHESIOLOGY 2021; 135:1015–26)

Opioid use remains a challenging public health crisis in the United States. While progress has been made to reduce opioid prescribing, the rate remains high, with 51.4 opioid prescriptions filled per 100 persons in the United States in 2018.[1] Many patients who present for surgery utilize opioids on a chronic basis, with studies reporting rates of chronic preoperative use between 23.8 and 65.1% among patients undergoing orthopedic surgery.[2,3] Chronic preoperative opioid utilization has been associated with worse perioperative outcomes, including higher mortality, higher

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costs, higher rate of surgical complications, longer hospital length of stay, and more frequent readmissions.[4–6] In addition, postoperative pain in chronic opioid users is often difficult to control, relating to pharmacologic tolerance and opioid-induced hyperalgesia.[7–9] The resulting resistance to opioid analgesic effects and heightened susceptibility to pain can perpetuate a cycle of inadequate pain control and persistent opioid requirements.

The preoperative period is an ideal time to optimize patients for surgery, and is the focus of efforts such as the Perioperative Surgical Home and Enhanced Recovery after Surgery programs.[10,11] For example, smokers are often counseled to cease smoking preoperatively, as doing so is associated with improved outcomes.[12,13] Along these lines, it remains unknown if changes in the amount of opioid utilized in the weeks to months leading up to surgery can affect postoperative outcomes among chronic opioid users. Several smaller studies have suggested preoperative opioid weaning may be beneficial,[14–16] and some institutions are undertaking substantial initiatives to taper patients before surgery due to the hypothesized benefits.[17] However, evidence supporting opioid tapering remains limited. Furthermore, it is unknown if escalation of opioid doses in the immediate preoperative period leads to worsened perioperative outcomes. This study used a national database of healthcare claims to examine whether decreasing or increasing patterns in opioid utilization before surgery are associated with differences in opioid utilized during postoperative days 91 to 365, as well as postoperative adverse events, number of days admitted, and healthcare costs within the first 30 days. We hypothesized that a decreasing pattern may be associated with improved outcomes, while an increasing pattern may be associated with worsened outcomes.

Materials and Methods

Data

This study used a retrospective cohort analysis of administrative health claims data. The data was provided by Optum's Clinformatics Data Mart (Optum, USA), a statistically de-identified database of administrative health claims for members of a large national managed care company affiliated with Optum. Patients in the data receive private insurance coverage, often through their employers. In addition, the database contains claims for elderly (age 65 yr and older) patients who receive private insurance coverage through the Medicare Advantage program. The data are detailed and include clinical data such as diagnosis and procedure codes, as well as socioeconomic data. Pharmacy claims data were used to identify prescriptions filled for the opioids codeine, fentanyl, hydrocodone, hydromorphone, meperidine, methadone, morphine, oxycodone, oxymorphone, and tramadol by matching against the generic name of the drug provided in the data. Prescriptions were converted to oral morphine milligram equivalents, and the daily dose of opioid was calculated for each patient using the unit strength, number of units prescribed, and days supplied from the data.[18] Importantly, while the data describe prescriptions filled, the actual amount and timing of opioid consumed by patients may significantly differ and remains unknown.[19,20]

This study was included in the umbrella Institutional Review Board protocol for de-identified data managed by the Center for Population Heath Sciences at Stanford University (Stanford, California; PHS-40974), which included a waiver of consent. A data analysis and statistical plan was written, date-stamped, and recorded in the investigators' files before data were accessed.

Sample

The initial sample included 2,261,766 surgical procedures between January 1, 2004, and June 30, 2018, for patients 18 to 89 yr old undergoing one of the following: primary total knee arthroplasty, primary total hip arthroplasty, laparoscopic cholecystectomy, open cholecystectomy, laparoscopic appendectomy, open appendectomy, cesarean section, functional endoscopic sinus surgery, transurethral resection of the prostate, or simple mastectomy. Procedures were identified using current procedural terminology codes using previously described methods (Supplemental Digital Content, e-table 1, http://links.lww.com/ALN/C736).[21]

We excluded patients who underwent any other surgical procedure in the year before or after the surgery of interest (n = 185,471), except for postoperative days 0 to 30 to measure postoperative complications. We then excluded patients who did not have continuous enrollment in their insurance plan during this 2-yr period (n = 1,107,135) and hip arthroplasties associated with fracture within the previous 30 days (n = 4,192).[22] From the remaining 964,968 patients with 3,993,731 opioid prescriptions (585 of which were excluded due to invalid strength data), we excluded patients who did not meet our definition of chronic preoperative opioid utilization, which we defined as having 10 or more opioid prescriptions filled or 120 days of opioid prescribed in the year before surgery (n = 907,373).[21] Finally, to avoid the influence of extreme outliers, we excluded patients with the top 1% of opioid utilized during the year before surgery (n = 576; greater than 458 morphine milligram equivalents per day). The final sample consisted of 57,019 patients (Supplemental Digital Content, e-fig. 1, http://links.lww.com/ALN/C736). No statistical power calculation was conducted before the study as the study used all available data.

Outcomes

The primary outcome was the amount of opioid prescribed during postoperative days 91 to 365. Secondary outcomes included the incidence of persistent postoperative opioid utilization during days 91 to 365, the average daily dose of opioid during preoperative day 7 to postoperative day 30 (including the 7 days before surgery to account for patients

who prefilled their postoperative prescriptions), the incidence of adverse events, healthcare costs, and the number of days admitted within the first 30 days. Persistent postoperative opioid utilization was modeled using a range of eight definitions based upon the number of prescriptions filled and days with an opioid prescribed (at least 4/60, 5/70, 6/80, 7/90, 8/100, 9/110, 10/120, and 11/130 prescriptions filled/days with an opioid prescribed) during postoperative days 91 to 365.[21] Postoperative adverse events included surgical site infection, urinary tract infection, pneumonia, sepsis, thromboembolic event, myocardial infarctions, and narcotic overdose. All adverse events were identified by diagnosis codes using previously described methods.[23,24] Healthcare costs were calculated as the sum of all charges requested to be reimbursed by the insurance plan.[25,26]

Exposure

Our independent variable of interest was decreasing or increasing opioid utilization before surgery, assessed by comparing the average daily opioid dose between preoperative days 91 to 365 and preoperative days 7 to 90. A 20% or greater decrease, 20% or greater increase, or remaining within ±20% were classified as decreasing, increasing, and stable utilization, respectively. Opioid prescriptions in the 7 days before surgery were not included since patients may fill their postoperative opioid prescriptions during this period.

Other Variables

Variables captured as potential confounders included age, sex, type of surgery, and year of surgery. Using previously described methods, medical comorbidities were measured using the Elixhauser index based upon relevant diagnosis codes.[27,28] In addition, we included variables for the average daily opioid dose from preoperative days 7 to 90 and 91 to 365 to adjust for effects on our outcomes attributable to the specific dose rather than a change in utilization. For sensitivity analyses, we obtained socioeconomic variables (race, household income, and education level), as well as the National Provider Identifier of the surgeon.

Statistical Analysis

Demographic and comorbidity data were reported as means and 95% CIs. Independent samples *t* tests for continuous variables and chi-square tests for categorical variables were used to assess differences between patient cohorts, with Hedges' g provided as a measure of effect size.[29,30] Two-tailed hypothesis testing was used for all analyses in the study.

We estimated the associations between preoperative opioid utilization patterns and our outcomes using multivariable regression models that included adjustments for the potential confounders shown in table 1 and Supplemental Digital Content, e-table 2 (http://links.lww.com/ALN/C736). In the case of the primary outcome, average daily morphine milligram equivalents prescribed during postoperative days 91 to 365, a significant percentage of patients did not fill any prescription for an opioid during this period (n = 4,920, 8.6%). Therefore, a simple regression that included all patients (including those with no opioid prescribed) would be downward-biased.[31] To mitigate this issue, we modeled postoperative opioid utilization using a two-step analysis.[32–34] In the first step, a logistic regression was used to assess the association between preoperative opioid utilization patterns and whether the patient was prescribed any opioid at all during postoperative days 91 to 365. In the second step, a linear regression was used to assess the association between preoperative opioid utilization patterns and average daily morphine milligram equivalents and was restricted to patients who were prescribed some opioid during postoperative days 91 to 365.

For the secondary outcomes, multivariable linear regressions were used for continuous outcomes and multivariable logistic regressions were used for binary outcomes with the same set of covariates described above. We also applied a Bonferroni-corrected threshold for significance to adjust for multiple comparisons for our 18 reported secondary outcomes ($\alpha = 0.002$).[35] Our analyses were performed using MATLAB, version R2015a (MathWorks, Inc., USA) and STATA 14/MP (StataCorp, USA).

Subgroup Analyses

To gain additional insight into how the association between preoperative opioid utilization patterns and our primary outcome varies for different surgical situations, we analyzed several subgroups of procedures. First, we compared elective procedures, defined as procedures where preoperative optimization is possible, to nonelective procedures, where optimization is generally not possible. Elective procedures included primary total knee/hip arthroplasty, cesarean section, transurethral resection of the prostate, and simple mastectomy. Nonelective procedures included laparoscopic/open appendectomy. Laparoscopic and open cholecystectomies were classified as elective or nonelective based upon the presence of a diagnosis code for acute cholecystitis.[36] We also compared procedures related to chronic pain (total knee and hip arthroplasties) to procedures unrelated to chronic pain (the remaining procedures) and analyzed each procedure as an independent subgroup.

Sensitivity Analyses

We considered the robustness of our findings to several sensitivity analyses. First, since our main analysis measured the pattern of preoperative opioid utilized using a 90-day cutoff, we repeated the analysis using 30- and 180-day cutoffs. Second, our main analysis assigned cohorts using a 20% or greater change in opioid dose, so we repeated our main analyses using a 50% or greater change. Third, to assess the influence of socioeconomic variables, we repeated our analyses on the subset of patients for whom socioeconomic data were available (n =

Table 1. Patient Characteristics

Variable	Patients with Stable Opioid Utilization, n = 23,342 (40.9%)	Patients with Decreasing Opioid Utilization, n = 12,347 (21.7%)			Patients with Increasing Opioid Utilization, n = 21,330 (37.4%)		
			P Value	Hedges' g		*P* Value	Hedges' g
Demographics							
Age, yr, mean ± SD	64 ± 12	62 ± 15	< 0.001	0.147	63 ± 14	< 0.001	0.097
Female, n (%)	15,382 (65.9%)	8,526 (69.1%)	< 0.001	–0.067	14,137 (66.3%)	0.398	–0.008
Opioid utilization in preoperative year, mean ± SD							
No. of opioid prescriptions	14 ± 8	12 ± 7	< 0.001	0.343	12 ± 7	< 0.001	0.251
No. of days with opioid prescription	290 ± 78	214 ± 82	< 0.001	0.948	218 ± 85	< 0.001	0.877
Average daily morphine milligram equivalents utilized in preoperative days 91–365	59.9 ± 77.3	43.5 ± 65.1	< 0.001	0.224	27.4 ± 42.2	< 0.001	0.516
Average daily morphine milligram equivalents utilized in preoperative days 7–90	60.5 ± 78.5	20.1 ± 37.1	< 0.001	0.602	49.7 ± 69.1	< 0.001	0.145
Type of surgery, n (%)							
Total knee arthroplasty	8,204 (35.1%)	3,982 (32.3%)	< 0.001	0.061	7,066 (33.1%)	< 0.001	0.043
Total hip arthroplasty	3,650 (15.6%)	1,695 (13.7%)	< 0.001	0.054	5,584 (26.2%)	< 0.001	–0.263
Laparoscopic cholecystectomy	6,253 (26.8%)	3,399 (27.5%)	0.136	–0.017	4,761 (22.3%)	< 0.001	0.104
Open cholecystectomy	421 (1.8%)	220 (1.8%)	0.884	0.002	340 (1.6%)	0.087	0.016
Laparoscopic appendectomy	793 (3.4%)	445 (3.6%)	0.309	–0.011	623 (2.9%)	0.004	0.018
Open appendectomy	150 (0.6%)	86 (0.7%)	0.549	–0.007	106 (0.5%)	0.042	0.019
Cesarean section	228 (1.0%)	565 (4.6%)	< 0.001	–0.246	300 (1.4%)	< 0.001	–0.040
Functional endoscopic sinus surgery	1,636 (7.0%)	968 (7.8%)	0.004	–0.032	1,264 (5.9%)	< 0.001	0.044
Transurethral resection of the prostate	667 (2.9%)	344 (2.8%)	0.668	0.004	438 (2.1%)	< 0.001	0.052
Simple mastectomy	1,340 (5.7%)	643 (5.2%)	0.037	0.023	848 (4.0%)	< 0.001	0.082

P values reflect the comparison between the decreasing or increasing cohort and patients with stable utilization and were computed using chi-square and independent samples *t* tests for categorical and continuous variables, respectively. Hedges' g measures effect size as a standardized difference between cohorts, with values less than 0.2 representing small differences, values between 0.2 and 0.5 representing moderate differences, and values greater than 0.5 representing large differences.

45,764; 80.3%) to adjust for race, household income, and education level. Finally, to adjust for provider-specific effects, we added clustering based upon the surgeon's National Provider Identifier when available (n = 54,659; 95.9%).

Revisions to Analysis Plan

The following analyses were not included in the original analysis plan and were added during peer review: secondary analyses for measures of persistent postoperative opioid utilization, subgroup analyses for elective *versus* nonelective procedures and procedures related *versus* unrelated to chronic pain, and sensitivity analyses for socioeconomic status and provider-specific effects. Furthermore, while the original analysis included data for surgeries up to December 31, 2016, during review, additional data for procedures through June 30, 2018, became available and were included in the final version of the manuscript.

Results

Patient Characteristics

The average ± SD age was 63 ± 13 yr, with 38,045 (66.7%) female patients. Preoperative opioid utilization was decreasing for 12,347 patients (21.7%), increasing for 21,330 (37.4%) patients, and stable for 23,342 (40.9%) patients. Patient characteristics are shown by cohort in table 1 and Supplemental Digital Content, e-table 2 (http://links.lww.com/ALN/C736).

Main Analysis

Overall, 52,099 (91.4%) of patients had at least one prescription for an opioid during postoperative days 91 to 365. Before adjusting for confounders, the incidence of having any opioid prescribed in this period was lower for patients with both decreasing (85.1%; 95% CI, 84.8 to 85.3%; odds ratio, 0.272; 95% CI, 0.251 to 0.294; $P < 0.001$) and increasing (90.6%; 95% CI, 90.3 to 90.8%; odds ratio, 0.46; 95% CI, 0.42 to 0.50; $P < 0.001$) opioid utilization compared to patients with stable utilization (95.4%; 95% CI, 95.2 to 95.7%). The average daily dose of opioid during postoperative days 91 to 365 was also lower for patients with both decreasing (29.7 morphine milligram equivalents; 95% CI, 28.5 to 30.8; difference, –27.7; 95% CI, –29.2 to –26.1; $P < 0.001$) and increasing (41.0 morphine milligram equivalents; 95% CI, 40.0 to 42.0; difference, –16.3; 95% CI, –17.8 to –14.9; $P < 0.001$) opioid utilization compared to patients with stable utilization (57.3 morphine milligram equivalents; 95% CI, 56.3 to 58.4; table 2, fig. 1).

After adjusting for potential confounders, the incidence of having any opioid prescribed during postoperative days

Table 2. Outcomes

	Patients with Stable Opioid Utilization, n = 23,342 (40.9%)	Patients with Decreasing Opioid Utilization, n = 12,347 (21.7%)		Patients with Increasing Opioid Utilization, n = 21,330 (37.4%)	
Primary outcomes					
Incidence of utilizing any opioid during postoperative days 91–365, %					
Unadjusted	95.4% (95.2 to 95.7%)	85.1% (84.4 to 85.7%)	Odds ratio 0.272 (0.251 to 0.294); $P < 0.001$	90.6% (90.2 to 91.0%)	Odds ratio 0.46 (0.42 to 0.50); $P < 0.001$
Adjusted	96.2% (96.0 to 96.5%)	89.2% (88.5 to 89.9%)	Odds ratio 0.323 (0.296 to 0.352); $P < 0.001$	93.6% (93.2 to 93.9%)	Odds ratio 0.57 (0.52 to 0.62); $P < 0.001$
Average daily opioid dose utilized during postoperative days 91–365, morphine milligram equivalents					
Unadjusted	57.3 (56.3 to 58.4)	29.7 (28.5 to 30.8)	Difference –27.7 (–29.2 to –26.1); $P < 0.001$	41.0 (40.0 to 42.0)	Difference –16.3 (–17.8 to –14.9); $P < 0.001$
Adjusted	46.5 (45.9 to 47.0)	46.7 (45.8 to 47.6)	Difference 0.2 (–0.8 to 1.2); $P = 0.684$	44.3 (43.6 to 44.9)	Difference –2.2 (–3.1 to –1.3); $P < 0.001$
Secondary outcomes*					
Average daily opioid dose utilized during preoperative day 7 to postoperative day 30, morphine milligram equivalents					
Unadjusted	74.4 (72.7 to 76.1)	41.1 (39.7 to 42.5)	Difference –33.3 (–35.5 to –31.1); $P < 0.001$	62.1 (60.4 to 63.8)	Difference –12.3 (–14.7 to –9.9); $P < 0.001$
Adjusted	62.8 (62.1 to 63.6)	67.4 (66.2 to 68.6)	Difference 4.6 (3.1 to 6.0); $P < 0.001$	60.6 (59.7 to 61.5)	Difference –2.3 (–3.5 to –1.0); $P < 0.001$
Incidence of narcotic overdose, %					
Unadjusted	0.4% (0.3 to 0.5%)	0.3% (0.1 to 0.4%)	Odds ratio 0.66 (0.36 to 1.20); $P = 0.037$	0.4% (0.2 to 0.5%)	Odds ratio 0.85 (0.53 to 1.34); $P = 0.276$
Adjusted	—	—	—	—	—
Total healthcare costs, US$					
Unadjusted	$48,632 (47,754 to 49,511)	$45,987 (44,785 to 47,189)	Difference –$2,645 (–4,134 to –1,156); $P < 0.001$	$51,430 (50,500 to 52,359)	Difference $2,797 (1,518 to 4,076); $P < 0.001$
Adjusted	$48,732 (47,937 to 49,528)	$49,054 (47,884 to 50,224)	Difference $322 (–1,084 to 1,727); $P = 0.494$	$49,544 (48,657 to 50,431)	Difference $812 (–412 to 2,035); $P = 0.047$
Number of days admitted					
Unadjusted	0.7 (0.6 to 0.7)	0.7 (0.6 to 0.8)	Difference 0.0 (–0.1 to 0.1); $P = 0.314$	0.8 (0.7 to 0.9)	Difference 0.2 (0.1 to 0.3); $P < 0.001$
Adjusted	0.7 (0.6 to 0.8)	0.7 (0.6 to 0.8)	Difference 0.0 (–0.1 to 0.1); $P = 0.610$	0.8 (0.7 to 0.8)	Difference 0.1 (–0.0 to 0.2); $P = 0.087$

The incidences, average daily dose of opioid, healthcare costs, and number of days admitted are reported with both unadjusted and adjusted values. Adjustment modeled outcomes controlling for age, sex, type and year of surgery, and medical comorbidities. For the average daily dose of opioid, patients who were not prescribed any opioid in the relevant period were excluded to prevent downward biasing of the results. Primary outcomes are reported with 95% CIs. Fields marked "—" represent regression models that were unable to converge due to limited incidence of the outcome in the sample.

*Secondary outcomes applied a Bonferroni correction for multiple comparisons. With 18 reported outcomes (four in this table, six in Supplemental Digital Content, e-table 2 [http://links.lww.com/ALN/C736], and eight definitions for persistent postoperative utilization shown in fig. 2), the threshold for significance is $\alpha = 0.05/18 = 0.002$. Thus, 99.8% CIs are reported. Except where otherwise specified, secondary outcomes were measured during postoperative days 0 to 30.

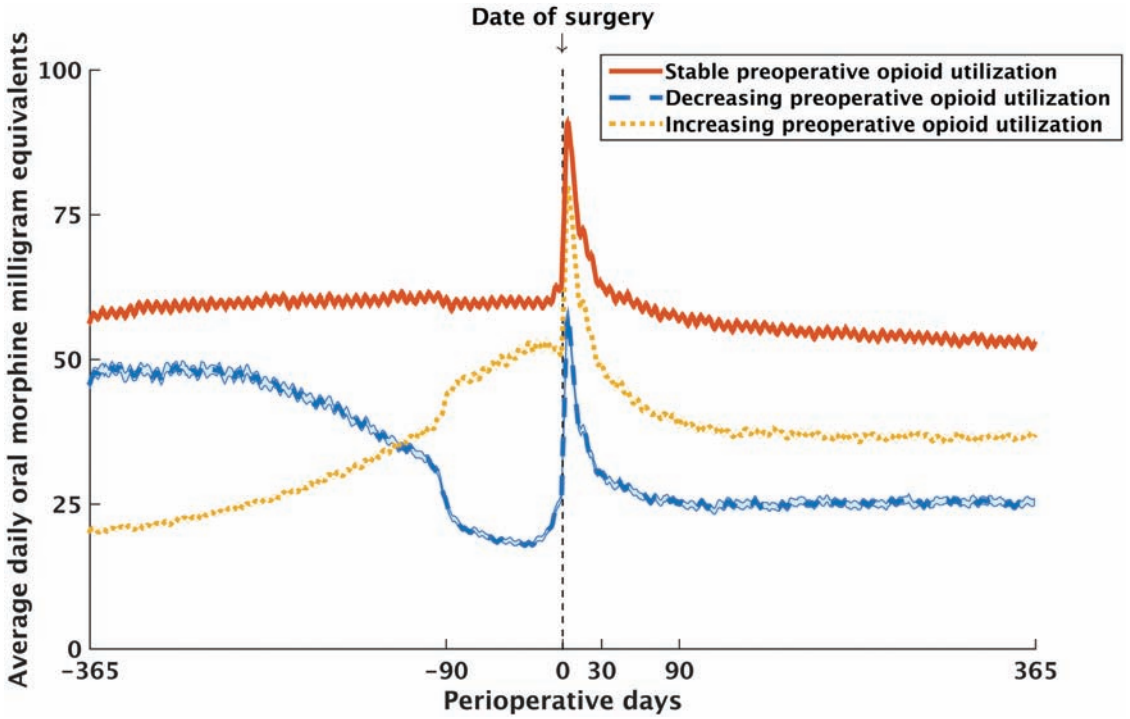

Fig. 1. Average daily dose of opioid prescribed during the 2-yr perioperative window. Compared to preoperative days 91 to 365, patients with stable utilization maintained their average daily opioid dose within ±20% during preoperative days 7 to 90, while patients with decreasing utilization reduced their average daily dose by at least 20%, and patients with increasing utilization escalated their average daily dose by at least 20% in the same period.

91 to 365 remained lower for patients with both decreasing (89.2%; 95% CI, 88.5 to 89.9%; odds ratio, 0.323; 95% CI, 0.296 to 0.352; $P < 0.001$) and increasing opioid utilization (93.6%; 95% CI, 93.2 to 93.9%; odds ratio, 0.57; 95% CI, 0.52 to 0.62; $P < 0.001$) compared to patients with stable utilization (96.2%; 95% CI, 96.0 to 96.5%). Among patients who continued to utilize opioids in this period, the average daily dose of opioid was not different for patients with decreasing utilization (46.7 morphine milligram equivalents; 95% CI, 45.8 to 47.6; difference, 0.2; 95% CI, –0.8 to 1.2; $P = 0.684$), but was slightly lower for patients with increasing utilization (44.3 morphine milligram equivalents; 95% CI, 43.6 to 44.9; difference, –2.2; 95% CI, –3.1 to –1.3; $P < 0.001$) compared to patients with stable utilization (46.5 morphine milligram equivalents; 95% CI, 45.9 to 47.0; table 2).

For our secondary outcomes, we modeled a range of eight definitions for persistent postoperative opioid utilization that consistently demonstrated lower rates of incidence for patients with both decreasing and increasing preoperative opioid utilization. For example, using a definition for persistent postoperative opioid utilization of 10 or more prescriptions filled or 120 or more days supplied during postoperative days 91 to 365, the adjusted incidence was 56.2% (99.8% CI, 54.5 to 57.9%; odds ratio, 0.314; 99.8% CI, 0.289 to 0.341; $P < 0.001$) for patients with decreasing utilization and 69.0% (99.8% CI, 67.9 to 70.2%; odds ratio, 0.55; 95% CI, 0.51 to 0.59; $P < 0.001$) for patients with increasing utilization compared to patients with stable utilization (80.3%; 99.8% CI, 77.3 to 79.1%; fig. 2).

The adjusted average daily dose of opioid during preoperative day 7 to postoperative day 30 was higher for patients with decreasing utilization (67.4 morphine milligram equivalents; 99.8% CI, 66.2 to 68.6; difference, 4.5; 99.8% CI, 3.1 to 6.0; $P < 0.001$) and lower for patients with increasing utilization (60.6 morphine milligram equivalents; 99.8% CI, 59.7 to 61.5; difference, –2.3; 99.8% CI, –3.5 to –1.0; $P < 0.001$) compared to patients with stable utilization (62.8 morphine milligram equivalents; 99.8% CI, 62.1 to 63.6) among patients who filled a prescription for opioids in this period. No differences were found in the rate of postoperative adverse events, healthcare costs, or the number of days admitted for patients with either decreasing or increasing preoperative opioid utilization compared to patients with stable utilization (table 2 and Supplemental Digital Content, e-table 3, http://links.lww.com/ALN/C736).

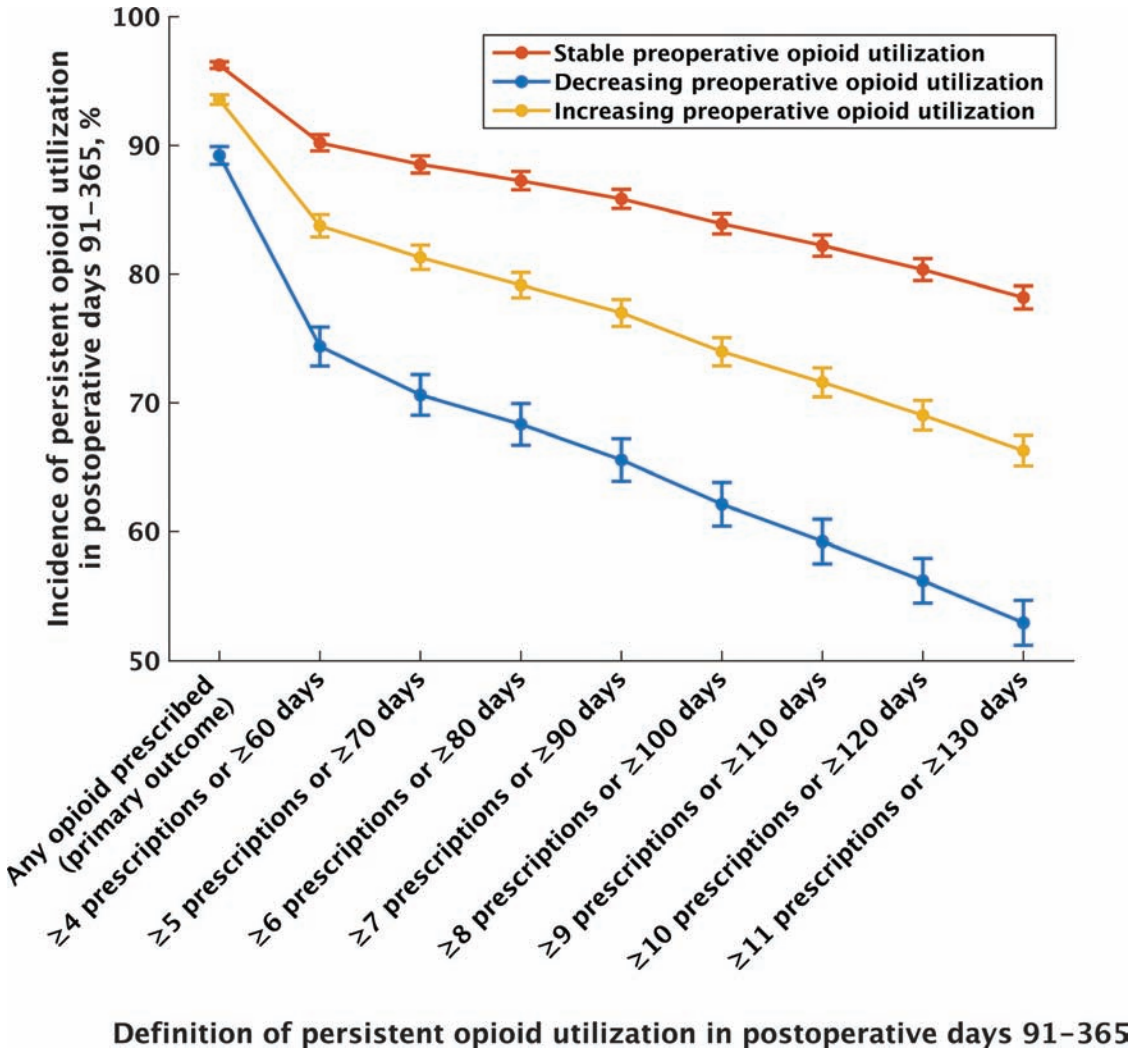

Fig. 2. The association between patterns of preoperative opioid utilization and persistent postoperative opioid utilization. The adjusted incidence of persistent postoperative opioid utilization for a range of eight definitions is shown. Patients with both decreasing and increasing preoperative opioid utilization had reduced incidence of persistent postoperative opioid utilization compared to patients with stable utilization. Values are shown with 99.8% CIs, which use the Bonferroni correction for multiple comparisons as described in the Materials and Methods section.

Subgroup and Sensitivity Analyses

Subgroup analyses stratifying patients by procedure urgency, relation to chronic pain treatment, and type of surgery (table 3), as well sensitivity analyses that varied the timing and magnitude of changes in dose required to classify patterns in opioid utilization and added additional adjustments for socioeconomic and surgeon-related factors (Supplemental Digital Content, e-table 4, http://links.lww.com/ALN/C736) yielded qualitatively similar results to our main analysis.

Discussion

In this retrospective analysis of 57,019 chronic opioid users aged 18 to 89 yr undergoing one of 10 common surgeries, either a decrease or an increase in the daily dose of opioid by at least 20% in the 90 days before surgery was associated with slightly less long-term opioid utilization, with the adjusted incidence of any opioid prescribed during postoperative days 91 to 365 being 89.2% for patients with decreasing utilization and 93.6% for patients with increasing utilization, compared to 96.4% for patients with stable utilization. However, for patients continuing to utilize opioids, the adjusted average daily dose prescribed for patients with decreasing utilization was not different from patients with stable utilization. Surprisingly, patients with increasing preoperative opioid utilization continuing opioids during postoperative days 91 to 365 had a slightly lower adjusted average daily dose (44.3 morphine milligram equivalents per

Table 3. Subgroup Analyses by Type of Procedure

Subgroup	No. of Patients with Preoperative Chronic Opioid Use (% of full sample)	No. of Patients with Any Opioid Prescribed in Postoperative Days 91–365 (% of subgroup)	Patients with Stable Opioid Utilization			Patients with Decreasing Opioid Utilization			Patients with Increasing Opioid Utilization		
			No. of Patients (%)	Adjusted Incidence of Any Opioid Prescribed in Postoperative Days 91–365	Adjusted Average Daily Dose of Opioid in Postoperative Days 91–365 (morphine milligram equivalents)	No. of Patients (%)	Adjusted Incidence and Odds Ratio of Any Opioid Prescribed in Postoperative Days 91–365	Adjusted Amount and Difference of Average Daily Opioid Dose in Postoperative Days 91–365 (morphine milligram equivalents)	No. of Patients (%)	Adjusted Incidence and Odds Ratio of Any Opioid Prescribed in Postoperative Days 91–365	Adjusted Amount and Difference of Average Daily Opioid Dose in Postoperative Days 91–365 (morphine milligram equivalents)
Procedure urgency*											
Elective procedures	48,199 (84.5%)	43,837 (91.0%)	19,438 (40.3%)	95.8% (95.5 to 96.1)	45.6 (45.0 to 46.2)	10,232 (21.2%)	88.8% (88.0 to 89.5%) 0.348 (0.317 to 0.381) $P < 0.001$	46.0 (45.0 to 46.9) 0.3 (–0.7 to 1.5) $P = 0.540$	18,529 (38.4%)	91.8% (91.4 to 92.2%) 0.49 (0.45 to 0.54) $P < 0.001$	42.2 (41.6 to 42.9) –3.3 (–4.3 to –2.4) $P < 0.001$
Nonelective procedures	8,820 (15.5%)	8,262 (93.7%)	3,904 (44.3%)	97.6% (97.0 to 98.0%)	52.8 (51.5 to 54.2)	2,115 (24.0%)	90.1% (88.2 to 91.6%) 0.227 (0.177 to 0.291) $P < 0.001$	53.0 (50.9 to 55.1) 0.2 (–2.4 to 2.7) $P = 0.905$	2,801 (31.8%)	96.0% (95.2 to 96.7%) 0.60 (0.46 to 0.78) $P < 0.001$	52.2 (50.5 to 54.0) –0.6 (–2.8 to 1.7) $P = 0.610$
Pain-related procedures†											
Procedure treats chronic pain	30,181 (52.9%)	26,844 (88.9%)	11,854 (39.3%)	94.3% (93.9 to 94.7%)	42.1 (41.4 to 42.8)	5,677 (18.8%)	86.3% (85.3 to 87.3%) 0.380 (0.341 to 0.423) $P < 0.001$	41.0 (39.9 to 42.2) –1.1 (–2.4 to 0.2) $P = 0.111$	12,650 (41.9%)	90.3% (89.7 to 90.9%) 0.56 (0.51 to 0.62) $P < 0.001$	39.0 (38.2 to 39.8) –3.1 (–4.2 to –2.0) $P < 0.001$
Procedure does not treat chronic pain	26,838 (47.1%)	25,255 (94.1%)	11,488 (42.8%)	97.7% (97.4 to 98.0%)	51.1 (50.3 to 52.0)	6,670 (24.9%)	91.5% (90.5 to 92.3%) 0.252 (0.218 to 0.292) $P < 0.001$	53.3 (52.1 to 54.6) 2.2 (0.6 to 3.7) $P = 0.005$	8,680 (32.3%)	96.0% (95.5 to 96.4%) 0.56 (0.48 to 0.66) $P < 0.001$	49.5 (48.4 to 50.5) –1.7 (–3.1 to –0.3) $P = 0.018$
Individual surgical procedures											
Primary total knee arthroplasty	19,252 (33.8%)	17,799 (92.5%)	8,204 (42.6%)	96.5% (96.1 to 96.9%)	42.0 (41.2 to 42.9)	3,982 (20.7%)	90.8% (89.6 to 91.9%) 0.359 (0.308 to 0.419) $P < 0.001$	43.4 (42.1 to 44.7) 1.3 (–0.2 to 2.9) $P = 0.088$	7,066 (36.7%)	94.3% (93.7 to 94.9%) 0.60 (0.52 to 0.69) $P < 0.001$	40.3 (39.3 to 41.3) –1.7 (–3.0 to –0.44) $P = 0.009$
Primary total hip arthroplasty	10,929 (19.2%)	9,045 (82.8%)	3,650 (33.4%)	89.6% (88.5 to 90.6%)	41.6 (40.3 to 43.0)	1,695 (15.5%)	79.7% (77.5 to 81.8%) 0.46 (0.39 to 0.54) $P < 0.001$	36.9 (34.7 to 39.2) –4.7 (–7.2 to –2.2) $P < 0.001$	5,584 (51.1%)	85.1% (84.0 to 86.2%) 0.66 (0.58 to 0.76) $P < 0.001$	37.0 (35.8 to 38.2) –4.6 (–6.5 to –2.7) $P < 0.001$
Laparoscopic cholecystectomy	14,413 (25.3%)	13,588 (94.3%)	6,253 (43.4%)	97.8% (97.4 to 98.1%)	53.1 (52.0 to 54.2)	3,399 (23.6%)	92.2% (91.0 to 93.3%) 0.268 (0.219 to 0.328) $P < 0.001$	55.0 (53.4 to 56.7) 1.9 (0.0 to 3.9) $P = 0.055$	4,761 (33.0%)	96.3% (95.7 to 96.8%) 0.58 (0.47 to 0.72) $P < 0.001$	50.5 (49.1 to 51.8) –2.7 (–4.4 to –0.9) $P = 0.003$
Open cholecystectomy	981 (1.7%)	901 (91.8%)	421 (42.9%)	—	58.9 (53.8 to 63.9)	220 (22.4%)	—	59.0 (50.8 to 67.1) 0.1 (–9.5 to 9.8) $P = 0.978$	340 (34.7%)	—	56.6 (50.4 to 62.8) –2.2 (–10.4 to 6.0) $P = 0.592$
Laparoscopic appendectomy	1,861 (3.3%)	1,742 (93.6%)	793 (42.6%)	—	49.8 (46.7 to 53.0)	445 (23.9%)	—	47.2 (42.2 to 52.2) –2.6 (–8.6 to 3.3) $P = 0.387$	623 (33.5%)	—	54.2 (50.3 to 58.0) 4.3 (–0.8 to 9.4) $P = 0.095$
Open appendectomy	342 (0.6%)	318 (93.0%)	150 (43.9%)	—	—	86 (25.1%)	—	—	106 (31.0%)	—	—
Cesarean section	1,093 (1.9%)	1,000 (91.5%)	228 (20.9%)	—	—	565 (51.7%)	—	—	300 (27.4%)	—	—
Functional endoscopic sinus surgery	3,868 (6.8%)	3,667 (94.8%)	1,636 (42.3%)	98.8% (98.2 to 99.2%)	51.2 (48.4 to 53.9)	968 (25.0%)	93.2% (90.5 to 95.1%) 0.162 (0.102 to 0.258) $P < 0.001$	53.2 (49.1 to 57.2) 2.0 (–2.9 to 6.9) $P = 0.418$	1,264 (32.7%)	97.2% (96.2 to 98.0%) 0.42 (0.257 to 0.68) $P < 0.001$	49.4 (46.1 to 52.8) –1.7 (–6.2 to 2.8) $P = 0.454$

(*Continued*)

Table 3. (Continued)

Subgroup	No. of Patients with Preoperative Chronic Opioid Use (% of full sample)	No. of Patients with Any Opioid Prescribed in Postoperative Days 91–365 (% of subgroup)	Patients with Stable Opioid Utilization			Patients with Decreasing Opioid Utilization			Patients with Increasing Opioid Utilization		
			No. of Patients (%)	Adjusted Incidence of Any Opioid Prescribed in Postoperative Days 91–365	Adjusted Average Daily Dose of Opioid in Postoperative Days 91–365 (morphine milligram equivalents)	No. of Patients (%)	Adjusted Incidence and Odds Ratio of Any Opioid Prescribed in Postoperative Days 91–365	Adjusted Amount and Difference of Average Daily Opioid Dose in Postoperative Days 91–365 (morphine milligram equivalents)	No. of Patients (%)	Adjusted Incidence and Odds Ratio of Any Opioid Prescribed in Postoperative Days 91–365	Adjusted Amount and Difference of Average Daily Opioid Dose in Postoperative Days 91–365 (morphine milligram equivalents)
Transurethral resection of the prostate	1,449 (2.5%)	1,351 (93.2%)	667 (46.1%)	—	44.0 (41.8 to 46.3)	344 (23.7%)	—	46.5 (42.9 to 50.1) 2.4 (–1.8 to 6.7) *P* = 0.277	438 (30.2%)	—	44.8 (41.7 to 47.8) 0.8 (–3.1 to 4.6) *P* = 0.703
Simple mastectomy	2,831 (5.0%)	2,688 (94.9%)	1,340 (47.3%)	—	43.7 (41.6 to 45.7)	643 (22.7%)	—	43.3 (39.8 to 46.7) –0.4 (–4.4 to 3.6) *P* = 0.837	848 (30.0%)	—	45.4 (42.6 to 48.2) 1.7 (–1.8 to 5.3) *P* = 0.337

Subgroup analyses modeled the primary outcomes of the study stratifying patients by surgical context and specific procedures. Fields marked "—" represent regression models that were unable to converge due to limited sample size of the subgroup. Adjustment modeled outcomes controlling for age, sex, type and year of surgery, and medical comorbidities. For the average daily dose of opioid, patients who were not prescribed any opioid in the relevant period were excluded to prevent downward biasing of the results. Values are reported with 95% CIs.

*"Elective" is defined as surgeries for which preoperative optimization is typically feasible, and includes primary total knee arthroplasty, primary total hip arthroplasty, laparoscopic and open cholecystectomy without associated acute cholecystitis, cesarean section, transurethral resection of the prostate, and simple mastectomy, while "nonelective" includes laparoscopic and open cholecystectomy with acute cholecystitis, and laparoscopic and open appendectomy.

†Procedures related to chronic pain treatment include total knee arthroplasty and total hip arthroplasty, while procedures not intended to treat chronic pain include laparoscopic and open cholecystectomy, laparoscopic and open appendectomy, cesarean section, functional endoscopic sinus surgery, transurethral resection of the prostate, and simple mastectomy.

day) compared to patients with stable utilization (46.7 morphine milligram equivalents per day), although this likely represents a clinically insignificant difference. For example, several studies in chronic pain patients used a threshold of 8 to 30 morphine milligram equivalents per day to define a clinically significant reduction in opioid use.[37,38] We hypothesize that increasing preoperative utilization may be attributable to worsening pain that was improved by surgery, allowing cessation or further reduction in opioid utilization postoperatively.

Importantly, while the relative reduction in the odds of filling a prescription for an opioid during postoperative days 91 to 365 was substantial for patients with both decreasing (adjusted odds ratio, 0.323) and increasing (adjusted odds ratio, 0.57) preoperative opioid utilization, the absolute reductions were small (–7.0% and –2.6%, respectively). This suggests that preoperative changes in opioid utilization may have limited clinical associations with several measures of long-term postoperative opioid utilization. However, a secondary analysis that defined persistent postoperative opioid utilization using a minimum number of opioid prescriptions and/or days supplied did find large absolute reductions in the incidence of persistent postoperative opioid utilization for both decreasing and increasing patterns (56.2% and 69.0%, respectively, compared to 80.3% for stable patterns using 10 or more prescriptions filled or 120 or more days supplied), indicating further study is warranted.

For our secondary outcomes, both decreasing and increasing preoperative opioid utilizations were associated with small, likely clinically insignificant differences in opioid doses prescribed during preoperative day 7 to postoperative day 30. Additionally, no difference in postoperative adverse events, number of days admitted, or healthcare costs in either cohort were observed.

This study has several important limitations. First, by limiting this study to patients with no other surgical interventions in a 2-yr period, the sample population may be biased toward healthier patients who are less likely to have complications with shorter length of stay and lower total costs. This, along with the relatively short duration that preoperative changes in dose were sustained, may explain why no significant associations were detected despite previous literature suggesting that chronic preoperative opioid utilization negatively correlates with these outcomes.[4–6]

Second, due to the limited nature of claims data, we cannot assess why patients altered their opioid dose before surgery, and the possibility of hidden confounders associated with changes in opioid utilization is real. For example, patients with decreasing utilization may have received preoperative guidance from surgeons, pain specialists, or primary care physicians, and this management approach may have been continued postoperatively. These patients may also have been self-motivated, and success with reducing their opioid requirements preoperatively may facilitate postoperative cessation. Patients with decreasing utilization may also have had unrelated improvements in chronic pain preoperatively, which could lead to reduced pain and opioid requirements postoperatively. Conversely, patients with increasing utilization may have experienced worsening of their underlying pain conditions, which was then improved by surgery leading to decreased pain and a reduced postoperative opioid requirement. However, one source of reassurance against hidden confounding is that our results held for the subgroup of nonelective procedures, as any preoperative changes in opioid utilization could not relate to the preparation for surgery. An additional source of confounding could be regression artifacts such as "regression to the mean," which may be of particular concern in our study since it defined exposure groups based upon preoperative opioid use and modeled postoperative opioid utilization based on these same groups.[39] However, these regression artifacts would tend to bias our results upwards (*i.e.*, bias toward finding a larger effect than the actual effect). Since our adjusted results were generally small in magnitude, this suggests that regression to the mean has minimal actual influence on our findings. Third, claims data measure drug utilization (*i.e.*, the fulfillment of prescriptions) but not drug use (the actual amount and timing of opioid consumed). While utilization and use would generally correlate, studies have suggested that many patients do not actually consume the entire amount of opioid that is prescribed.[19,20]

While it has been suggested that preoperative opioid weaning may be beneficial,[15] there have been few studies on this topic to date.[14,16] In this context, our study has mixed findings. On the one hand, our results suggest that preoperative changes in opioid utilization are not associated with statistically and/or clinically significant differences for a broad variety of perioperative outcomes. However, a secondary analysis did demonstrate a clinically and statistically significant association between changes in preoperative opioid utilization and a lower incidence of persistent postoperative opioid utilization (*e.g.*, the adjusted incidence of at least 10 opioid prescriptions or 120 days of prescription coverage in postoperative days 91 to 365 was 56.2% for patients with decreasing utilization and 69.0% for patients with increasing utilization, compared to 80.4% for patients with stable utilization), suggesting potential benefit for more meaningful measures of persistent postoperative opioid use. Our results may also provide cautious reassurance for the management of patients who experience worsening pain before surgery, as we found no evidence that preoperative escalation of opioid was associated with worsened outcomes. Ultimately, further study in the form of randomized trials may be necessary to clarify whether efforts to impact preoperative opioid utilization can improve perioperative outcomes.

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Competing Interests

Dr. Angst reports consulting fees unrelated to this work from Syneos Health (Morrisville, North Carolina); Fraser, Watson, Croutch LLP (Orange, California); and Hassard and Bonnington LLP (San Francisco, California). Dr. Sun reports consulting fees unrelated to this work from the Analysis Group (Boston, Massachusetts), the Mission Lisa Foundation (Tampa, Florida), and Lucid Lane (Los Altos, California), LLC. Dr. Rishel declares no competing interests.

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ANESTHESIOLOGY

Arterial and Mixed Venous Kinetics of Desflurane and Sevoflurane, Administered Simultaneously, at Three Different Global Ventilation to Perfusion Ratios in Piglets with Normal Lungs

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- The role of lung gas exchange in whole-body kinetics can be studied by direct measurements of anesthetic partial pressures in mixed venous (P_{mv}) and arterial (P_{art}) blood samples
- Washin and washout of desflurane should be more rapid than sevoflurane because sevoflurane has higher gas solubilities in blood and tissues

What This Article Tells Us That Is New

- The washin and washout kinetics of simultaneously administered desflurane and sevoflurane were assessed in seven piglets by measuring P_{mv} and P_{art} during uptake and elimination under normal, low, and high ventilation/perfusion ratio ($\dot{V}_A/\dot{Q}$) conditions
- Faster arterial kinetics for desflurane were generally maintained for both washin and washout under all $\dot{V}_A/\dot{Q}$ conditions
- The low $\dot{V}_A/\dot{Q}$ condition decreased the differences in scaled P_{art} between 0 and 5 min; the high $\dot{V}_A/\dot{Q}$ condition increased these differences from the low $\dot{V}_A/\dot{Q}$ value to a value approaching or exceeding the value for normal $\dot{V}_A/\dot{Q}$
- Mixed venous kinetics were slower than arterial kinetics for washin and washout and were less influenced by $\dot{V}_A/\dot{Q}$

ABSTRACT

Background: Previous studies have established the role of various tissue compartments in the kinetics of inhaled anesthetic uptake and elimination. The role of normal lungs in inhaled anesthetic kinetics is less understood. In juvenile pigs with normal lungs, the authors measured desflurane and sevoflurane washin and washout kinetics at three different ratios of alveolar minute ventilation to cardiac output value. The main hypothesis was that the ventilation/perfusion ratio ($\dot{V}_A/\dot{Q}$) of normal lungs influences the kinetics of inhaled anesthetics.

Methods: Seven healthy pigs were anesthetized with intravenous anesthetics and mechanically ventilated. Each animal was studied under three different $\dot{V}_A/\dot{Q}$ conditions: normal, low, and high. For each $\dot{V}_A/\dot{Q}$ condition, desflurane and sevoflurane were administered at a constant, subanesthetic inspired partial pressure (0.15 volume% for sevoflurane and 0.5 volume% for desflurane) for 45 min. Pulmonary arterial and systemic arterial blood samples were collected at eight time points during uptake, and then at these same times during elimination, for measurement of desflurane and sevoflurane partial pressures. The authors also assessed the effect of $\dot{V}_A/\dot{Q}$ on paired differences in arterial and mixed venous partial pressures.

Results: For desflurane washin, the scaled arterial partial pressure differences between 5 and 0 min were 0.70 ± 0.10, 0.93 ± 0.08, and 0.82 ± 0.07 for the low, normal, and high $\dot{V}_A/\dot{Q}$ conditions (means, 95% CI). Equivalent measurements for sevoflurane were 0.55 ± 0.06, 0.77 ± 0.04, and 0.75 ± 0.08. For desflurane washout, the scaled arterial partial pressure differences between 0 and 5 min were 0.76 ± 0.04, 0.88 ± 0.02, and 0.92 ± 0.01 for the low, normal, and high $\dot{V}_A/\dot{Q}$ conditions. Equivalent measurements for sevoflurane were 0.79 ± 0.05, 0.85 ± 0.03, and 0.90 ± 0.03.

Conclusions: Kinetics of inhaled anesthetic washin and washout are substantially altered by changes in the global $\dot{V}_A/\dot{Q}$ ratio for normal lungs.

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An understanding the kinetics of inhaled anesthetic uptake and elimination is fundamental to the clinical practice of anesthesia. Although the impact of different body compartments (*e.g.*, vessel rich group or viscera; muscle group; fat; specific organs) in uptake and elimination kinetics is well-established by many previous studies,[1–19] the role of lung gas exchange efficiency is less appreciated.[2,20–26] Our study examines the role of the global lung ventilation/perfusion ratio ($\dot{V}_A/\dot{Q}$; where ($\dot{V}_A$ represents alveolar minute ventilation and $\dot{Q}$ represents cardiac output value) on the washin and washout kinetics of desflurane and sevoflurane in pigs with normal lungs expected to have a unimodal and narrow $\dot{V}_A/\dot{Q}$ distribution. The global lung $\dot{V}_A/\dot{Q}$ ratio was manipulated by changes in both minute ventilation and cardiac output.

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To assess washin and washout kinetics, we measured anesthetic partial pressures in mixed venous (P_{mv}) and arterial (P_{art}) blood samples at multiple times during uptake and elimination of desflurane and sevoflurane for three different lung $\dot{V}_A/\dot{Q}$ ratios. The benefits of direct measurements of arterial and mixed venous partial pressures in blood, for studies of inhaled anesthetic kinetics, are well recognized.[15,17,24,27,28] Because of the technical difficulties in making these measurements, however, and the invasiveness, the majority of kinetic studies have measured either gas phase samples alone (*e.g.*, end-tidal partial pressure)[4,9–13,19,29–31] or end-tidal partial pressure and P_{art}.[21–23,25,32,33] Direct measurements of P_{art} and P_{mv} provide kinetic information that specifically focuses on pulmonary blood, and are well-suited for examining the role of lung gas exchange in whole-body kinetics. We compared P_{art} and P_{mv} kinetics for different $\dot{V}_A/\dot{Q}$ conditions graphically, and also analyzed the differences in partial pressures between fixed time points. Our primary hypothesis was that the kinetics of P_{art} and P_{mv} washin and washout would be altered by differences in the global $\dot{V}_A/\dot{Q}$ ratio.

The experimental maneuvers we used to alter $\dot{V}_A/\dot{Q}$ could potentially have confounding effects on tissue kinetics that would also impact P_{mv} and P_{art}, independent of the pulmonary effects. To more specifically examine the effect of global $\dot{V}_A/\dot{Q}$ on the pulmonary contribution to washin and washout kinetics, we also assessed the differences between P_{art} and P_{mv} and compared these differences between the three experimental $\dot{V}_A/\dot{Q}$ conditions. Our secondary hypothesis was that an increased global $\dot{V}_A/\dot{Q}$ ratio is associated with increased separation between P_{art} and P_{mv}.

Compared to desflurane, sevoflurane has higher gas solubilities in blood, tissues of the vessel rich group, muscle, and fat, suggesting that desflurane washin and washout should be more rapid than sevoflurane washin and washout.[13,34] Kinetics of desflurane have been confirmed to be faster than sevoflurane in several experimental studies.[13,35,36] The effect of overall lung $\dot{V}_A/\dot{Q}$ ratio, however, on differences in kinetics between sevoflurane and desflurane has not been reported. Our third hypothesis was that kinetics of washin and washout, as assessed by both arterial and mixed venous measurements, are faster for desflurane than for sevoflurane, and that this kinetic difference is maintained at both high and low $\dot{V}_A/\dot{Q}$ ratios.

Materials and Methods

Ethics Approval

The Animal Ethics Committee of Uppsala University (Uppsala, Sweden) approved this prospective nonrandomized animal study. The care and handling of animals were in accordance with the guidelines laid out in the *Guide for the Care and Use of Laboratory Animals, 8th edition*.[37] The estimation of sample size was based on a previous experimental porcine study,[24] which used an analogous experimental setup. Power calculation using a two-sided paired *t* test at a significance level of 5% ($\alpha = 0.05$), a SD of 1.6 min for the time to 90% washin for desflurane,[24] and a power of 80% ($\beta = 0.20$) revealed that at least seven animals were needed to detect a difference of more than 50% (time to 90% washin of 4.4 min for baseline condition; absolute difference from baseline condition of 2.2 min) between the $\dot{V}_A/\dot{Q}$ conditions in the volatile washin period.

Animals

Seven juvenile, 2.5-month-old piglets (weight, mean ± SD 25 ± 2 kg) of Yorkshire/Norwegian country breeds of either sex (five males and two females), were used in the study. The animals fasted overnight with free access to water. The experiments were conducted between 8:00 AM and 3:00 PM. All piglets underwent the same preparatory algorithm (induction and maintenance of anesthesia, monitoring).

Anesthetic Management

As described previously in detail,[24,25] anesthesia was induced by an intramuscular injection of xylazine (2.2 mg/kg; Rompun; Bayer, Germany) and tiletamine/zolazepam (6 mg/kg; Zoletil; Virbac, France). The pigs were placed in the supine position, and the trachea was intubated orally with a 7.0-mm ID cuffed endotracheal tube (Mallinckrodt, Ireland). After testing for hind limb reflex absence, muscle relaxation was induced with an intravenous bolus of 2 mg/kg rocuronium (Esmeron; N.V. Organon, The Netherlands), followed by a continuous infusion of 2.5 mg · kg^{-1} · h^{-1} rocuronium. Anesthesia was maintained by continuous intravenous infusions of fentanyl (0.04 mg · kg^{-1} · h^{-1}; Leptanal; Janssen-Cilag AB, Sweden), midazolam (0.12 mg · kg^{-1} · h^{-1}; midazolam Actavis; Actavis Group, Iceland), and propofol (Diprivan; Astra, Sweden) *via* 18-gauge catheters (Becton Dickinson, Germany) placed in ear veins.

After intubation and during mechanical ventilation, a median tracheotomy was performed, and the orotracheal tube was replaced by a 9-mm ID cuffed endotracheal tube (Mallinckrodt, Ireland). Thereafter, the lungs were mechanically ventilated in volume-controlled mode, with fractional inspired oxygen tension of 0.4 and positive end-expiratory pressure set at 5 cm H_2O by a Servo 900 C ventilator (Maquet Critical Care, Sweden). The tidal volume was set to 10 ml/kg, inspiratory:expiratory ratio was set at 1:2, and respiratory frequencies were adjusted to achieve a normal end-tidal carbon dioxide of 40 to 45 mmHg.

Ventilation variables were measured at the proximal end of the endotracheal tube with a standard anesthesia monitor (SC 9000 XL; Siemens, Germany) and additionally assessed by a $NICO_2$ system that included volumetric capnometry (Respironics Novametrix, Inc., USA). Volatile anesthetic concentrations were monitored continuously with

an infrared analyzer (Capnomac Ultima; Datex Ohmeda, Finland) calibrated to the manufacturer's standards.

A flow-directed pulmonary artery catheter (7.0 French, Swan-Ganz thermodilution catheter; Baxter, USA) and a central venous catheter (4.0 French, Becton-Dickinson Critical Care Systems, Singapore) were inserted *via* the right external jugular vein. The pulmonary artery catheter was used for cardiac output measurements and mixed venous blood sampling. The pulmonary artery catheter was repositioned before each experimental step to ensure that the tip was always located in regions with high pulmonary blood flow. Cardiac output was measured by thermal dilution in duplicate and averaged for every time point for which blood samples were taken for desflurane and sevoflurane measurements.

All pigs received a right carotid arterial catheter for continuous arterial pressure measurements and for blood sampling (20-gauge; Becton-Dickinson Critical Care Systems).

Blood gas analysis was performed immediately after bubble-free blood sampling with standard blood gas electrodes specifically set up to analyze pig blood (ABL 500 and OSM 3; Radiometer, Denmark). Finally, a suprapubic urinary catheter (Sympakath; Ruesch AG, Switzerland) was placed to monitor urine output.

Administration of Simultaneous Inhaled Anesthetics

Sevoflurane and desflurane were administered simultaneously *via* two KION ventilators (Siemens-Elema AB, Sweden) in an open system. The separate KION ventilators and their individual vaporizers were used to prepare controlled fresh gas flows and concentrations of each agent separately, and then the gas streams were combined for delivery to the animal by a third ventilator. Sevoflurane (Sevorane; Abbvie, Sweden) and desflurane (Suprane; Baxter International, USA) were administered with the vaporizers set at 0.3 volume% for sevoflurane and at 1 volume% for desflurane. The two KION ventilators were set to spontaneous breathing with equal fresh gas flow. The inspiratory limbs were connected to a 2.5-l mixing chamber, which connected to the low pressure port of the Servo 900 C ventilator. The total fresh gas flow was set to exceed double minute ventilation to make delivered gas fractions close to inspired gas fractions (0.15 volume% for sevoflurane and 0.5 volume% for desflurane after dilution in the mixing chamber). We used the lowest possible inspired fractions of sevoflurane and desflurane that delivered an acceptable signal-to-noise ratio in the arterial blood. This was done to minimize cardiovascular and pulmonary effects of the volatile agents.

Measurement of Sevoflurane and Desflurane by Micropore Membrane Inlet Mass Spectrometry

Arterial and mixed venous blood samples were collected in glass syringes (5 ml; FORTUNA OPTIMA; Luer-lock, Poulten & Graf GmbH, Germany) coated with EDTA for analysis by micropore membrane inlet mass spectrometry (MMIMS System; Oscillogy LLC, USA). The system uses a polymer membrane confined to multiple small micropores that separate the blood sample from the mass spectrometer and high-vacuum system. As blood samples flow over this membrane, gases diffuse through the membrane into the mass spectrometer for direct analysis of the gas partial pressures in the blood sample.[38,39] Sevoflurane ion currents were measured at the mass/charge ratio of 131. Desflurane ion currents were monitored at a mass/charge ratio of 101 and corrected for spectral overlap from sevoflurane. Before the animal experiments, we assessed spectral overlap in the mass spectrometer using pure, air-diluted desflurane and sevoflurane vapors and found no overlap of desflurane on the sevoflurane 131 peak, but an overlap of 0.337 of the 131 peak for sevoflurane on the 101 peak for desflurane.

Baseline Measurement of Global Alveolar $\dot{V}_A/\dot{Q}$

For each $\dot{V}_A/\dot{Q}$ condition (normal, low, high) during the base line period before inhaled anesthetic administration, data were collected for *post hoc* determination of the global $\dot{V}_A/\dot{Q}$ ratio. Cardiac output was measured in duplicate and averaged. Fifteen volumetric capnometry waveforms, with exclusion of waveforms with obvious artifacts, were selected from 2 min of $NICO_2$ data stored for *post hoc* analysis. The alveolar minute ventilation reported by the $NICO_2$ for each breath was averaged over these 15 breaths. The $NICO_2$ system calculates alveolar minute ventilation as exhaled minute ventilation minus airways and apparatus dead space, as determined by the Fowler method.[40] Averaged alveolar minute ventilation was then divided by averaged cardiac output to calculate $\dot{V}_A/\dot{Q}$ for each baseline period for each pig, and $\dot{V}_A/\dot{Q}$ was averaged across the seven pigs.

Experimental Protocol

Baseline

After an alveolar recruitment maneuver (40 cm H_2O for 10 s) and 30 min of stabilization after instrumentation, baseline hemodynamic, ventilation, and gas exchange data were obtained. After this baseline period, each animal underwent all three $\dot{V}_A/\dot{Q}$ conditions in nonrandomized order (normal, low, high), without blinding.

Normal $\dot{V}_A/\dot{Q}$

At the normal minute ventilation setting and for unmanipulated cardiac output, the inhaled anesthetics were begun at time zero. Arterial and mixed venous blood samples were obtained simultaneously after 0, 1, 2, 5, 10, 20, 30, and 45 min (washin). Thereafter, the inhalation of the volatile agents was discontinued, and the sampling sequence was repeated (washout).

Low Ventilation, High Cardiac Output

After completion of the washout and 15 min of stabilization, a continuous infusion of dobutamine was titrated with the target of doubling the cardiac output. When this goal was reached (mean, 5.4 mcg · kg^{-1} · min^{-1}), the minute ventilation was decreased to 40% of the control state by adjustment of the respiratory rate, keeping the tidal volume constant. The washin and washout sequence was repeated. The dobutamine infusion was discontinued and the minute ventilation normalized.

High Ventilation, Low Cardiac Output

In a final step after a stabilization period of about 30 min, a transfemorally placed Fogarty catheter (8-French; Edwards Lifesciences Nordic AB, Sweden) was inflated in the right atrium to decrease cardiac output, with a target of 30% reduction in cardiac output. The minute ventilation was increased by 40% by adjustment of the respiratory rate, keeping tidal volume constant, and the washin and washout sequence was again repeated.

The experimental protocol is depicted graphically in figure 1.

At the end of each study, the animals were euthanized with an intravenous injection of potassium chloride while under general anesthesia.

Graphic and Statistical Analysis

Hemodynamic and respiratory variables (tables 1 and 2) were tested for normality by the Shapiro–Wilk test (Sigmaplot version 13; Systat Software Inc., USA).

For each individual animal, and each of the three $\dot{V}_A/\dot{Q}$ conditions, arterial (P_{art}) and mixed venous (P_{mv}) mass spectrometer signals from the micropore membrane inlet mass spectrometry by the Micropore Membrane Inlet Mass Spectrometry System were scaled to that individual's arterial signal at the end of the 45-min desflurane and sevoflurane administration. For each $\dot{V}_A/\dot{Q}$ condition, the scaled signals at each time point were averaged across the seven animals and 99% CI determined using the Student's *t* distribution, and plotted as the means and CI for each time and each $\dot{V}_A/\dot{Q}$ condition (figs. 2 and 3). The mean values for washin and washout were also replotted for side-by-side comparisons of the effects of $\dot{V}_A/\dot{Q}$ condition on kinetics (fig. 4), and side-by-side comparisons of desflurane *versus* sevoflurane kinetics (fig. 5).

For each gas, each individual, and each $\dot{V}_A/\dot{Q}$ condition, we calculated the differences in scaled partial pressures between two time points to characterize the shapes of the washin and washout curves. For uptake, the fast phase of washin was characterized by the scaled partial pressure difference between 5 min and 0 min (SPP5-SPP0). The slow phase of washin was characterized by the scaled partial pressure difference between 30 min and 5 min (SPP30-SPP5). For elimination, the fast phase of washout was characterized by the scaled partial pressure difference between 0 min and 5 min (SPP0-SPP5). The slow phase of washout was characterized by the scaled partial pressure difference between 5 min and 30 min (SPP5-SPP30). Means and 95% CIs for these shape parameters are plotted in figure 6.

Secondary analysis of the scaled partial pressure differences was carried out by two-way ANOVA for repeated measures (Sigmaplot version 13; table 3). Individual analyses were carried out for each phase of washin or washout (fast phase and slow phase), for uptake and elimination, and for arterial and mixed venous measurements, yielding eight total analyses. Data sets were first tested for normality (Shapiro–Wilk) and equal variance (Brown–Forsythe), and all data sets passed both tests. Two-way ANOVA (first factor gas with two levels; second factor $\dot{V}_A/\dot{Q}$ condition, with three levels) for repeated measures (seven pigs) was carried out, and if significant differences ($P < 0.05$) were found, all-pairwise multiple comparison procedures were carried out *post hoc* (Holm–Sidak method). Significant differences are labeled in figure 6.

For each gas and each $\dot{V}_A/\dot{Q}$ condition, differences between P_{art} and P_{mv} were calculated at each time point (fig. 7). Areas under the ($P_{art} - P_{mv}$) *versus* time curves were

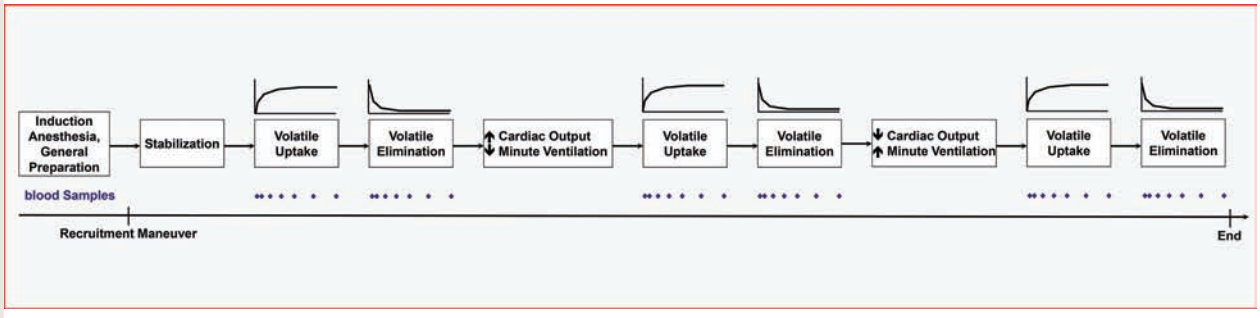

Fig. 1. Schematic of experimental protocol.

Table 1. Hemodynamic, Ventilation, and Gas Exchange Data—Uptake

	Normal $\dot{V}_A/\dot{Q}$			Low $\dot{V}_A/\dot{Q}$			High $\dot{V}_A/\dot{Q}$		
	0 Min	5 Min	30 Min	0 Min	5 Min	30 Min	0 Min	5 Min	30 Min
Hemodynamics									
CO, l/min	3.6 ± 0.8	3.5 ± 0.6	3.3 ± 0.7	6.6 ± 0.5	6.8 ± 0.4	6.5 ± 0.6	2.6 ± 0.3	2.4 ± 0.3	2.2 ± 0.2
MAP, mmHg	82 ± 10	76 ± 11	67 ± 11	84 ± 9	88 ± 6	83 ± 4	45 ± 2	45 ± 4	43 ± 2
MPAP, mmHg	22 ± 2	22 ± 2	22 ± 4	27 ± 3	29 ± 3	29 ± 3	21 ± 5	19 ± 2	18 ± 2
CVP, mmHg	11 ± 3	11 ± 1	11 ± 2	11 ± 2	11 ± 2	12 ± 2	10 ± 2	9 ± 1	9 ± 2
HR, 1/min	98 ± 12	89 ± 11	80 ± 16	123 ± 29	138 ± 19	130 ± 21	110 ± 17	113 ± 21	145 ± 37
Ventilation									
RR, 1/min	21 ± 1	21 ± 1	21 ± 1	15 ± 1	15 ± 0	15 ± 1	30 ± 1	30 ± 1	30 ± 1
$\dot{V}_E$, l/min	5.7 ± 0.6	5.9 ± 0.7	5.9 ± 0.7	3.8 ± 0.2	3.9 ± 0.3	3.9 ± 0.2	8.2 ± 0.4	8.3 ± 0.4	8.3 ± 0.4
Alveolar minute ventilation, l/min	3.0 ± 0.3	—	—	1.9 ± 0.4	—	—	3.8 ± 0.4	—	—
V_T, ml	278 ± 24	282 ± 23	283 ± 26	236 ± 31	250 ± 13	253 ± 17	275 ± 11	278 ± 9	279 ± 11
P_{MAX}, cm H_2O	19.1 ± 1.6	19.3 ± 1.4	19.9 ± 0.9	18.9 ± 1.9	19 ± 1.8	19.3 ± 1.5	21.7 ± 1.6	22.1 ± 1.8	22.7 ± 1.6
P_{MEAN}, cm H_2O	9.4 ± 0.8	9.7 ± 0.5	9.7 ± 0.5	9.1 ± 0.7	9.1 ± 0.7	9.1 ± 0.7	10.4 ± 0.5	10.3 ± 0.5	10.6 ± 0.5
PEEP, cm H_2O	5.9 ± 0.4	6 ± 0	5.9 ± 0.4	6.1 ± 0.7	5.9 ± 0.4	5.9 ± 0.4	6.1 ± 0.7	6 ± 0	5.9 ± 0.4
C_{dyn}, ml/cm H_2O	26 ± 4	25 ± 4	24 ± 2	23 ± 3	24 ± 2	22 ± 2	23 ± 3	22 ± 3	20 ± 3
Gas exchange									
Pao_2, mmHg	195 ± 8	187 ± 14	182 ± 10	134 ± 12	135 ± 11	133 ± 14	180 ± 9	164 ± 21	158 ± 12
$Paco_2$, mmHg	51 ± 5	50 ± 5	54 ± 5	68 ± 7	71 ± 8	78 ± 12	42 ± 3	43 ± 6	44 ± 5
P_{ETCO_2}, mmHg	49 ± 5	47 ± 5	46 ± 6	68 ± 14	68 ± 14	70 ± 14	39 ± 2	37 ± 3	37 ± 4
Sao_2, %	97 ± 1	98 ± 1	97 ± 1	96 ± 1	96 ± 1	95 ± 1	98 ± 1	97 ± 1	97 ± 1
Pvo_2, mmHg	42 ± 1	40 ± 5	38 ± 7	53 ± 3	56 ± 4	45 ± 22	26 ± 3	23 ± 2	22 ± 2
$Pvco_2$, mmHg	67 ± 11	69 ± 7	72 ± 8	73 ± 6	80 ± 7	83 ± 5	69 ± 12	66 ± 12	73 ± 13
Svo_2, %	57 ± 4	51 ± 8	46 ± 12	72 ± 11	68 ± 2	66 ± 3	21 ± 8	18 ± 5	15 ± 5

All data passed the Shapiro–Wilk W test for normality and are presented as mean ± SD.

C_{dyn}, dynamic compliance; CO, cardiac output; CVP, central venous pressure; HR, heart rate; MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; $Paco_2$, arterial carbon dioxide tension; Pao_2, arterial oxygen tension; PEEP, positive end-expiratory pressure; P_{ETCO_2}, end-tidal pressure of carbon dioxide; P_{MAX}, peak airway pressure; P_{MEAN}, mean airway pressure; $Pvco_2$, mixed venous carbon dioxide tension; Pvo_2, mixed venous oxygen tension; RR, respiratory rate; Sao_2, arterial oxygen saturation; Svo_2, mixed venous oxygen saturation; $\dot{V}_E$, minute ventilation; V_T, tidal volume; $\dot{V}_A/\dot{Q}$, ventilation/perfusion ratio.

calculated by the trapezoidal rule, and the areas were analyzed by two-way ANOVA for repeated measures (table 4). If significant differences ($P < 0.05$) were found, all pairwise multiple comparison procedures were carried out *post hoc* (Holm–Sidak method).

Arterial scaled partial pressure data were also analyzed by t90 and t10 analyses (table 5). For each animal, each gas, and each $\dot{V}_A/\dot{Q}$ condition, data points for scaled arterial signals during uptake were connected with straight line segments, and then the time point corresponding to the scaled signal reaching 0.90 (t90) was determined from this curve. Similarly, data points for scaled arterial signals during elimination were connected with straight line segments, and then the time point corresponding to the scaled signal reaching 0.10 (t10) was determined from this curve. Differences in means between desflurane *versus* sevoflurane, and between $\dot{V}_A/\dot{Q}$ conditions, were assessed by two-way repeated measures ANOVA.

Results

All seven piglets that entered the study completed the entire study. All measurements of arterial and mixed venous desflurane and sevoflurane partial pressures were completed at all time points, and there were no rejections for artifact.

Table 1 presents the hemodynamic, ventilation and respiratory mechanics, and gas exchange data for the three $\dot{V}_A/\dot{Q}$ conditions for three time points: the beginning of uptake, 5 min into uptake, and 30 min into uptake (45 min into uptake = time 0 for elimination and is presented in table 2). Table 2 presents data for time points in the elimination period. The hemodynamics, respiratory mechanics, and gas exchange were stable over the uptake and elimination of desflurane and sevoflurane (administered simultaneously) and were not systematically affected by the changing inhaled anesthetic concentrations at these low doses. Compared to the normal $\dot{V}_A/\dot{Q}$ condition, dobutamine administration increased cardiac output from 3.3 l/min to 6.5 l/min in the low $\dot{V}_A/\dot{Q}$ condition, and reduction of respiratory rate decreased alveolar minute ventilation from 2.9 l/min to 2.0 l/min. In the high $\dot{V}_A/\dot{Q}$ condition, inflation of the atrial balloon reduced cardiac output to 2.2 l/min, and the increase in respiratory rate increased alveolar minute ventilation to 3.7 l/min.

The kinetics of desflurane partial pressures in arterial and mixed venous blood during washin are shown in figure 2, top (fig. 2A to 2C), for the three conditions of $\dot{V}_A/\dot{Q}$: (1) normal $\dot{V}_A/\dot{Q}$ of 0.91; (2) low $\dot{V}_A/\dot{Q}$ of 0.32; and (3) high

Table 2. Hemodynamic, Ventilation and Gas Exchange Data—Elimination

	Normal $\dot{V}_A/\dot{Q}$			Low $\dot{V}_A/\dot{Q}$			High $\dot{V}_A/\dot{Q}$		
	0 Min	5 Min	45 Min	0 Min	5 Min	45Min	0 Min	5 Min	45 Min
Hemodynamics									
CO, l/min	3.3 ± 0.6	3.7 ± 0.7	3.6 ± 0.2	6.5 ± 0.5	5.9 ± 1.6	6.6 ± 0.3	2.2 ± 0.2	2.1 ± 0.2	2.1 ± 0.2
MAP, mmHg	73 ± 11	74 ± 10	73 ± 10	85 ± 3	84 ± 4	90 ± 3	45 ± 3	46 ± 4	44 ± 4
MPAP, mmHg	22 ± 3	22 ± 3	23 ± 1	28 ± 2	26 ± 11	30 ± 3	18 ± 2	19 ± 3	21 ± 2
CVP, mmHg	11 ± 1	12 ± 1	12 ± 2	12 ± 3	12 ± 3	11 ± 2	9 ± 2	9 ± 1	9 ± 1
HR, 1/min	83 ± 16	83 ± 13	81 ± 10	131 ± 23	126 ± 17	136 ± 21	161 ± 34	169 ± 35	190 ± 34
Ventilation									
RR, 1/min	21 ± 1	21 ± 1	21 ± 1	15 ± 1	15 ± 0	15 ± 1	30 ± 1	30 ± 1	30 ± 1
$\dot{V}_E$, l/min	5.9 ± 0.7	5.8 ± 0.6	5.8 ± 0.6	3.9 ± 0.2	3.8 ± 0.2	3.8 ± 0.3	8.2 ± 0.4	8.2 ± 0.4	8.2 ± 0.3
Alveolar minute ventilation, l/min	2.9 ± 0.3	—	—	2.0 ± 0.2	—	—	3.7 ± 0.4	—	—
V_T, ml	281 ± 25	277 ± 28	276 ± 26	252 ± 15	246 ± 15	246 ± 16	276 ± 12	273 ± 12	272 ± 11
P_{MAX}, cm H_2O	21 ± 1	21 ± 1	21 ± 2	19 ± 2	19 ± 2	20 ± 2	22 ± 2	23 ± 2	24 ± 1
P_{MEAN}, cm H_2O	9.9 ± 0.4	9.9 ± 0.4	9.9 ± 0.4	9.3 ± 0.8	9.6 ± 0.8	9.9 ± 0.7	10.6 ± 0.5	10.7 ± 0.5	10.7 ± 0.5
PEEP, cm H_2O	5.9 ± 0.4	5.9 ± 0.4	6.0 ± 0.6	5.7 ± 0.5	5.9 ± 0.4	5.9 ± 0.4	5.9 ± 0.4	5.9 ± 0.4	5.9 ± 0.4
C_{dyn}, ml/cm H_2O	23 ± 3	22 ± 2	22 ± 2	22 ± 2	22 ± 2	21 ± 2	20 ± 2	16 ± 8	18 ± 2
Gas exchange									
Pa_{O_2}, mmHg	179 ± 12	182 ± 18	184 ± 17	132 ± 12	130 ± 13	128 ± 14	154 ± 20	160 ± 22	163 ± 22
Pa_{CO_2}, mmHg	53 ± 7	53 ± 7	51 ± 3	74 ± 6	79 ± 6	73 ± 9	42 ± 5	43 ± 6	42 ± 4
P_{ETCO_2}, mmHg	48 ± 6	48 ± 5.	48 ± 5	70 ± 14	71 ± 15	71 ± 15	37 ± 3	37 ± 3	37 ± 3
Sa_{O_2}, %	97 ± 1	97 ± 1	97 ± 1	95 ± 1	95 ± 1	95 ± 1	97 ± 1	97 ± 1	97 ± 1
Pv_{O_2}, mmHg	38 ± 7	39 ± 8	37 ± 4	55 ± 4	47 ± 23	53 ± 3	22 ± 2	24 ± 3	23 ± 3
Pv_{CO_2}, mmHg	68 ± 7	70 ± 5	69 ± 5	87 ± 7	92 ± 16	82 ± 8	70 ± 12	71 ± 10	70 ± 10
Sv_{O_2}, %	48 ± 14	48 ± 14	46 ± 8	65 ± 3	65 ± 3	65 ± 4	14 ± 5	16 ± 5	13 ± 3

All data passed the Shapiro–Wilk W test for normality and are presented as mean ± SD.

C_{dyn}, dynamic compliance; CO, cardiac output; CVP, central venous pressure; HR, heart rate; MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; Pa_{CO_2}, arterial carbon dioxide tension; Pa_{O_2}, arterial oxygen tension; PEEP, positive end-expiratory pressure; P_{ETCO_2}, end-tidal pressure of carbon dioxide; P_{MAX}, peak airway pressure; P_{MEAN}, mean airway pressure; Pv_{CO_2}, mixed venous carbon dioxide tension; Pv_{O_2}, mixed venous oxygen tension; RR, respiratory rate; Sa_{O_2}, arterial oxygen saturation; Sv_{O_2}, mixed venous oxygen saturation; $\dot{V}_E$, minute ventilation; V_T, tidal volume; $\dot{V}_A/\dot{Q}$, ventilation/perfusion ratio.

$\dot{V}_A/\dot{Q}$ of 1.73. The arterial and mixed venous data for desflurane partial pressures during washout are shown in figure 2, bottom (fig. 2D to 2F). Sevoflurane washin and washout data are shown in figure 3.

Side-by-side comparisons of the results for all three $\dot{V}_A/\dot{Q}$ conditions are presented in figure 4, where lines connecting the mean values are shown without CI or symbols to enhance readability. For desflurane (fig. 4A), for washin, the experimental interventions that altered $\dot{V}_A/\dot{Q}$ slowed arterial increases toward equilibrium for both interventions, with more slowing for the low $\dot{V}_A/\dot{Q}$ condition. Washin kinetics as measured in mixed venous blood were also slowed by both interventions, with more slowing for the high $\dot{V}_A/\dot{Q}$ condition. For desflurane washout, compared to normal $\dot{V}_A/\dot{Q}$, low $\dot{V}_A/\dot{Q}$ slowed arterial kinetics, and high $\dot{V}_A/\dot{Q}$ accelerated arterial kinetics. The mixed venous kinetics, however, were slowed by both $\dot{V}_A/\dot{Q}$ perturbations, in the low $\dot{V}_A/\dot{Q}$ condition paralleling the slower arterial washout, and in the high $\dot{V}_A/\dot{Q}$ condition contrasting the faster arterial washout.

For sevoflurane (fig. 4B), the low $\dot{V}_A/\dot{Q}$ condition slowed arterial washin compared to normal $\dot{V}_A/\dot{Q}$, whereas high $\dot{V}_A/\dot{Q}$ had little effect on arterial washin. Compared to normal $\dot{V}_A/\dot{Q}$, neither intervention had much effect on mixed venous washin kinetics. For sevoflurane washout, very similar to the desflurane results, high $\dot{V}_A/\dot{Q}$ accelerated arterial kinetics, and low $\dot{V}_A/\dot{Q}$ slowed arterial kinetics, whereas both interventions slowed mixed venous kinetics.

Side-by-side visual comparisons of desflurane and sevoflurane are presented in figure 5, where lines connecting the mean values are shown without CI or symbols to enhance readability. In nearly all side-by-side comparisons, desflurane kinetics were slightly faster than sevoflurane kinetics, with two exceptions: the kinetics were nearly equivalent for mixed venous washin in the low $\dot{V}_A/\dot{Q}$ condition, and mixed venous washin was slightly faster for sevoflurane than for desflurane in the high $\dot{V}_A/\dot{Q}$ condition.

Figure 6A shows the mean and CI, for the uptake period, for the scaled partial pressure difference between 5 min and 0 min (SPP5-SPP0, the fast phase shape parameter for uptake) as influenced by gas (sevoflurane *vs.* desflurane), sample site (arterial *vs.* mixed venous), and $\dot{V}_A/\dot{Q}$ condition (normal, low, or high). For arterial samples, the order of magnitude for SPP5-SPP0 compared between $\dot{V}_A/\dot{Q}$ conditions was normal ≈ high > low for both gases, where a larger SPP5-SPP0 indicates faster kinetics. For desflurane washin, the SPP5-SPP0 values were 0.70 ± 0.10, 0.93 ± 0.08, and 0.82 ± 0.07 for the low, normal, and high $\dot{V}_A/\dot{Q}$ conditions (mean ± 95% CI). For sevoflurane washin, the SPP5-SPP0 values were 0.55 ± 0.06, 0.77 ± 0.04, and 0.75

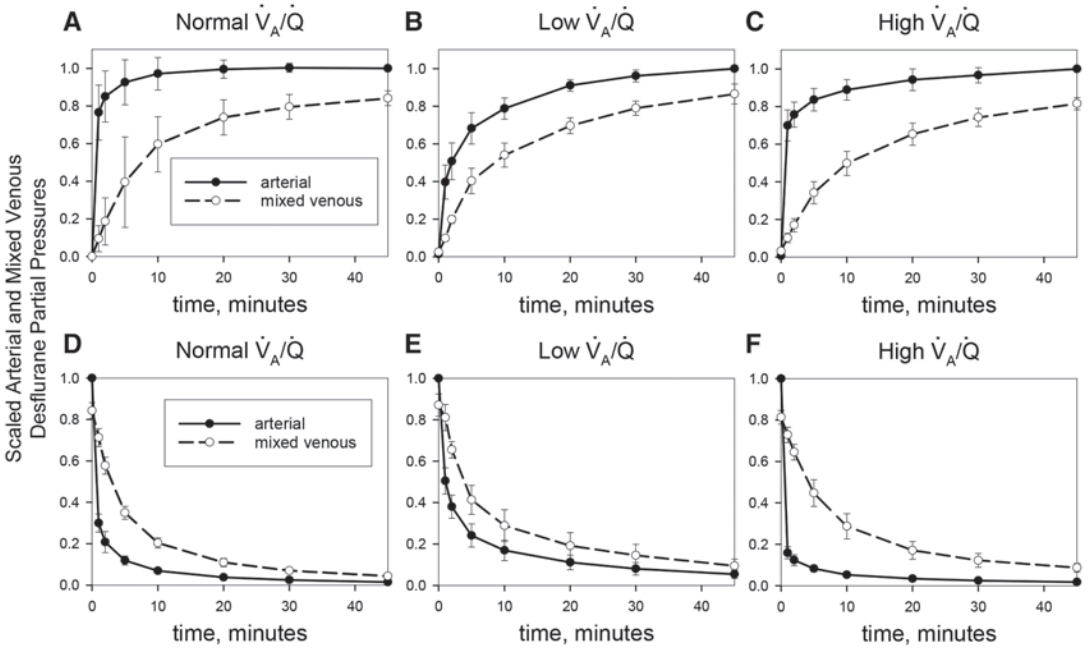

Fig. 2. Scaled desflurane partial pressures in arterial blood (*solid line* and *filled circles*) and mixed venous blood (*dashed line* and *open circles*) during the uptake period (*upper, A to C*), for the three ventilation/perfusion ratio ($\dot{V}_A/\dot{Q}$) conditions (normal, low, and high). Mean values for seven pigs, with 99% CI; no excluded data points. Partial pressures for each pig are scaled to the arterial partial pressure at the end of uptake (45 min) for that pig. Scaled desflurane partial pressures during the elimination period are shown in the *lower* panels (*D to F*). No excluded data points. Partial pressures for each pig are scaled to the arterial partial pressure at the end of uptake (45 min) for that pig.

± 0.08 for the low, normal, and high $\dot{V}_A/\dot{Q}$ conditions. The ANOVA analysis found that for both gases, the high $\dot{V}_A/\dot{Q}$ group SPP5-SPP0 was significantly different from low, and the normal $\dot{V}_A/\dot{Q}$ was significantly different from low. The normal $\dot{V}_A/\dot{Q}$ was significantly different from high $\dot{V}_A/\dot{Q}$ for desflurane but not for sevoflurane. As assessed by the arterial samples, desflurane washin was faster than sevoflurane washin, an effect found to be significant in the ANOVA analysis. For the mixed venous samples, for desflurane, the order of SPP5-SPP0 was normal > low > high, and all three differences were significant in the ANOVA analysis. The $\dot{V}_A/\dot{Q}$ condition made little difference to the magnitude of SPP5-SPP0 for sevoflurane, for mixed venous measurements. As assessed by the mixed venous samples, desflurane washin kinetics were faster than sevoflurane washin kinetics, a difference identified as statistically significant in the ANOVA analysis.

Figure 6B shows the mean and CI, for the uptake period, for the scaled partial pressure difference between 30 min and 5 min (SPP30-SPP5, the slow phase shape parameter for uptake). For arterial samples, the order of magnitude for SPP30-SPP5 compared between $\dot{V}_A/\dot{Q}$ conditions was low > high ≈ normal for both gases. The ANOVA analysis found that for both gases, the normal $\dot{V}_A/\dot{Q}$ group SPP30-SPP5 was significantly different from low, and for sevoflurane, the high $\dot{V}_A/\dot{Q}$ was significantly different from low. As assessed by the arterial samples, sevoflurane washin was slightly faster than desflurane washin, an effect that was statistically significant in the ANOVA analysis. For the mixed venous samples, for desflurane, the order of SPP30-SPP5 was high > low > normal, but the differences were small. $\dot{V}_A/\dot{Q}$ condition made little difference to the magnitude of SPP30-SPP5 for sevoflurane, for mixed venous measurements. As assessed by the mixed venous samples, sevoflurane washin kinetics were faster than desflurane washin kinetics, and this difference was statistically significant in the ANOVA analysis.

Figure 6C shows the mean and CI, for the elimination period, for the scaled partial pressure difference between 0 minutes and 5 minutes (SPP0-SPP5, the fast phase shape parameter for elimination). For arterial samples, the order of magnitude for SPP0-SPP5 compared between $\dot{V}_A/\dot{Q}$ conditions was high > normal > low for both gases. For desflurane washout, the SPP0-SPP5 values were 0.76 ± 0.04, 0.88 ± 0.02, and 0.92 ± 0.01 for the low, normal, and high $\dot{V}_A/\dot{Q}$ conditions (mean ± 95% CI). For sevoflurane washout, the SPP0-SPP5 values were 0.79 ± 0.05, 0.85 ± 0.03, and 0.90 ± 0.03 for the low, normal, and high $\dot{V}_A/\dot{Q}$ conditions. All three differences (normal *vs.* low, normal *vs.* high, and high *vs.* low), for sevoflurane, were statistically significant in the ANOVA analysis. For desflurane, normal *versus* low and

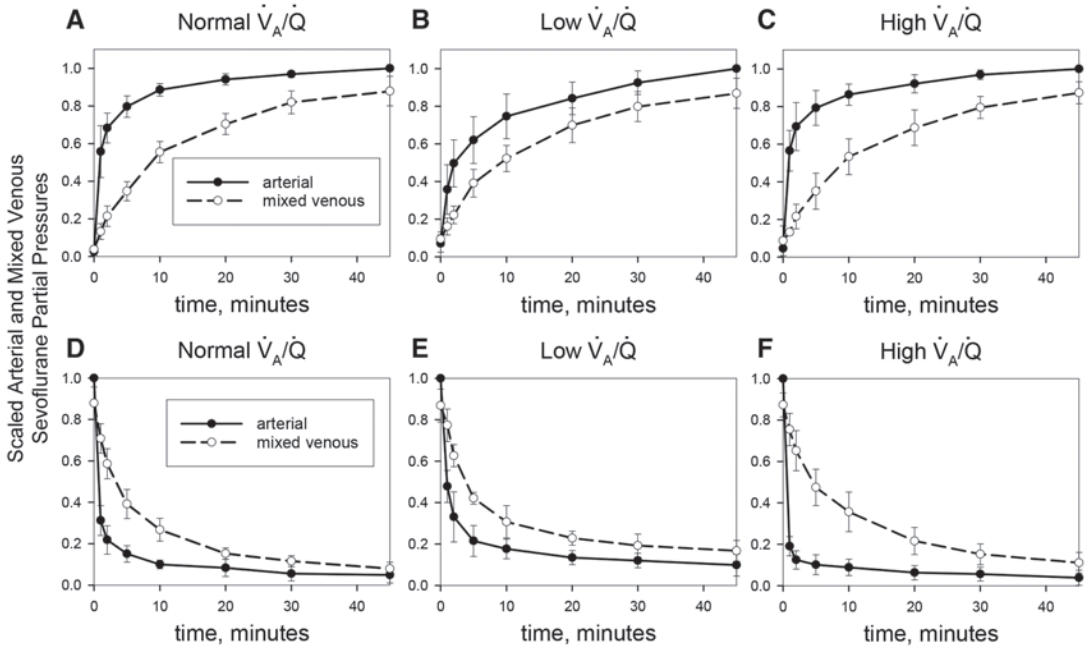

Fig. 3. Scaled sevoflurane partial pressures in arterial blood (*solid line* and *filled circles*) and mixed venous blood (*dashed line* and *open circles*) during the uptake period (*upper, A to C*), for the three ventilation/perfusion ratio ($\dot{V}_A/\dot{Q}$) conditions (normal, low, and high). Mean values for seven pigs, with 99% CI; no excluded data points. Partial pressures for each pig are scaled to the arterial partial pressure at the end of uptake (45 min) for that pig. Scaled sevoflurane partial pressures during the elimination period are shown in the *lower* panels (*D to F*). No excluded data points. Partial pressures for each pig are scaled to the arterial partial pressure at the end of uptake (45 min) for that pig.

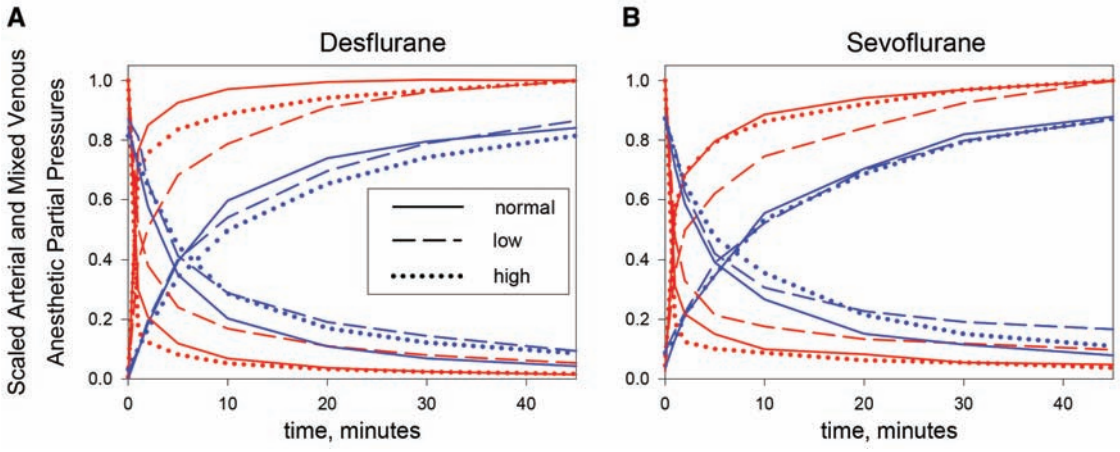

Fig. 4. Side-by-side comparisons of the effects of ventilation/perfusion ratio ($\dot{V}_A/\dot{Q}$) conditions on washin and washout curves for desflurane (*A*) and sevoflurane (*B*). For clarity, the CI and symbols from figures 2 and 3 are omitted, and only the lines connecting time points are presented. Normal $\dot{V}_A/\dot{Q}$ is represented with *solid lines*, low $\dot{V}_A/\dot{Q}$ with *dashed lines*, and high $\dot{V}_A/\dot{Q}$ with *dotted lines*. Arterial measurements are represented in *red*, and mixed venous measurements are represented in *blue*.

high *versus* low were significantly different. As assessed by the arterial samples, desflurane washout speed was approximately equal to the speed of sevoflurane washout, with no significant difference in the ANOVA analysis. For the mixed venous samples, for both gases, the order of SPP0-SPP5 was normal > low > high, but the differences were small, and none of the differences between the $\dot{V}_A/\dot{Q}$ groups were significant for either gas. As assessed by the mixed venous

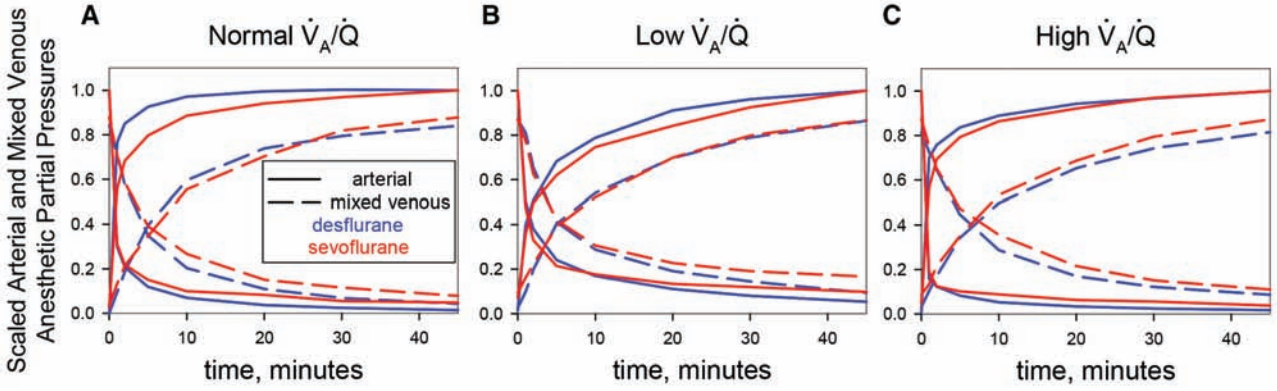

Fig. 5. Side-by-side comparisons of uptake and elimination kinetics for desflurane *versus* sevoflurane, for the three ventilation/perfusion ratio ($\dot{V}_A/\dot{Q}$) conditions. For clarity, the CI and symbols from figures 2 and 3 are omitted, and only the lines connecting time points are presented. Desflurane in *blue*, sevoflurane in *red*; arterial measurements represented by *solid lines*, mixed venous by *dashed lines*.

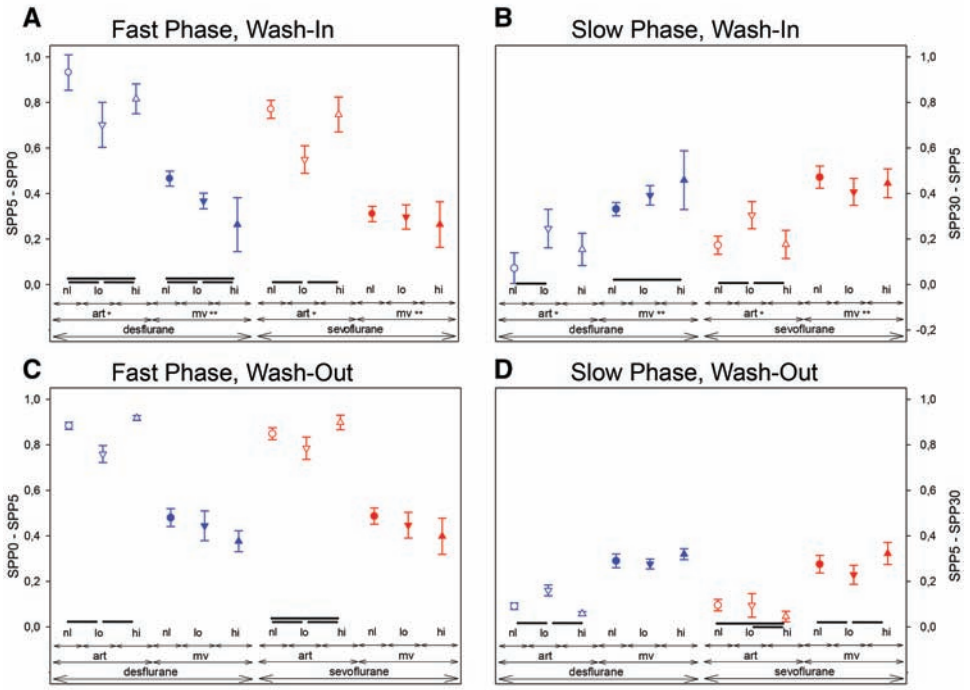

Fig. 6. Means and 95% CIs for the curve shape parameters describing the fast and slow phases of washin and washout. The fast phases of washin curves are characterized by the difference in scaled partial pressure between 5 min and 0 min (SPP5-SPP0; *A, upper left*). The slow phases of washin curves are characterized by the difference in scaled partial pressure between 30 min and 5 min (SPP30-SPP5; *B, upper right*). For washout (*lower, C and D*), fast and slow phases are characterized by SPP0-SPP5 (*C, lower left*), and SPP5-SPP30 (*D, lower right*). "nl, lo, hi" represent the ventilation/perfusion ratio ($\dot{V}_A/\dot{Q}$) condition (normal, low, and high $\dot{V}_A/\dot{Q}$) . The $\dot{V}_A/\dot{Q}$ condition is also encoded by symbol shape: *circle* = normal, *inverted triangle* = low, *triangle* = high. "art" = arterial measurements, "mv" = mixed venous measurements, also encoded in the symbols (*open* = arterial, *filled* = mixed venous). Desflurane in *blue*, sevoflurane in *red. Overhead lines* connecting $\dot{V}_A/\dot{Q}$ conditions signify significant differences ($P < 0.05$) between the conditions from the ANOVA analysis. *Significant differences ($P < 0.05$) between desflurane and sevoflurane from the ANOVA analyses of arterial samples. **Significant differences ($P < 0.05$) between desflurane and sevoflurane from the ANOVA analyses of mixed venous samples.

Table 3. Results of the Two-way Repeated Measures ANOVA for Arterial and Mixed Venous Shape Parameters for Washin and Washout of the Anesthesia Gases

		Washin						Washout					
		Arterial			Mixed Venous			Arterial			Mixed Venous		
Source of Variation	Degrees of Freedom	Mean Square	F Ratio	*P* Value	Mean Square	F Ratio	*P* Value	Mean Square	F Ratio	*P* Value	Mean Square	F Ratio	*P* Value
SPP5 – SPP0 (fast phase shape parameter)													
Subject	6	0.009			0.007			0.0006			0.008		
Gas	1	0.17	60.5	< 0.001	0.06	10.7	0.017	0.0009	0.57	0.479	0.001	0.62	0.462
$\dot{V}_A/\dot{Q}$	2	0.19	21.7	< 0.001	0.05	9.36	0.004	0.07	69.6	< 0.001	0.03	7.58	0.007
Gas × $\dot{V}_A/\dot{Q}$	2	0.009	2.27	0.145	0.02	3.68	0.057	0.004	2.61	0.114	0.0003	0.18	0.838
SPP30 – SPP5 (slow phase shape parameter)													
Subject	6	0.006			0.006			0.0006			0.002		
Gas	1	0.04	23.9	0.003	0.02	6.06	0.049	0.007	4.61	0.076	0.004	3.29	0.12
$\dot{V}_A/\dot{Q}$	2	0.09	11.3	0.002	0.01	1.70	0.224	0.02	32.7	< 0.001	0.02	10.6	0.002
Gas × $\dot{V}_A/\dot{Q}$	2	0.005	1.55	0.252	0.02	4.98	0.027	0.005	4.09	0.044	0.002	1.88	0.195

Gas, levels of gas, either desflurane or sevoflurane; $\dot{V}_A/\dot{Q}$, levels of ventilation/perfusion ratio, either normal, low, or high; gas × $\dot{V}_A/\dot{Q}$, interaction of gas and $\dot{V}_A/\dot{Q}$.

samples, speeds of sevoflurane and desflurane washout were approximately equal.

Figure 6D shows the mean and CI, for the elimination period, for the scaled partial pressure difference between 5 min and 30 min (SPP5-SPP30, the slow phase shape parameter for elimination). For arterial desflurane samples, the order of magnitude for SPP5-SPP30 was low > normal > high, and the normal *versus* low and high *versus* low comparisons were identified as significant in the ANOVA analysis. For arterial sevoflurane samples, the order of magnitude for SPP5-SPP30 was normal ≈ low > high, and the normal *versus* high and low *versus* high comparisons were identified as significant in the ANOVA analysis. For the mixed venous samples, the order of magnitude for SPP5-SPP30 compared between $\dot{V}_A/\dot{Q}$ conditions was high > normal > low, for both gases, but the differences were small, and only for sevoflurane were the normal *versus* low and high *versus* low differences significant. As assessed by both arterial and mixed venous samples, desflurane and sevoflurane washout had similar slow phase kinetics.

Table 3 presents the two-way repeated measures ANOVA analyses of the data in figure 6.

Figure 7, upper (fig. 7A to 7C), presents the results for the arterial-mixed venous differences in anesthetic partial pressure *versus* time ($P_{art} - P_{mv}$) for the uptake period. Figure 7, lower (fig. 7D to 7F), presents the results for the partial pressure differences *versus* time ($P_{mv} - P_{art}$) for the elimination period. Table 4 presents the areas under the curves for these plots and the results for two-way repeated measures ANOVA analysis of these area-under-the-curve results. There was an association between higher $\dot{V}_A/\dot{Q}$ and more separation between the arterial and mixed venous partial pressures for both washin and washout.

All data points were included for every plot for figures 2 to 7 and for their ANOVA analyses (tables 3 and 4)

Table 5 shows the results of the t90 (time for the scaled signal to reach 90% of its final value, on uptake) and t10 (time for the scaled signal to reach 10% of its initial value, on elimination) analyses for the arterial washin and washout data. For table 5, all animal subjects, $\dot{V}_A/\dot{Q}$ groups, and data points were included for the washin t90 ANOVA analysis. For the t10 washout analysis, three animals in the low $\dot{V}_A/\dot{Q}$ group did not reach 10% at 45 minutes, and these data points were excluded from the analysis. The remaining t10 data points passed tests for normality and equal variance after log transformation, and two-way repeated measures ANOVA was carried out on the log-transformed data.

Discussion

Our study experimentally examined the effects of global lung $\dot{V}_A/\dot{Q}$, for normal lungs, expected to have a unimodal and narrow $\dot{V}_A/\dot{Q}$ distribution, on the arterial and mixed venous kinetics of desflurane and sevoflurane during uptake and elimination. Previous studies that have explored the

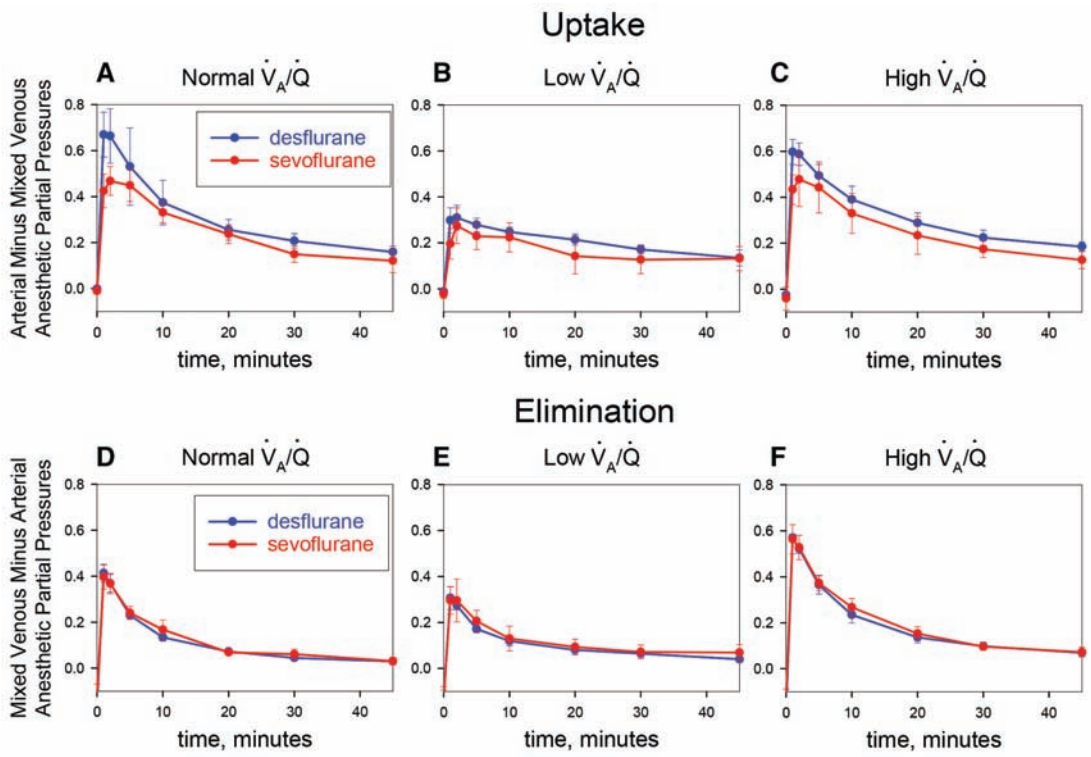

Fig. 7. Arterial minus mixed venous scaled partial pressure differences during the uptake period (*upper, A to C*), for the three ventilation/perfusion ratio ($\dot{V}_A/\dot{Q}$) conditions (normal, low, and high). Mixed venous minus arterial scaled partial pressure differences during the elimination period are shown in the *lower* panels (*D to F*). Desflurane represented in *blue*, sevoflurane in *red*. Mean values and 95% CIs, no outliers excluded.

effects of lung gas exchange inefficiency on uptake and elimination kinetics have focused on $\dot{V}_A/\dot{Q}$ distribution abnormalities, including shunt,[20,21,23] dead space,[22] and other types of abnormal $\dot{V}_A/\dot{Q}$ distributions.[20,24–26] Also, some previous experimental and mathematical modeling studies have investigated the effects of individual changes in minute ventilation or cardiac output on anesthetic kinetics,[2,6–8,14,15,30,41,42] or parallel changes in both cardiac output and minute ventilation.[5]

The interventions that produced the three different $\dot{V}_A/\dot{Q}$ conditions (normal, low, and high $\dot{V}_A/\dot{Q}$) caused marked changes in the time course of P_{art} and P_{mv} for both washin and washout (figs. 2 to 4), suggesting that the global $\dot{V}_A/\dot{Q}$ ratio has an important impact on uptake and elimination kinetics. The majority of the scaled partial pressure differences between 0 and 5 minutes, and between 5 and 30 minutes, were substantially different between the $\dot{V}_A/\dot{Q}$ conditions (fig. 6), supporting the visual impression from figures 2 to 4 that $\dot{V}_A/\dot{Q}$ markedly affects washin and washout kinetics.

Although individual comparisons between different experimental conditions (desflurane *vs.* sevoflurane; normal *vs.* low *vs.* high $\dot{V}_A/\dot{Q}$; arterial *vs.* mixed venous measurements; uptake period *vs.* elimination period; and fast *vs.* slow phases) are complex and vary with the individual comparisons, several general features emerge from the data presented in figures 4 to 6. First, desflurane was generally faster than sevoflurane, most prominently for arterial measurements during washin (figs. 5 and 6A). The desflurane–sevoflurane kinetic differences were also observed for the slow phase of washout (fig. 5) for both arterial and mixed venous measurements.

Second, the experimental interventions to create the different $\dot{V}_A/\dot{Q}$ conditions generally had a substantial impact on the anesthetic kinetics, most prominently for arterial measurements for both washin and washout. Compared to the normal $\dot{V}_A/\dot{Q}$ condition, the low $\dot{V}_A/\dot{Q}$ condition decreased the differences in scaled arterial partial pressures between 0 and 5 minutes, whereas the high $\dot{V}_A/\dot{Q}$ condition increased these differences from the low $\dot{V}_A/\dot{Q}$ value to a value approaching or exceeding the value for normal $\dot{V}_A/\dot{Q}$.

Third, the assessment of anesthetic kinetics from mixed venous measurements produces different results than assessment from arterial measurements. Mixed venous kinetics were not only slower than arterial kinetics for both washin and washout but also less influenced by $\dot{V}_A/\dot{Q}$ (fig. 4).

Our experimental design prioritized the creation of a wide range of global $\dot{V}_A/\dot{Q}$ for assessing the effects of $\dot{V}_A/\dot{Q}$

Table 4. Two-way Repeated Measures ANOVA Analysis of the Area under the Curve for Washin ($P_{art} - P_{mv}$) and Washout ($P_{mv} - P_{art}$) and Pairwise Multiple Comparison (Holm–Sidak)

	Desflurane Normal $\dot{V}_A/\dot{Q}$	Desflurane Low $\dot{V}_A/\dot{Q}$	Desflurane High $\dot{V}_A/\dot{Q}$	Sevoflurane Normal $\dot{V}_A/\dot{Q}$	Sevoflurane Low $\dot{V}_A/\dot{Q}$	Sevoflurane High $\dot{V}_A/\dot{Q}$
Uptake						
AUC mean, min	13.27	9.17	13.73	10.79	7.33	11.07
Two-way repeated measures ANOVA for AUC $P_{art} - P_{mv}$						
Source of Variation	Degrees of freedom	Type III sum of squares	Mean square	F ratio	*P* value	
Subject	6	42.2	7.04			
Gas	1	57.0	57.0	61.2	< 0.001	
Gas × subject	6	5.59	0.93			
$\dot{V}_A/\dot{Q}$	2	148	73.9	11.1	0.002	
$\dot{V}_A/\dot{Q}$ × subject	12	80.1	6.68			
Gas × $\dot{V}_A/\dot{Q}$	2	1.29	0.64	0.32	0.733	
Pairwise Multiple Comparison for AUC $P_{art} - P_{mv}$						
Comparison	Diff of Means	t	*P* value			
Desflurane *vs.* sevoflurane	2.33	7.82	< 0.001			
High $\dot{V}_A/\dot{Q}$ *vs.* low $\dot{V}_A/\dot{Q}$	4.15	4.25	0.003			
Normal $\dot{V}_A/\dot{Q}$ *vs.* low $\dot{V}_A/\dot{Q}$	3.78	3.87	0.004			
High $\dot{V}_A/\dot{Q}$ *vs.* normal $\dot{V}_A/\dot{Q}$	0.38	0.39	0.707			
Elimination						
AUC mean, min	4.49	4.29	7.84	4.96	4.97	8.33
Two-way repeated measures ANOVA for AUC $P_{mv} - P_{art}$						
Source of variation	Degrees of freedom	Type III sum of squares	Mean square	F ratio	*P* value	
Subject	6	14.4	2.41			
Gas	1	3.09	3.09	26.7	0.002	
Gas × subject	6	0.69	0.12			
$\dot{V}_A/\dot{Q}$	2	108	54.2	74.7	< 0.001	
$\dot{V}_A/\dot{Q}$ × subject	12	8.71	0.73			
Gas × $\dot{V}_A/\dot{Q}$	2	0.10	0.05	0.09	0.919	
Pairwise multiple comparison for AUC $P_{mv} - P_{art}$						
Comparison	Diff of means	t	*P* value			
Sevoflurane *vs.* desflurane	0.54	5.17	0.002			
High $\dot{V}_A/\dot{Q}$ *vs.* low $\dot{V}_A/\dot{Q}$	3.46	10.7	< 0.001			
High $\dot{V}_A/\dot{Q}$ *vs.* normal $\dot{V}_A/\dot{Q}$	3.36	10.4	< 0.001			
Normal $\dot{V}_A/\dot{Q}$ *vs.* low $\dot{V}_A/\dot{Q}$	0.10	0.30	0.767			

AUC, area under the curve; $\dot{V}_A/\dot{Q}$, ventilation/perfusion ratio.

on kinetics. For the low $\dot{V}_A/\dot{Q}$ condition, we decreased ventilation while simultaneously increasing cardiac output; for the high $\dot{V}_A/\dot{Q}$ condition, the opposite changes were induced. These perturbations, however, could have also influenced tissue blood flow and distribution of tissue flow between the several tissue groups, thereby altering the kinetics of P_{art} and P_{mv} independent of the effects of the $\dot{V}_A/\dot{Q}$ condition on lung factors. The increase in tissue blood flow from increased cardiac output, for example, is expected to alter the tissue time constants and speed tissue uptake and elimination. The dobutamine infusion that increased total blood flow might also have altered the distribution of blood flow between the vessel rich group, the muscle group, and fat, and could have altered tissue kinetics in unpredictable ways. The atrial occlusion used to reduce cardiac output could also lead to alterations in flow distribution by altering the contributions of superior and inferior caval flow to total cardiac output. Similar effects could result from the mechanical changes in thoracic pressure with manipulation of minute ventilation. Hypocarbia and hypercarbia from altered minute ventilation could also alter the distribution of flows between tissues. The overall effects of these potential confounding factors are complicated and difficult to predict, and would be very difficult to control experimentally.

We therefore attempted to look more specifically at the effects of global $\dot{V}_A/\dot{Q}$ and lung gas exchange on kinetics, and minimize potential confounding from tissue effects, by also examining the differences between P_{art} and P_{mv}. At high $\dot{V}_A/\dot{Q}$, as $\dot{V}_A/\dot{Q}$ approaches infinity, we would expect alveolar partial pressure and arterial partial pressure to approach the partial pressure of inspired gas (open circuit inspired partial pressure for uptake, 0 for elimination) and to be more separated from P_{mv}. At low $\dot{V}_A/\dot{Q}$, as $\dot{V}_A/\dot{Q}$ approaches 0, we would expect P_{alv} and P_{art} to approach P_{mv}. At any given time, the P_{art}-P_{mv} difference reflects the extent of equilibration of mixed venous blood as it traverses the lung, and the time-averaged difference should be less dependent on

Table 5. Arterial t90 (Washin) and t10 (Washout)

	Desflurane	Sevoflurane
t90, min		
Normal $\dot{V}_A/\dot{Q}$	4.6 ± 4.3*	12.5 ± 3.7*
Low $\dot{V}_A/\dot{Q}$	19.0 ± 2.5*†	25.7 ± 6.2*†
High $\dot{V}_A/\dot{Q}$	12.7 ± 7.2*†	15.5 ± 5.4*‡
t10, min		
Normal $\dot{V}_A/\dot{Q}$	6.2 ± 1.1*	12.5 ± 6.4*
Low $\dot{V}_A/\dot{Q}$	23.2 ± 6.6†	31.8 ± 3.9†
High $\dot{V}_A/\dot{Q}$	3.6 ± 1.1*†‡	9.2 ± 8.1*†‡

Presented as mean ± SD.

*$P < 0.05$ between gases. †$P < 0.05$ *vs.* control within same gas. ‡$P < 0.05$ *vs.* low $\dot{V}_A/\dot{Q}$ within same gas.

t90, time for scaled arterial partial pressure to reach 90% of its value at 45 min, for wash-in; t10, time for scaled arterial partial pressure to reach 10% of its value at 45 min, for washout;

$\dot{V}_A/\dot{Q}$, ventilation/perfusion ratio.

confounding tissue kinetic effects than direct comparisons of P_{art} *versus* P_{art}, and P_{mv} *versus* P_{mv}. Our results support the concept that higher $\dot{V}_A/\dot{Q}$ widens the gap between P_{art} and P_{mv} (fig. 7; table 4), and if all other factors were equal, a higher $\dot{V}_A/\dot{Q}$ would therefore accelerate the kinetics of both uptake and elimination.

Our study also provides a side-by-side comparison of desflurane *versus* sevoflurane kinetics under different $\dot{V}_A/\dot{Q}$ conditions (figs. 2, 3, 5, and 6). Previous experimental studies in small pigs[13] and in human volunteers[35,36] have established that washin and washout are faster for desflurane than for sevoflurane, as assessed by end-tidal anesthetic measurements. The effect of global $\dot{V}_A/\dot{Q}$ on this relationship, however, has not been previously reported. Our results (figs. 5 and 6) demonstrate that faster arterial kinetics for desflurane are generally maintained at all three $\dot{V}_A/\dot{Q}$ conditions for both washin and washout. Of interest, however, is the finding that for mixed venous kinetics, these kinetic differences are sometimes reversed—for example, in the high $\dot{V}_A/\dot{Q}$ condition during uptake (fig. 5C).

Our study has several limitations. We did not directly measure the $\dot{V}_A/\dot{Q}$ distributions in our piglets. Previous measurements in this normal pig model in our laboratory, however, have shown normal distributions, *i.e.*, a single, narrow primary $\dot{V}_A/\dot{Q}$ mode with little shunt or alveolar dead space.[24,25] Our experiments were not blinded, and the order of $\dot{V}_A/\dot{Q}$ conditions was not randomized. To create a wide range of $\dot{V}_A/\dot{Q}$, $\dot{V}$ and $\dot{Q}$ were both altered simultaneously, rather than fixing the $\dot{Q}$ constant and varying $\dot{V}$, and *vice versa*. Finally, the fractional weights of the tissue groups and fractional flows to these groups in our juvenile piglets are unlikely to exactly match the corresponding values in adult human patients.

Our study also has several strengths. The mass spectrometer–based measurement system we used features high sensitivity, allowing the use of subanesthetic partial pressures that would be expected to have little effect on cardiac output, distributions of cardiac output, or ventilation mechanics and lung $\dot{V}_A/\dot{Q}$ distributions. Anesthetic gas partial pressures were measured directly in small blood samples, with no extraction into a gas phase, no errors from extraction techniques, and no dependence on individual variations in solubility.[38,39] We measured mixed venous as well as arterial anesthetic partial pressures to fully characterize anesthetic entry into, and exit from, pulmonary blood. Finally, the combination of small blood sample volumes and rapid analysis time facilitated relatively dense sampling times during washin and washout.

In summary, the global $\dot{V}_A/\dot{Q}$ ratio for normal lungs had substantial and complex effects on the washin and washout kinetics for desflurane and sevoflurane, most prominently for the arterial measurements. Increased $\dot{V}_A/\dot{Q}$ ratio was associated with increased arterial–mixed venous differences for the anesthetic gases. For all three $\dot{V}_A/\dot{Q}$ ratios, desflurane kinetics were faster than sevoflurane kinetics.

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Competing Interests

Dr. Baumgardner is president of Oscillogy LLC (Pittsburgh, Pennsylvania), the manufacturer of the MIGET (multiple inert gas elimination technique) by MMIMS (micropore membrane inlet mass spectrometry) System. The other authors declare no competing interests.

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ANESTHESIOLOGY

Effect of Global Ventilation to Perfusion Ratio, for Normal Lungs, on Desflurane and Sevoflurane Elimination Kinetics

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Understanding the elimination kinetics of inhaled anesthetics is of more practical importance than understanding their uptake kinetics
- Normal lungs are assumed to play a major role in the elimination of inhaled anesthetics in the early rapid stages and a negligible role subsequently
- The fraction of cardiac output that is completely cleared of anesthetic in one pass is the fractional clearance

What This Article Tells Us That Is New

- A mathematical model of inhaled anesthetic elimination was developed in a *post hoc* analysis of anesthetic partial pressures measured in mixed venous and arterial blood samples after simultaneous administration of desflurane and sevoflurane to seven piglets under normal, low, and high ventilation/perfusion ratio conditions
- After a brief and rapid decline in alveolar anesthetic partial pressure, the fractional clearance of anesthetic became constant, and incomplete clearance from the lungs slowed tissue washout
- Slowing of tissue elimination by incomplete lung clearance became more pronounced at low ventilation/perfusion ratios, and was predicted to become more pronounced as blood/gas solubility increases

ABSTRACT

Background: Kinetics of the uptake of inhaled anesthetics have been well studied, but the kinetics of elimination might be of more practical importance. The objective of the authors' study was to assess the effect of the overall ventilation/perfusion ratio ($\dot{V}_A/\dot{Q}$), for normal lungs, on elimination kinetics of desflurane and sevoflurane.

Methods: The authors developed a mathematical model of inhaled anesthetic elimination that explicitly relates the terminal washout time constant to the global lung $\dot{V}_A/\dot{Q}$ ratio. Assumptions and results of the model were tested with experimental data from a recent study, where desflurane and sevoflurane elimination were observed for three different $\dot{V}_A/\dot{Q}$ conditions: normal, low, and high.

Results: The mathematical model predicts that the global $\dot{V}_A/\dot{Q}$ ratio, for normal lungs, modifies the time constant for tissue anesthetic washout throughout the entire elimination. For all three $\dot{V}_A/\dot{Q}$ conditions, the ratio of arterial to mixed venous anesthetic partial pressure P_{art}/P_{mv} reached a constant value after 5 min of elimination, as predicted by the retention equation. The time constant corrected for incomplete lung clearance was a better predictor of late-stage kinetics than the intrinsic tissue time constant.

Conclusions: In addition to the well-known role of the lungs in the early phases of inhaled anesthetic washout, the lungs play a long-overlooked role in modulating the kinetics of tissue washout during the later stages of inhaled anesthetic elimination. The $\dot{V}_A/\dot{Q}$ ratio influences the kinetics of desflurane and sevoflurane elimination throughout the entire elimination, with more pronounced slowing of tissue washout at lower $\dot{V}_A/\dot{Q}$ ratios.

(ANESTHESIOLOGY 2021; 135:1042–54)

The time course of inhaled anesthetic uptake and elimination has been the topic of many previous studies.[1–36] The majority of these studies have focused on kinetics of anesthetic uptake; the kinetics of inhaled anesthetic elimination have received less attention. An understanding of anesthetic uptake is of fundamental importance for the clinical practice of anesthesia. In some ways, however, an understanding of elimination kinetics is of more practical importance. During uptake, overpressure techniques can be very effective in speeding uptake in arterial blood and in brain. No similar option exists for speeding elimination.[1,2,32] Additionally, induction of anesthesia in adults is almost universally expedited by use of intravenous drugs, again with no equivalent option to speed emergence. Finally, workflow tasks during uptake of inhaled anesthetics, for example prepping and draping, can proceed in parallel, whereas delays in emergence might directly influence operating room efficiency.

This article is featured in "This Month in Anesthesiology," page A1. This article is accompanied by an editorial on p. 948 and a companion article on p. 1027. This article has a video abstract. This article has a visual abstract available in the online version. Part of the results presented in this article has been presented at the Anesthesiology 2016 Annual Meeting, Chicago, Illinois, October 22 to 26, 2016.

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Several types of abnormalities in the distribution of lung ventilation/perfusion ratios ($\dot{V}_A/\dot{Q}$) cause inefficient gas exchange for oxygen and carbon dioxide.[37] Previous studies have demonstrated that several types of abnormalities in the distribution of lung $\dot{V}_A/\dot{Q}$ ratios can also impact the kinetics of inhaled anesthetic uptake and elimination.[9,25,26,35,36,38] The traditional view, however, is that normal lungs (with efficient gas exchange and a unimodal, narrow $\dot{V}_A/\dot{Q}$ distribution) play a major role only in the early, rapid stages of elimination. After the completion of these early stages, lungs with normal gas exchange efficiency have generally been regarded as having little influence on later, slower stages of elimination.[7,15–18]

In a recent experimental study, in pigs with normal lungs, we measured anesthetic partial pressures in mixed venous (P_{mv}) and arterial (P_{art}) blood samples at multiple times during uptake and elimination of desflurane and sevoflurane, for three different lung $\dot{V}_A/\dot{Q}$ ratios.[39] In the cur rent study, we further analyze this experimental data and develop a simplified and approximate mathematical model of anesthetic elimination that demonstrates the dependence of whole-body elimination kinetics on the global $\dot{V}_A/\dot{Q}$ ratio for normal lungs. The study reported here is an exploratory, *post hoc* analysis of a subset of a larger data set. The objective was to develop a mathematical model of inhaled anesthetic elimination that explicitly states the dependence of washout kinetics on overall $\dot{V}_A/\dot{Q}$ ratio.

Materials and Methods

Experimental Measurements

Details of experimental methods and experimental results are presented in the companion experimental paper.[39] In brief, seven juvenile, 2.5-month-old piglets (weight, mean ± SD 25 ± 2 kg) with normal lungs were anesthetized with intravenous anesthetics. Subanesthetic levels of sevoflurane and desflurane were administered simultaneously with an open circuit technique for 45 min. Arterial and mixed venous blood samples were collected at predetermined times during the 45 min washin and during 45 min of washout. Sevoflurane and desflurane partial pressures in the blood samples were measured with a mass spectrometer–based method.[40,41] Uptake and elimination measurements were carried out for three different conditions[39] of alveolar minute ventilation ($\dot{V}_A$) and cardiac output value ($\dot{Q}$): normal $\dot{V}_A/\dot{Q}$ (0.91); low $\dot{V}_A/\dot{Q}$ (0.32); and high $\dot{V}_A/\dot{Q}$ (1.73). Minute ventilation was varied between these three conditions by adjustment of respiratory rate. Cardiac output was increased with dobutamine infusion and decreased by inflation of a right atrial balloon.

Approximate and Simplified Mathematical Model of Elimination

We start our simplified mathematical modeling approach by considering the kinetics of anesthetic elimination from body tissues. A single well-mixed compartment, as depicted in figure 1A, has a uniform anesthetic partial pressure and is being supplied with fresh, anesthetic-free blood flowing in at rate $\dot{Q}$, and flowing out also at rate $\dot{Q}$, where the outflowing blood is equilibrated to the gas partial pressure of the compartment. The differential equation describing the washout of anesthetic gas from this single well-mixed compartment is

$$\frac{d(\lambda_{bg} \bullet Vol_{cmpt} \bullet P(t))}{dt} = -\lambda_{bg} \bullet \dot{Q} \bullet P(t) \qquad (1)$$

where P(t) is the gas partial pressure in the compartment and in exiting blood at time t; Vol_{cmpt} is the volume of the compartment (up to this point considered to be occupied only by the flowing fluid, *i.e.*, blood), $\dot{Q}$ is the liquid fluid flow (units of volume/time), and λ_{bg} is the Ostwald solubility of the gas in blood (units of ml gas · ml blood^{-1} · atm^{-1}) that links gas partial pressure (units of pressure) to gas content of the fluid (units of volume of gas/volume of liquid). When gas partial pressure is expressed in atmospheres, the Ostwald blood gas solubility is numerically equal to the blood/gas partition coefficient (dimensionless). For constant blood flow $\dot{Q}$, the kinetics of gas washout, starting from an initial gas partial pressure of P_i at time zero, are well known[4]:

$$P(t) = P_i \bullet e^{-(\frac{t}{\tau_{cmpt}})} \qquad (2)$$

The decay in gas partial pressure P(t) from any starting pressure P_i is a monoexponential function of time t, with time constant τ_{cmpt} given by

$$\tau_{cmpt} = \frac{\lambda_{bg} \bullet Vol_{cmpt} \bullet P(t)}{\lambda_{bg} \bullet \dot{Q} \bullet P(t)} = \frac{Vol_{cmpt}}{\dot{Q}} \quad \text{(2A: blood-filled tank)}$$

The numerator of this time constant represents the total gas content in the compartment at time t, and the denominator represents how quickly this compartment is being flushed out by fresh blood flow.

The well-mixed compartment of interest here is filled not only with blood, but rather a small volume of blood (V_{bld}) supplying a much larger volume of tissue (V_{tiss}), as depicted in figure 1B. The gas content of the compartment is then (*total content*) = P(t) · ($Vol_{bld} \cdot \lambda_{bg} + Vol_{tiss} \cdot \lambda_{tg}$), where λ_{tg} is the Ostwald solubility coefficient for gas dissolved in tissue.[5,23,42] Equation 2 still applies, but the monoexponential time constant becomes

$$\tau_{cmpt} = \frac{\lambda_{bg} \bullet Vol_{bld} + \lambda_{tg} \bullet Vol_{tiss}}{\lambda_{bg} \bullet \dot{Q}} \quad \text{(2B: tank with blood and tissue)}$$

Blood volume in many body tissues is a small fraction of tissue volume, and most anesthetics, including desflurane and sevoflurane, partition preferentially from blood into tissue (*i.e.*, $\lambda_{tg} > \lambda_{bg}$). Therefore, $\lambda_{tg} \cdot Vol_{tiss} >> \lambda_{bg} \cdot Vol_{bld}$, and

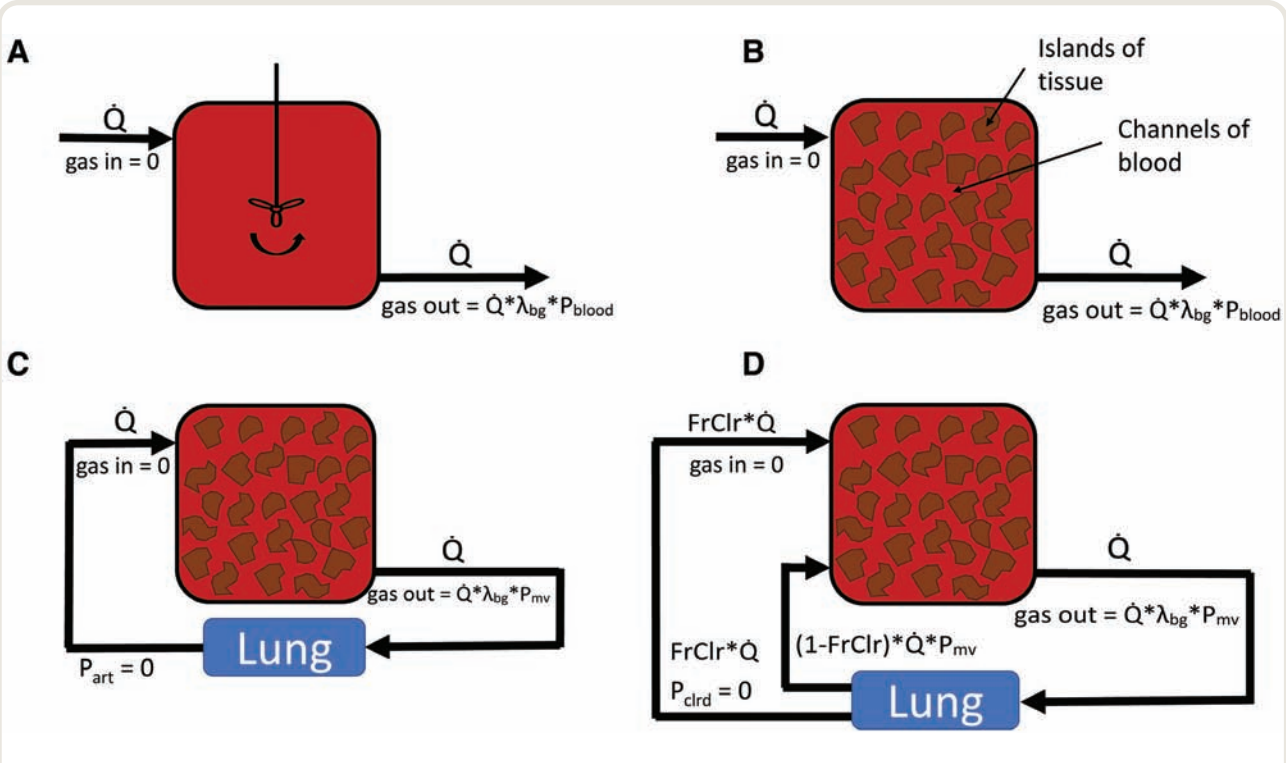

Fig. 1. (*A*) Stirred, well-mixed tank of volume Vol_{cmpt}, filled with blood at anesthetic gas partial pressure P_{blood}. Blood flow $\dot{Q}$ is entering the tank with no anesthetic gas and exiting equilibrated to the tank gas partial pressure P_{blood}. λ_{bg} is the anesthetic blood-gas partition coefficient. (*B*) Well-mixed tank is now filled with blood and tissue. (*C*) Single well-mixed compartment with blood and tissue now represents the tissue for the whole body. $\dot{Q}$ flowing into and out of the body tissue compartment is the cardiac output. Gas partial pressure in the tank and equilibrated with exiting mixed venous blood is P_{mv}. Mixed venous blood returns to the lung, where it is completely cleared in one pass, returning to the body compartment at a gas partial pressure in arterial blood (P_{art}) of zero. (*D*) The lung now only partially clears the anesthetic gas, returning a fraction (FrClr) of cardiac output ($\dot{Q}$) to the body compartment with zero gas ($P_{clrd} = 0$), and a fraction (1 − FrClr) of cardiac output with gas at mixed venous gas partial pressure P_{mv}.

as an approximation, the first term in the numerator can be neglected. Also, for a well-mixed tissue compartment, compartment gas partial pressure P(t) equals exiting venous blood partial pressure $P_v(t)$. The mass balance for the tissue compartment then becomes a slight modification of equation 1:

$$\frac{d(\lambda_{tg} \bullet Vol_{cmpt} \bullet P_v)}{dt} = -\lambda_{bg} \bullet \dot{Q} \bullet P_v \qquad (1A)$$

The solution for washout from starting gas partial pressure P_i is a monoexponential decay (*i.e.*, equation 2 still applies) with time constant

$$\tau_{cmpt} = \frac{\lambda_{tg} \bullet Vol_{tiss}}{\lambda_{bg} \bullet \dot{Q}} \qquad (2C: \text{tissue, approximate})$$

This approximation emphasizes that the important parameter for body tissue elimination kinetics is not the gas solubility in blood that describes how the gas partitions between a blood phase and gas phase, but rather the tissue/blood partition coefficient $\lambda_{tg}/\lambda_{bg}$ that describes how gas partitions between tissue and blood.[1,4,7,8,15,17,18,21,28]

In the interest of arriving at simplified approximate equations that directly show the importance of parameter groups, we start by treating the entire body as one well-mixed compartment, a composite of the traditional vessel-rich, or visceral, group; the muscle group; and the fat group. In figure 1C, the blood flowing out of our compartment exits at mixed venous gas partial pressure, and the blood flow to the whole-body compartment is the entire cardiac output. Mixed venous blood is recycled back to the compartment through a gas exchanger (the lung) capable of clearing all the anesthetic gas in one pass. It is obvious that equation 2 still applies, and the time constant compared to figure 1B has not changed.

In figure 1D, we now consider a lung that does not clear all of the anesthetic in one pass. Partial clearance in the lung for the entire cardiac output can be divided conceptually into a partial lung blood flow that is not cleared at all and is recycled into the body compartment, and a partial lung blood flow that is cleared completely and is returned to the

body tissue compartment as gas-free blood. It is obvious in figure 1D that the part of blood flow that is not cleared at all is simply recycled into the well-mixed compartment and has no role in elimination kinetics. It is also obvious that the effective blood flow washing out the well-mixed compartment is the fraction of cardiac output that is cleared in one pass. Consistent with traditional pharmacokinetic terminology, we denote the amount of blood flow that is completely cleared of anesthetic as "clearance," with units of milliliters blood/min. The fraction of cardiac output that is cleared in one pass will then be called "fractional clearance" and denoted as FrClr (dimensionless). The whole-body elimination time constant becomes

$$\tau_{body} = (\frac{\lambda_{tg}}{\lambda_{bg}}) \bullet \frac{Vol_{tiss}}{FrClr \bullet \dot{Q}} \quad (3)$$

If, for example, the lung fractional clearance (FrClr) was 20% or one fifth, the overall elimination time constant would be increased, by the incomplete lung clearance, five-fold compared to the intrinsic tissue time constant of equation 2C.

An illustration of the potential effect of incomplete lung clearance on the tissue washout time constant is shown in figure 2. Tissue parameter data for the plots in figure 2 were chosen to mimic the muscle tissue compartment for the population averages for the pigs of our experiments.[39] A muscle compartment volume of 13,960 ml was estimated based the "standard 30-kg dog" presented by Cowles *et al.*,[23] scaled to our average pig weight of 25 kg. Average cardiac output for our piglets, for the "normal" $\dot{V}_A/\dot{Q}$ condition, was measured at 3,300 ml/min. The fraction of cardiac output to muscle in the Cowles 30-kg dog of 0.31 was applied to estimate muscle blood flow at 1,023 ml/min. The tissue/gas partition coefficient λ_{tg} for desflurane in pig muscle of 0.56, and the blood/gas partition coefficient for desflurane in pig blood of 0.40, were taken from Zhou and Liu.[43] For purposes of illustration, the single muscle compartment was connected in figure 2 to a lung with fractional clearance assumed to be constant throughout the elimination. Under these assumptions, the intrinsic muscle tissue time constant (equation 2c or equation 3 with FrClr = 1.0) is estimated as 19.1 min. The marked effect on the muscle washout kinetics of progressively decreasing lung clearance from 1.0 to 0.2 is readily apparent in figure 2.

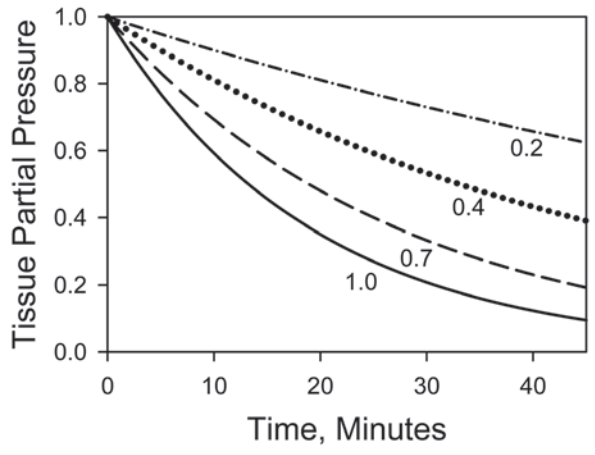

Fig. 2. Hypothetical plots of desflurane washout from tissue to illustrate the potential magnitude of the effect of incomplete lung clearance on tissue washout kinetics. Tissue desflurane partial pressure (scaled to the initial pressure at the beginning of washout) is plotted *versus* time for a single muscle tissue compartment connected to a normal lung as in figure 1D, and the lung maintains constant fractional clearance (1, *solid line*; 0.7, *dashed line*; 0.4, *dotted line*; 0.2, *dash-dot line*) throughout elimination. The washout is monoexponential in all cases, with an intrinsic muscle time constant (equation 2C) of 19.1 min.

We next consider behavior of the lung during anesthetic elimination, and we divide this consideration into early stages of elimination, and later stages. We consider a normal, homogeneous lung with a single, narrow mode in the $\dot{V}_A/\dot{Q}$ distribution. A mass balance on the lung provides the key differential equation[4]:

$$\frac{d(\frac{P_{alv}}{P_b} \bullet V_{lungeff})}{dt} = [\lambda_{bg} \bullet \dot{Q} \bullet (P_{mv} - P_{art}) \bullet \frac{P_0}{P_b}] - (\frac{P_{alv}}{P_b} \bullet \dot{V}_A) \quad (4)$$

P_{alv} is alveolar anesthetic gas partial pressure (atm), P_b is barometric pressure, $V_{lungeff}$ is effective lung volume, and P_0 is standard pressure (1 atm). Effective lung volume $V_{lungeff}$ is the total gas capacity of the lung, given by $V_{lungeff} = V_{frc} + V_{tave} + \lambda_{bg} \cdot V_{lungbld} \cdot P_0 + \lambda_{lungtiss} \cdot V_{lungtiss} \cdot P_0$,[5,23,29] where V_{frc} is functional residual capacity (milliliters gas); V_{tave} is time averaged tidal volume in the alveolus (for example, one half tidal volume for a sinusoidal breathing pattern); $V_{lungbld}$ is the lung blood volume; $\lambda_{lungtiss}$ is the gas solubility in lung tissue; and $V_{lungtiss}$ is the tissue volume of the lung. Equation 4 states that the time rate of change of the amount of gas in the lung is equal to the net delivery by blood into the alveolus (positive for elimination since $P_{mv} > P_{art}$) minus removal in the gas phase by tidal ventilation.

Two assumptions are commonly made to simplify equation 4. The first is that alveolar gas and arterial blood, for any homogenous lung unit, are equilibrated to the same gas partial pressure.[4,5,10,11,23,29,42,44,45] The second, applicable to later stages of elimination, is the pseudo steady-state assumption that the term in brackets (net delivery to the alveolus by blood) is approximately equal to the term in parentheses (net loss in expired gas).[44,45] Therefore, as P_{mv}, and P_{art} (= P_{alv}), are all changing slowly together, the net result is that dP_{alv}/dt becomes small enough to be neglected, and therefore the left term in brackets is approximately equal to the right term in parentheses. Equation 4 under these assumptions simplifies to the retention equation[44,45]:

$$\frac{P_{art}}{P_{mv}} = \frac{1}{1 + \frac{\dot{V}_A}{\lambda_{bg} \bullet \dot{Q} \bullet P_0}} \quad (5)$$

The retention equation is the underlying basis for the multiple inert gas elimination technique that has been used successfully hundreds of times in describing lung gas exchange.[37] During these later stages of elimination, the retention (defined as P_{art}/P_{mv}, the ratio of arterial to mixed venous anesthetic partial pressure) is predicted to become constant as both P_{art} and P_{mv} continue to change together. We refer in this manuscript to these later stages of elimination as the "retention equation plateau."

In equations 4 and 5, λ_{bg} is the Ostwald solubility coefficient, and the standard barometric pressure P_0 of 1.0 atm appears in these equations to maintain dimensional consistency. If instead we use the numerically equal value of the blood/gas partition coefficient (dimensionless) for λ_{bg}, equation 5 takes the slightly simpler form:

$$\frac{P_{art}}{P_{mv}} = \frac{1}{1 + \frac{\dot{V}_A}{\lambda_{bg} \bullet \dot{Q}}} \quad (6: \text{retention equation})$$

Fractional clearance of anesthetic gas from pulmonary blood is defined as the fraction of gas removed from mixed venous blood and can be expressed as

$$FrClr = \frac{P_{mv} - P_{art}}{P_{mv}} = 1 - \frac{P_{art}}{P_{mv}} \quad (7: \text{definition of FrClr})$$

It is clear that if retention is constant in the latter stages of elimination, fractional clearance FrClr will also be constant. Fractional clearance can also be expressed by substituting the expression in the retention equation for P_{art}/P_{mv}, and rearranging:

$$FrClr = \frac{1}{1 + \frac{\lambda_{bg} \bullet \dot{Q}}{\dot{V}_A}} \quad (8)$$

This equation for fractional clearance has been presented previously.[1,2,34,46] Retention and fractional clearance curves for a desflurane blood/gas partition coefficient in pig blood of 0.40[43] are shown in figure 3, with three points on each curve corresponding to our experimental values of $\dot{V}_A/\dot{Q}$. Figure 3 also shows the retention and fractional clearance curves, and the corresponding three points, for sevoflurane with a blood/gas partition coefficient in pig blood of 0.48.[43]

Constant fractional clearance in the later stages of elimination, where "later" is yet to be defined, will directly affect the terminal time constant (often called the "beta" constant in pharmacokinetics) for elimination for a single whole-body compartment interacting with the lungs, as discussed above. Substituting the expression for fractional clearance in equation 8 into equation 3, we obtain the late stage terminal time constant:

$$\tau_{late} = \left(\frac{\lambda_{tg}}{\lambda_{bg}}\right) \bullet \frac{Vol_{tiss}}{FrClr \bullet \dot{Q}} = \left(\frac{\lambda_{tg}}{\lambda_{bg}}\right) \bullet \frac{Vol_{tiss}}{\frac{1}{1 + \frac{\lambda_{bg} \bullet \dot{Q}}{\dot{V}_A}} \bullet \dot{Q}} \quad (9)$$

$$= \left(\frac{\lambda_{tg}}{\lambda_{bg}} \bullet \frac{Vol_{tiss}}{\dot{Q}}\right) \bullet \left(1 + \frac{\lambda_{bg} \bullet \dot{Q}}{\dot{V}_A}\right)$$

This simple connection between lung gas exchange and whole-body washout time constant shows that during later stages of elimination, lung gas exchange efficiency, even for normal lungs with a narrow unimodal $\dot{V}_A/\dot{Q}$ distribution, directly affects the whole-body elimination time constant, because incomplete clearance directly reduces the effective blood flow that is washing out the body compartment. In the rightmost version of equation 9, the term in left parentheses is recognized as the intrinsic tissue time constant from equation 2C. The term in right parentheses is the impact of the lung in slowing whole body washout, and this impact of the lung is determined by (1) the overall lung $\dot{V}_A/\dot{Q}$ ratio and (2) the blood/gas partition coefficient. Equation 9 can also be rearranged to more directly show the individual roles of cardiac output $\dot{Q}$ and alveolar minute ventilation $\dot{V}_{alv}$:

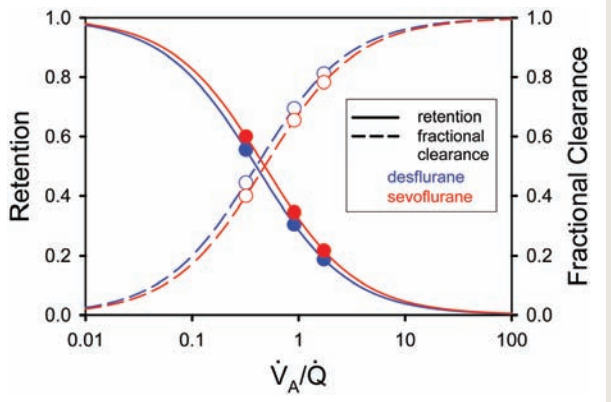

Fig. 3. Plots of the retention (defined as P_{art}/P_{mv}, calculated from retention equation; *solid lines*) and the corresponding fractional clearance ($1 - P_{art}/P_{mv}$; *dashed lines*) as a function of ventilation/perfusion ratio ($\dot{V}_A/\dot{Q}$) for a gas with blood/gas partition coefficient of 0.40 (matching the partition coefficient for desflurane in pig blood; in *blue*) and for a gas with blood/gas partition coefficient of 0.48 (matching the partition coefficient for sevoflurane in pig blood; in *red*). The three points on each curve correspond to the mean $\dot{V}_A/\dot{Q}$ ratios in the three conditions of our experiments: 0.32, 0.91, and 1.73.

$$\tau_{late} = \left(\frac{\lambda_{tg}}{\lambda_{bg}}\right) \bullet Vol_{tiss} \bullet \left(\frac{1}{\dot{Q}} + \frac{\lambda_{bg}}{\dot{V}_A}\right) \quad (10)$$

Equation 10 tells us that the direct effect of increased cardiac output in speeding the tissue compartment washout (the $\dot{Q}$ in equation 2C) always dominates over the indirect effect of increased cardiac output in decreasing clearance and slowing the late-stage whole-body washout (the $\dot{Q}$ in equation 8), and therefore the net effect of an increase in cardiac output is to speed late-stage elimination. This result, however, is restricted to the assumption of a single body compartment where a change in cardiac output cannot be accompanied by a change in the organ level distribution of blood flow.[2,11,28] Equation 10 also helps to clarify the concepts of perfusion-limited elimination and ventilation-limited elimination.[4,21,44,47] For a gas that has a solubility coefficient much greater than 1, or when $\dot{V}_A$ is much less than $\dot{Q}$, the second term in parentheses will dominate, changes in cardiac output will have little effect, changes in ventilation will have a large effect, and the late-stage elimination is ventilation-limited. For a gas that has a solubility coefficient much less than 1, or when $\dot{Q}$ is much smaller than $\dot{V}_A$, the $1/\dot{Q}$ term in parentheses will dominate, changes in ventilation will have little effect, changes in cardiac output will have a large effect, and the late-stage elimination is perfusion-limited.

Early in elimination, in contrast to the later stages of elimination, P_{alv} is changing rapidly, and the retention equation cannot be applied to predict P_{art}/P_{mv}. Some insight into the early stages of elimination can be gained, however, by considering the limiting case of an anesthetic gas with a solubility in blood approaching zero. For sparingly soluble gases, the term describing net delivery in blood in equation 4 approaches zero, and equation 4 reduces to

$$\frac{d\left(\frac{P_{alv}}{P_b} \bullet V_{lungeff}\right)}{dt} = -\left(\frac{P_{alv}}{P_b} \bullet \dot{V}_A\right) \quad (11: \text{sparingly soluble gas})$$

For a gas that is sparingly soluble in tissue ($\lambda_{tg} \approx 0$) as well as in blood ($\lambda_{bg} \approx 0$), effective lung volume becomes $V_{frc} + V_{tave}$, and the differential equation describing washout becomes

$$\frac{d(P_{alv})}{dt} = -\frac{\dot{V}_A}{V_{frc} + V_{tave}} \bullet P_{alv} \quad (12: \text{sparingly soluble gas})$$

The solution is a monoexponential decay in alveolar partial pressure from starting pressure P_i:

$$P(t) = P_i \bullet e^{-\frac{t}{\tau_{frc}}} \qquad \tau_{frc} = \frac{V_{frc} + V_{tave}}{\dot{V}_A} \quad (13: \text{sparingly soluble gas})$$

For our piglets, functional residual capacity is estimated as 669 ml by scaling the data of Ludwigs *et al.*[48] to our pig weight of 25 kg and linearly interpolating to our set positive end-expiratory pressure of 5 cm H_2O. An average tidal volume for our experiments, globally for all conditions, estimates tidal volume as 268 ml, giving functional residual capacity + ½ tidal volume as 803 ml. For the three different minute ventilation settings in our experiments, the three time courses predicted for alveolar washout for a hypothetical, very low solubility gas are graphed in figure 4. Of note, all of the functional residual capacity time constants, even for low minute ventilation, are small, with this part of washout completing in about 1 min or less.

For more soluble gases, the approach from $P_{art}/P_{mv} = 1$ to the retention equation plateau is not easily predicted with simplified models, because the kinetic behavior is governed by the behavior of the lung kinetics interacting with the tissue kinetics. It can be appreciated qualitatively that the approach to the retention equation plateau will be slower than predicted by τ_{frc} because gas exiting the alveolus in arterial blood speeds the decay, but gas entering from mixed venous blood slows the decay, and P_{mv} during elimination will be larger than P_{art}. More quantitative descriptions would require simultaneous solution of both differential equations for lung and body tissue (equations 1A and 4), either numerically[5,10,11,13,21,23,29,42] or analytically.[4,28] Alternatively, the early stages of anesthetic washout can be described with experimental data. In the current study, the experimental data for P_{art} and P_{mv} from our companion experimental study[39] are analyzed by calculating the retention at each time point and plotting retention *versus* time.

Graphic and Statistical Analysis of Experimental Measurements

Data for P_{art} and P_{mv} were taken from our companion experimental study.[39] For each individual animal, and each of the three $\dot{V}_A/\dot{Q}$ conditions, arterial (P_{art}) and mixed venous (P_{mv}) mass spectrometer signals were scaled to that individual's arterial signal at the end of the 45-min anesthetic (sevoflurane and desflurane) administration. For each $\dot{V}_A/\dot{Q}$ condition and each subject, the scaled P_{art} was divided by scaled P_{mv} to calculate the retention for that individual, $\dot{V}_A/\dot{Q}$ condition, and time. Then, for each $\dot{V}_A/\dot{Q}$ condition, P_{art}/P_{mv} was averaged for each time over the seven animals, 99% CIs were determined using the Student's *t* distribution, and values were plotted as means and CIs *versus* time (fig. 5 for desflurane and fig. 6 for sevoflurane). Scaled desflurane mixed venous partial pressure means and 99% CIs were plotted as spline-smoothed curves on a semi-log plot (fig. 7). Desflurane elimination kinetics in mixed venous blood from 20 to 45 min were compared to two theoretical monoexponential washout kinetics, the intrinsic time constant for the muscle compartment, and the fractional clearance–corrected time constant (fig. 7). A similar analysis for sevoflurane was performed, with a similar plot in figure 8. The rationale for focusing on the muscle compartment, when we restrict our attention to the time period

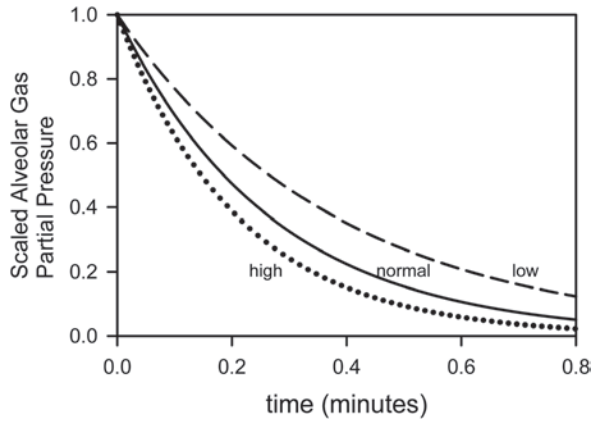

Fig. 4. Predicted washout of a very low solubility gas from the alveolar gas spaces for a normal, homogeneous lung. Alveolar gas partial pressure (scaled to the beginning partial pressure) is plotted *versus* time for a fixed effective alveolar volume (functional residual capacity + ½ tidal volume) of 803 ml for our 25-kg pigs at 5 cm H_2O of positive end-expiratory pressure. The three alveolar minute ventilations correspond to the average $\dot{V}_A$ for our experiments (high, 3.7 l/min, *dotted line*; normal, 2.9 l/min, *solid line*; low, 2.0 l/min, *dashed line*).

from 20 to 45 min, is presented in the appendix. The intrinsic muscle compartment time constants (equation 2C, or equation 3 with FrClr = 1) were calculated from the following: measured cardiac output times the fractional flow to muscle for the Cowles "standard 30-kg dog"[23]; muscle tissue volume from the Cowles 30-kg dog, scaled to our pig weight of 25 kg; pig tissue/gas partition coefficients for desflurane (0.56) and sevoflurane (1.17) in muscle from Zhou and Liu.[43]; and pig blood/gas partition coefficients of 0.40 for desflurane and 0.48 for sevoflurane from Zhou and Liu.[43] Fractional clearance for the clearance-corrected muscle time constant (equation 3) was calculated (equation 8) from measured cardiac output and alveolar minute ventilation, and λ_{bg} from Zhou and Liu.[43]

Results

Figure 5 shows the time course of calculated P_{art}/P_{mv} (retention) during desflurane elimination, as means (over the seven animals at each time point) and 99% CIs. In all three $\dot{V}_A/\dot{Q}$ conditions, the values reached the retention equation plateau within 5 min. The ratio of scaled P_{art} to scaled P_{mv} is initially greater than 1 in all cases, reflecting the fact that not all body tissues were completely equilibrated at the end of a 45 min administration. The experimental values of retention on this retention equation plateau are compared graphically to the values calculated from the retention equation (applied to the average values of $\dot{V}_A/\dot{Q}$ of 0.91, 0.32, and 1.73), with the central section of the graph of figure 3 reproduced and aligned to the right of the data plot in figure 5.

Figure 6 shows the corresponding analysis for the sevoflurane data. There is a similar trend for retentions to reach a plateau after the first 2 to 5 min, especially notable in the time period from 2 to 10 min. Later time periods in figure 6 are difficult to interpret; the noise in the sevoflurane data becomes large as the signals approach zero late in washout. As a consequence of the mass spectrometer setup and the chosen inspired concentrations of sevoflurane and desflurane, the signal to noise ratio for the sevoflurane data analysis was on the order of 20 to 50 times smaller than the corresponding desflurane signal to noise ratios. The result is the large error bars, compared to desflurane, in the sevoflurane retention plots late in washout, where two very small quantities are divided as they both approach zero. The very small signal for sevoflurane in late stages of washout also makes the calculation of the ratio of two small numbers susceptible to systematic, nonrandom measurement errors—for example, any small amount of drift in the mass spectrometer baseline.

Figure 7 presents the measured P_{mv} values for desflurane during elimination, connected by a spline-smoothed curve on a semi-log plot (means with 99% CIs). Also plotted are the monoexponential washouts (linear on a semi-log plot) from the 20-min time point that are predicted for the muscle compartment alone. The more rapid washout (steeper slope of a straight line on the semi-log plot; dot-dash line) is predicted by the intrinsic time constant of the muscle compartment (intrinsic tissue compartment time constant, methods), *i.e.*, the washout that is predicted for complete lung fractional clearance. The slower linear, monoexponential washout (solid line) is predicted by the intrinsic muscle time constant corrected for the fractional clearance by the lung (late-stage effective time constant; see Materials and Methods, equation 9). Figure 8 presents the corresponding analysis for sevoflurane.

Discussion

Our study develops a simplified mathematical model of inhaled anesthetic elimination that explicitly shows the dependence of elimination on overall lung $\dot{V}_A/\dot{Q}$, in contrast to both of the two most prominent previous approaches to mathematical modeling of elimination. One prominent approach to previous mathematical modeling of elimination has used numerical (or, in early studies, analog electrical) solutions to the system of differential equations that arise from compartmental modeling.[2,5,9–13,21–24,27–29,34,42,49,50] Each compartment included in the model (for example, lungs/central, visceral, muscle, and fat compartments in a four-compartment model)[2,23,42] is represented by a differential equation, and the resulting uptake and elimination curves can be compared to the experiment. Because this approach includes a differential equation for the lungs, equivalent or identical to equation 4, the effect of overall lung $\dot{V}_A/\dot{Q}$ is implicitly included. The numerical solutions, however, do not provide any

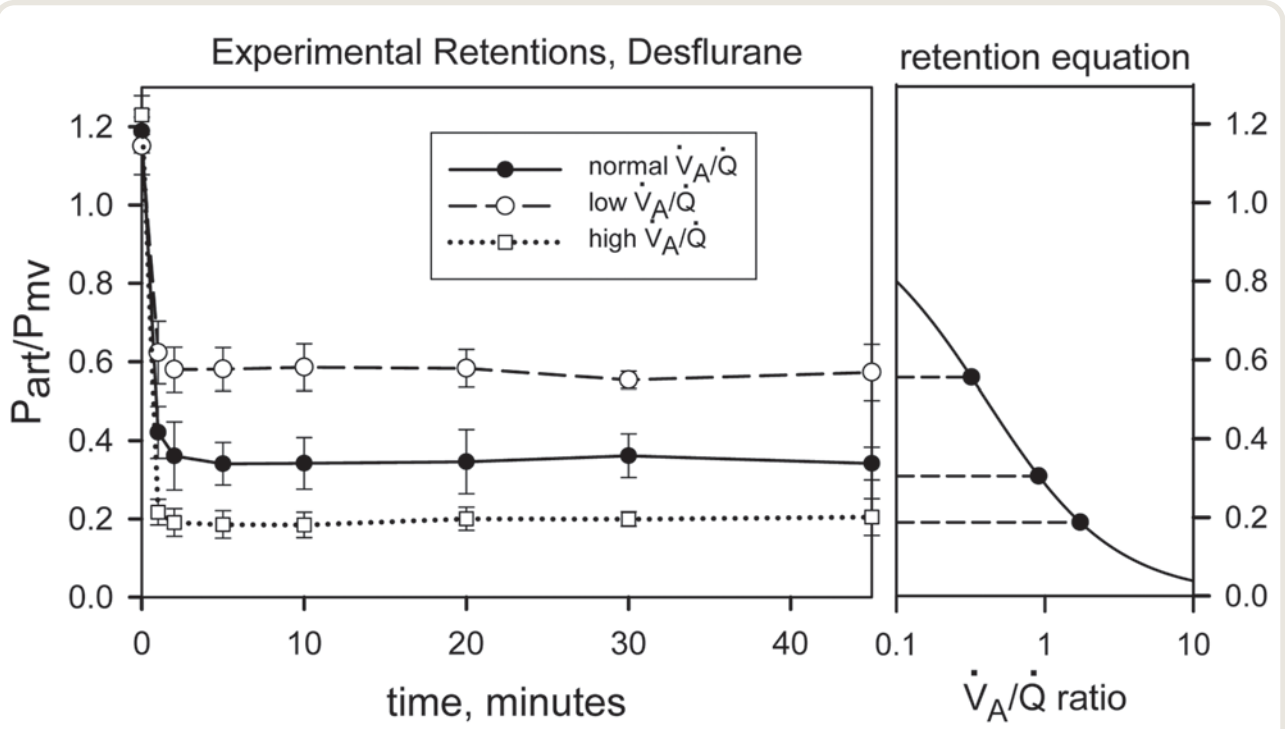

Fig. 5. Experimental measurements of P_{art}/P_{mv} (retention, defined as anesthetic gas partial pressure in arterial blood/anesthetic gas partial pressure in mixed venous blood) for desflurane, plotted *versus* time for the three ventilation/perfusion ratio ($\dot{V}_A/\dot{Q}$) conditions as means and 99% CIs for the seven animals. High $\dot{V}_A/\dot{Q}$, *dotted line* and *open squares*; normal $\dot{V}_A/\dot{Q}$, *solid line* and *filled circles*; low $\dot{V}_A/\dot{Q}$, *dashed line* and *open circles*. For comparison to theoretical calculations of retentions for each condition (the retention equation applied to mean $\dot{V}_A/\dot{Q}$ for that condition), the middle section of the retention curve from figure 3, for desflurane, is reproduced and aligned to the right of the experimental data plots.

equations that explicitly show the functional form of the dependence of kinetics on $\dot{V}_A/\dot{Q}$.

Another prominent approach to mathematical modeling of washout data is the empiric fitting of kinetic data for P_{art} (or for P_{et}) to sums of multiple exponential terms of the form

$$P_{art} = \sum_{i=1}^{n} A_i \cdot e^{-k_i \cdot t} \qquad (14)$$

Terms are empirically added to the model according to whether or not they improve the fit of the multiexponential curve to the data points. Carpenter *et al.* used five terms fit to prolonged (several days) washout data for multiple anesthetics.[15,16] Because the recovered rate constants k_i were substantially separated in magnitude, it was assumed as an approximation that each coefficient A_i and rate constant k_i corresponds to a distinct tissue group, resulting in the five-compartment model[15–18] for anesthetic elimination: lungs/central compartment, vessel-rich group, muscle group, fat group, and the "fourth compartment," attributed to intertissue diffusion.[1,15–18] Earlier work interpreted uptake kinetics in a similar way for a four-compartment model.[7]

The lungs/central compartment has the fastest kinetics compared to all the other compartments, and it has been assumed as an approximation[7,15–18] that after the early period of washin or washout, the role of the lungs in later stages of kinetics can be neglected. The expectation is then that the empirically recovered time constants for each compartment (the time constants $\tau_i = 1/k_i$) should reasonably match the intrinsic tissue time constants[7,15–18] as calculated from the equation for "intrinsic tissue compartment time constant," equation 2C in the Materials and Methods. Our study shows that this concept is incorrect. The lung overall $\dot{V}_A/\dot{Q}$ ratio, and more specifically the dimensionless parameter group $\dot{V}_A/(\lambda_{bg}\dot{Q})$, continues to directly influence the terminal elimination constant for the entire elimination. During these later stages of elimination, it is true that the influence of $V_{frc}/\dot{V}_A$ kinetics has decayed to a negligible role. The fractional clearance, however, takes on a constant value and plays a major role in modulating the intrinsic tissue time constants to determine the overall late-stage kinetics.

Figures 7 and 8 illustrate several features of late-stage desflurane and sevoflurane washout. First, although there is still some curvature in the time period from 20 to 45 min,

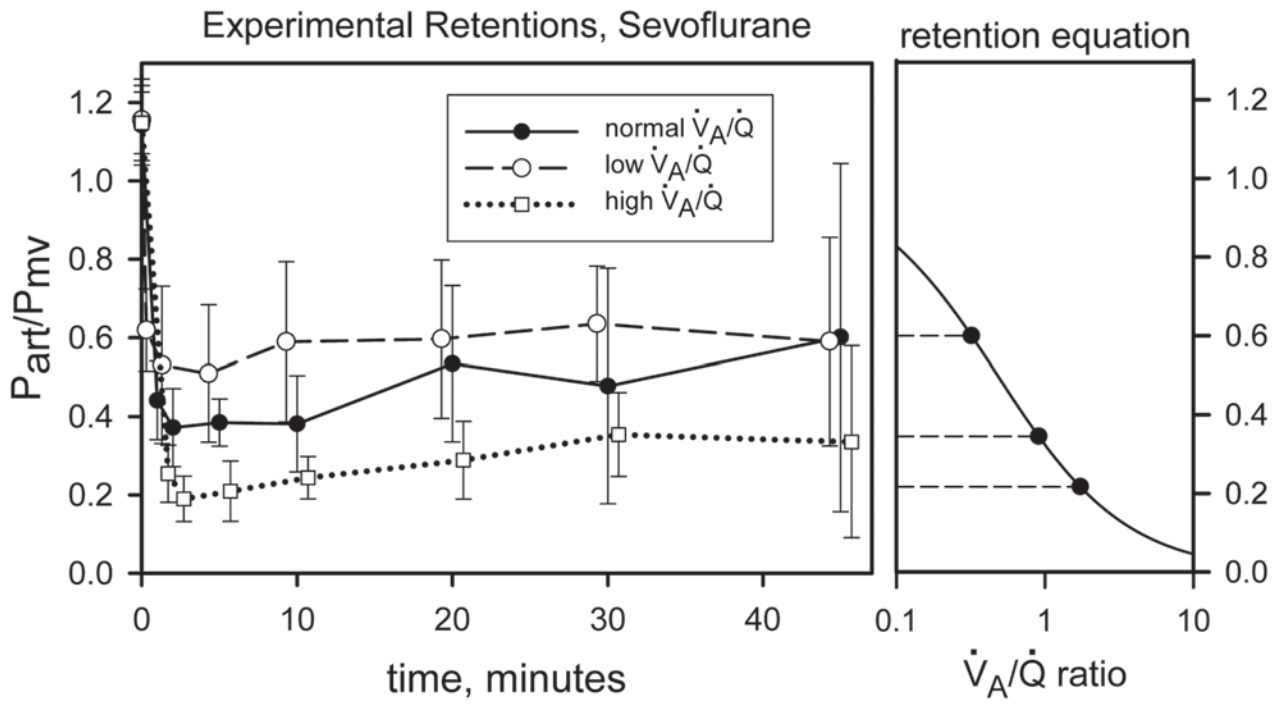

Fig. 6. Experimental measurements of P_{art}/P_{mv} (retention, defined as anesthetic gas partial pressure in arterial blood/anesthetic gas partial pressure in mixed venous blood) for sevoflurane, plotted *versus* time for the three ventilation/perfusion ratio ($\dot{V}_A/\dot{Q}$) conditions as means and 99% CIs for the seven animals. High $\dot{V}_A/\dot{Q}$, *dotted line* and *open squares*; normal $\dot{V}_A/\dot{Q}$, *solid line* and *filled circles*; low $\dot{V}_A/\dot{Q}$, *dashed line* and *open circles*. To separate the overlapping CIs, at each time point the three means and CIs are plotted with a slight time offset. For comparison to theoretical calculations of retentions for each condition (the retention equation applied to mean $\dot{V}_A/\dot{Q}$ for that condition), the middle section of the retention curve from figure 3, for sevoflurane, is reproduced and aligned to the right of the experimental data plots.

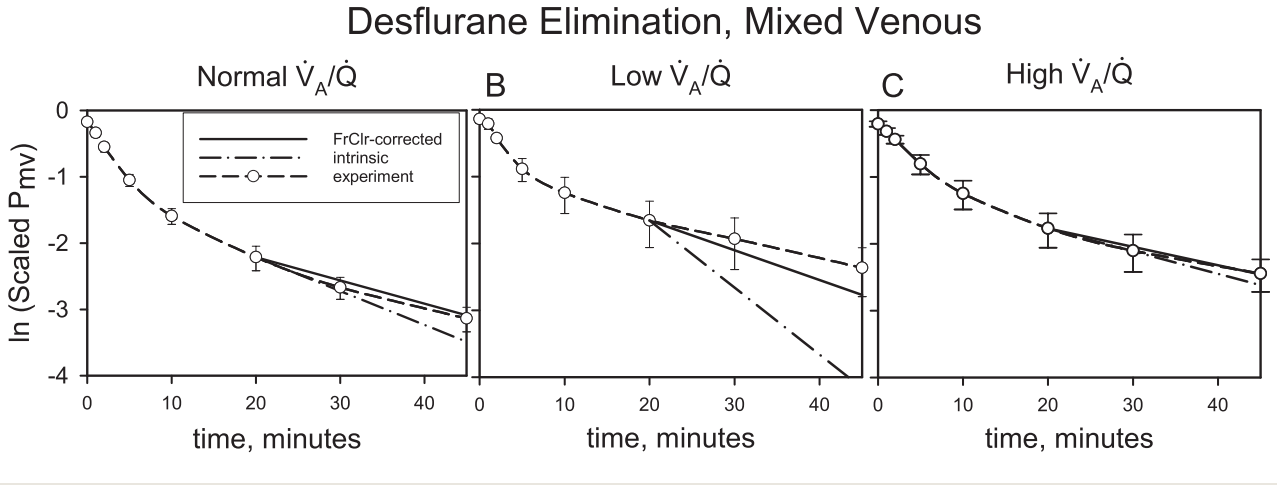

Fig. 7. Scaled desflurane mixed venous partial pressure means and 99% CIs for the seven animals, plotted with a smoothed spline curve on a semi-log plot (*dashed line*, *open circles*). ln(Scaled P_{mv}) is the natural logarithm of the scaled mixed venous partial pressure P_{mv}. Also plotted are the monoexponential washouts, from the time = 20 min point, predicted by a single muscle compartment connected to the lungs, for the intrinsic muscle group time constant (*dot-dash line*) and for the effective, or clearance-corrected (FrClr-corrected), time constant (*solid line*). $\dot{V}_A/\dot{Q}$, ventilation/perfusion ratio.

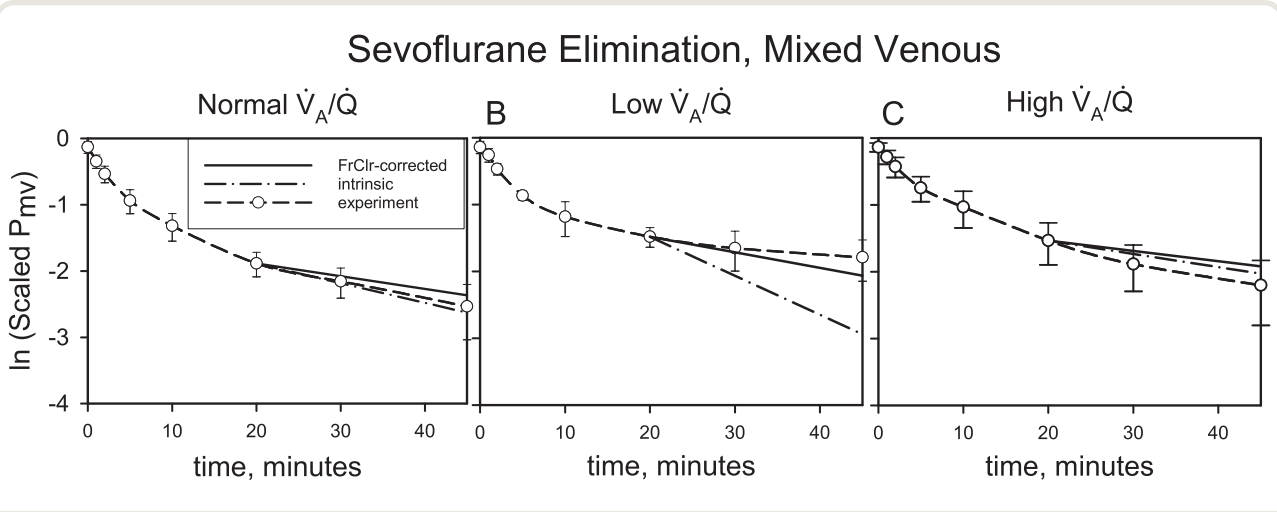

Fig. 8. Scaled sevoflurane mixed venous partial pressure means and 99% CIs for the seven animals, plotted with a smoothed spline curve on a semi-log plot (*dashed line*, *open circles*). ln(Scaled P_{mv}) is the natural logarithm of the scaled mixed venous partial pressure P_{mv}. Also plotted are the monoexponential washouts, from the time = 20 min point, predicted by a single muscle compartment connected to the lungs, for the intrinsic muscle group time constant (*dot-dash line*) and for the effective, or clearance-corrected (FrClr-corrected), time constant (*solid line*). $\dot{V}_A/\dot{Q}$, ventilation/perfusion ratio.

the washout during this time is a close approximation to a monoexponential washout that would plot as a straight line on a semi-log plot. This is consistent with the anticipation that this period of washout can be approximately represented by a single muscle compartment connected to the lungs, as described in the appendix. Second, the clearance-corrected time constant for a monoexponential muscle compartment washout is generally a better predictor of the experimental data than the intrinsic time constant, supporting our point that incomplete lung clearance slows washout during the entire elimination. Third, the clearance-corrected time constant makes a very good prediction of the experimental washout kinetics. This fit of theory to experimental data is striking, considering that this match did not use any adjusted parameters for "best fit." Finally, the correction for lung clearance makes little difference when lung fractional clearance approaches 1.0 (figs. 7C and 8C, high $\dot{V}_A/\dot{Q}$), *i.e.*, when $\dot{V}_A/\dot{Q}$ is high and/or solubility is small. When clearance is not close to 1.0, however, the uncorrected washout time constant substantially overestimates the speed of washout (figs. 7B and 8B, low $\dot{V}_A/\dot{Q}$). Of note, desflurane and sevoflurane are two of the least soluble inhaled anesthetics. These effects will be even more pronounced for higher solubility gases.

The dimensionless group $\dot{V}_A/(\lambda_{bg}\dot{Q})$, highlights two important factors in anesthetic elimination: the role of overall lung $\dot{V}_A/\dot{Q}$ and the role of the blood/gas partition coefficient. Even for normal lungs with efficient gas exchange for oxygen and carbon dioxide, and a narrow unimodal $\dot{V}_A/\dot{Q}$ distribution, the overall lung $\dot{V}_A/\dot{Q}$ ratio has a direct effect on anesthetic elimination kinetics. In general, higher $\dot{V}_A/\dot{Q}$ ratios produce higher fractional clearance in the lung (fig. 3) and therefore less slowing of tissue washout kinetics (equation 9 for τ_{late}).

It has been taught intuitively for many years that lower blood gas solubility leads to faster overall uptake and elimination kinetics,[1–3,6,9–11,13,24] a fact completely consistent with experimental data,[6,14–20,23,24] mathematical models of kinetics solved numerically[2,5,9–11,13,23,24,34] or analytically,[4,28] and routine clinical experience. Surprisingly, however, it is hard to find in previous literature any equation that directly shows a connection between the overall terminal elimination time constant and blood gas solubility. Equation 9 for τ_{late} directly makes a connection between the beta elimination half-life in the later stages of elimination, and blood gas solubility.

Our two companion studies, *i.e.*, the current modeling study and the experimental study that provided the data for analysis, have several limitations. First, the current study was an exploratory *post hoc* analysis of a subset of a larger data set. This type of analysis is recognized as a way to generate hypotheses, but is not appropriate for testing of hypotheses. Second, we did not perform a complete factorial design with three levels each of cardiac output times three levels of ventilation. Rather, our experiments explored a limited subset of all nine possible conditions, with cardiac output and ventilation both changing between conditions. Third, cardiac output was varied in the desired directions, but there was no way to assess or influence the distribution of blood flow that could have accompanied these changes. Redistribution of blood flow between body compartments can impact elimination kinetics beyond the change in cardiac output alone. Both of the maneuvers to manipulate cardiac output (dobutamine to increase cardiac

output; atrial obstruction to decrease cardiac output) could have changed distribution of flow as well as total flow. Additionally, both hypocarbia and hypercarbia can change the blood flow distribution. Fourth, an optimal condition for studying the kinetics of anesthetic elimination would be a starting point of complete equilibration of all of the body tissues to the same anesthetic partial pressure. Our 45-min administration obviously did not completely equilibrate all body tissues. Fifth, we did not directly measure the $\dot{V}_A/\dot{Q}$ distributions in our piglets. Previous measurements of $\dot{V}_A/\dot{Q}$ distributions in this model, however, have demonstrated normal distributions with a single narrow $\dot{V}_A/\dot{Q}$ mode, minimal shunt, and minimal alveolar dead space.[36] Based on the close matching of $\dot{V}_A$ and $\dot{Q}$ for normal lungs, our mathematical model further makes the approximation that matching between $\dot{V}_A$ and $\dot{Q}$ is perfect, *i.e.*, that the distribution is a single, idealized spike in both $\dot{V}_A$ and $\dot{Q}$. Finally, in the interests of arriving at relatively simple equations for kinetic time constants, we recognize that many approximations were made that do not represent the full complexity of anesthetic kinetics. In particular, representation of the whole body with a single time constant does not address the known complexity of multiple tissues and multiple compartments.

Conclusions

The ratio of alveolar minute ventilation, $\dot{V}_A$, to cardiac output, $\dot{Q}$, influences the kinetics of inhaled anesthetic elimination throughout the entire elimination. After a brief and rapid decline in alveolar anesthetic partial pressure, the fractional clearance of anesthetic by the normal lung becomes constant, and incomplete clearance from the lung slows the anesthetic washout from tissues. The increase in the elimination time constant for body tissues is a function of the dimensionless group $\dot{V}_A/(\lambda_{bg}\dot{Q})$ that combines $\dot{V}_A$, $\dot{Q}$, and the blood/gas partition coefficient λ_{bg}. Slowing of tissue elimination by incomplete lung clearance becomes more pronounced at low $\dot{V}_A/\dot{Q}$ ratios, and is predicted to become more pronounced as blood/gas solubility increases.

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Competing Interests

Dr. Baumgardner is president of Oscillogy LLC (Pittsburgh, Pennsylvania), the manufacturer of the multiple inert gas elimination technique by Micropore Membrane Inlet Mass Spectrometry system. The other authors declare no competing interests.

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Appendix

Rationale for the Approximation that the 20- to 45-Min Washout Period Reflects a Single Compartment, the Muscle Compartment, Connected to the Lung

The functional residual capacity–dominated early time constant produces a very rapid early decrease in desflurane and sevoflurane elimination, decaying in less than 5 min as shown by the rapid approach to the retention equation plateau for all $\dot{V}_A/\dot{Q}$ (figs. 5 and 6). The visceral group time constant can be estimated from Cowles *et al.*[23] and Mapleson's data[5] on compartment volumes and fractional flows, combined with tissue partition coefficient data for the various central organs from Zhou and Liu.[43] We estimate, for desflurane, in our pigs the intrinsic visceral time constants for the normal, low, and high $\dot{V}_A/\dot{Q}$ conditions, respectively, at 2.5, 1.3, and 3.7 min, and the clearance-corrected time constants at 3.5, 2.8, and 4.5 min. The corresponding estimates for sevoflurane for intrinsic visceral time constants are 3.8, 1.9, and 5.7 min, and the clearance-corrected time constants are estimated as 5.8, 4.8, and 7.3 min. Thus, after the first 20 min of elimination and approximately two to three effective visceral group time constants, the low arterial partial pressures (figs. 2 through 5 of the companion manuscript[39]) will be roughly matched in venous visceral blood with low venous partial pressures, and the visceral group will contribute little to the mixed venous washout kinetics. That leaves the muscle and fat groups (and possibly the intertissue diffusion group). Fat fractional flow, however, is about one tenth of the muscle fractional flow, limiting its contribution to mixed venous partial pressures. In addition, in our experiment, fat was very poorly equilibrated after 45 min, making it even less effective as a gas source for the mixed venous blood. It is therefore reasonable that the washout during 20 to 45 min is approximately monoexponential, since the washout is approximately described by a single muscle compartment.

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ANESTHESIOLOGY

Intubation Biomechanics: Clinical Implications of Computational Modeling of Intervertebral Motion and Spinal Cord Strain during Tracheal Intubation in an Intact Cervical Spine

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Cervical spinal cord injury can occur due to airway manipulation including tracheal intubation even in the presence of an intact cervical spine
- During intubation with an intact cervical spine, it is unknown whether cervical spine motion can exceed the range of voluntary motion and cause cord injury due to stretch or compression (strain) or whether injurious cord strain can occur without pathologic motion

What This Article Tells Us That Is New

- Based on simulation of an adult cervical spine, pathologic motion does not occur even with intubation force up to twice that commonly encountered during routine tracheal intubation
- However, in patients who have increased susceptibility to strain-related cord injury, potentially injurious cord strain may occur during routine tracheal intubation conditions

ABSTRACT

Background: In a closed claims study, most patients experiencing cervical spinal cord injury had stable cervical spines. This raises two questions. First, in the presence of an intact (stable) cervical spine, are there tracheal intubation conditions in which cervical intervertebral motions exceed physiologically normal maximum values? Second, with an intact spine, are there tracheal intubation conditions in which potentially injurious cervical cord strains can occur?

Methods: This study utilized a computational model of the cervical spine and cord to predict intervertebral motions (rotation, translation) and cord strains (stretch, compression). Routine (Macintosh) intubation force conditions were defined by a specific application location (mid-C3 vertebral body), magnitude (48.8 N), and direction (70 degrees). A total of 48 intubation conditions were modeled: all combinations of 4 force locations (cephalad and caudad of routine), 4 magnitudes (50 to 200% of routine), and 3 directions (50, 70, and 90 degrees). Modeled maximum intervertebral motions were compared to motions reported in previous clinical studies of the range of voluntary cervical motion. Modeled peak cord strains were compared to potential strain injury thresholds.

Results: Modeled maximum intervertebral motions occurred with maximum force magnitude (97.6 N) and did not differ from physiologically normal maximum motion values. Peak tensile cord strains (stretch) did not exceed the potential injury threshold (0.14) in any of the 48 force conditions. Peak compressive strains exceeded the potential injury threshold (–0.20) in 3 of 48 conditions, all with maximum force magnitude applied in a nonroutine location.

Conclusions: With an intact cervical spine, even with application of twice the routine value of force magnitude, intervertebral motions during intubation did not exceed physiologically normal maximum values. However, under nonroutine high-force conditions, compressive strains exceeded potentially injurious values. In patients whose cords have less than normal tolerance to acute strain, compressive strains occurring with routine intubation forces may reach potentially injurious values.

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Cervical spinal cord injury caused by tracheal intubation is a rare but catastrophic complication.[1–3] Cervical cord injuries are not limited to patients who have unstable spines. In an American Society of Anesthesiologists Closed Claims study, most (28 of 37) cervical cord injury claims occurred in patients who had stable cervical spines.[2] This closed claims study reported that probable contributors to perioperative cervical cord injury included direct surgical complications (9 of 37), head/neck positioning (7 of 37), and airway management (4 of 37).[2] Of the four patients in whom airway management was judged to be a probable contributor to cord injury, two patients had stable spines.[2]

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The occurrence of intubation-related cervical cord injury in the presence of a stable cervical spine suggests that intubation may cause cord injury by mechanisms not previously considered.

There are no clinical studies reporting unrestricted cervical spine motion during tracheal intubations in which intubations were more difficult and intubation forces were increased.[4–6] Thus, we wondered, in the presence of an intact (stable) cervical spine, is it possible under uncommon, high-force, or otherwise abnormal intubation conditions that pathologic cervical spine motion could occur? In other words, are there tracheal intubation conditions in which cervical intervertebral motions can exceed physiologically normal maximum values?

When the cervical spine moves, the cervical spinal cord deforms. The cord stretches and contracts axially[7] and thins and thickens transversely.[8] Measures of strain quantify the extent of tissue deformation (*e.g.*, change in length or width) in response to an applied stress (force/area = pressure). In animal models, high levels of cord strain cause acute and chronic spinal cord dysfunction and/or injury.[9–14] Thus, we wondered whether, in the presence of an intact cervical spine, even if pathologic spine motion does not take place, are there tracheal intubation conditions in which potentially injurious cervical cord strain can occur?

The aim of this study was to answer the two questions posed above. To do so, we used a computational model of the human cervical spine and spinal cord to simulate tracheal intubation. We studied large variations in laryngoscope force application conditions (location, magnitude, and direction) to include practically any set of tracheal intubation conditions that could occur in clinical practice. Model outputs included cervical spine motions (intervertebral rotation and translation) and peak cervical cord tensile (stretch) and compressive strains occurring during intubation.

Materials and Methods

Background, Rationale, and Validation of the Finite Element Model

Finite element modeling is a computational simulation method used to predict the behaviors of complex three-dimensional structures. The basis of finite element modeling lies in dividing a complex structure into many smaller, simpler structures called elements so that the overall structural response to loading may be mathematically calculated. The response of each element is expressed in terms of a finite number of degrees of freedom at a set of points called nodes that connect each element to other adjacent elements. To model biologic structures, finite element models require accurate three-dimensional representations of the geometry (anatomy) of all structurally distinct components such as vertebrae, intervertebral discs, ligaments, etc. These models also require knowledge of the material properties of each component (*e.g.*, elasticity) under all conditions under which the model will be tested.[15] For more than 25 yr, finite element models of the human cervical spine have been used to predict spine motions that occur under routine or hazardous (*e.g.*, high force) conditions. In addition, these models allow for characterization of processes and dynamics occurring inside the substance of the spine or cord that are impossible to directly measure, such as mechanical stress and strain.[15]

The model used in this study is of the complete human cervical spine (from the occiput to C7) and the cervical spinal cord.[16] It consists of 196,984 elements, 237,635 nodes, and has 671,997 degrees of freedom. In a previous validation study, this model closely predicted intervertebral motions (occiput–C1 through C4–C5) measured during orotracheal intubation in living patients.[16] It did so with intubations accomplished with both direct laryngoscopy (Macintosh) and videolaryngoscopy.[16] The results of the current study provide additional evidence of the validity of this model (see Results). Specifically, under routine (Macintosh) intubation conditions, this model predicted 1 to 2 degrees of flexion at C5–C6 and C6–C7. Flexion below C5 during Macintosh intubations has been previously reported by Turkstra *et al.*[17] Also, under routine conditions, this model predicted the occiput translates 1.4 mm posterior to C1, with progressively less posterior translation at C1–C2 and C2–C3, changing to anterior translation at C3–C4, with 1.0 mm or less of anterior translation in the remaining caudal segments. These predicted translations are compatible with translation values calculated from the clinical intubation data reported by Mentzelopoulos *et al.*[18] (occiput–C1 = 1.0 mm, C1–C2 = 0.6 mm, C2–C3 = 0.5 mm, C3–C4 = 0.4 mm, and C4–C5 = 0.3 mm). Therefore, this model predicts cervical spine motions measured during routine intubations reported in three different clinical studies. In addition, in our previous validation study, this model closely predicted spine motions in cadavers with type II odontoid fractures during intubations performed with both conventional and videolaryngoscopy.[16]

For additional information about this model, including development, anatomy, material properties, convergence studies, software, execution time, and code availability, see Supplemental Digital Content 1 (Finite Element Model Development, Material Properties, Calculations, and Limitations; http://links.lww.com/ALN/C740). We followed the applicable Enhancing the QUAlity and Transparency Of health Research (EQUATOR) guidelines for simulation.[19]

Selection of Tracheal Intubation Force Characteristics and Defining Routine Conditions

Although laryngoscope force is not uniformly distributed along the blade, it can be represented biomechanically as being applied at a single point.[20] Thus, laryngoscope blade contact force was modeled as being applied at a single

point (location) having both magnitude (N) and direction (degrees), *i.e.*, as a force vector.[16] Intubation force was simulated as a force vector applied to the anterior surface of a selected cervical spine vertebral body. In a previous finite element modeling study,[16] using radiographic images and simultaneous laryngoscope force distribution measurements from a previous clinical study,[20] the mean applied force location, magnitude, and direction for a routine intubation with a Macintosh blade were estimated to be the midpoint of the C3 vertebral body, 48.8 N, and 70 degrees from the body's coronal plane, respectively. This specific combination of laryngoscope force location, magnitude, and direction are hereafter referred to as routine conditions, denoting force conditions occurring during a routine direct (Macintosh) laryngoscopy and intubation.

As shown in figure 1, laryngoscope force application location, magnitude, and direction were each varied over a range of values. Four laryngoscope force application locations were studied: the superior half of the anterior surface of the C2 vertebral body ($C2_{SUP}$), the inferior half of the anterior surface of the C2 body ($C2_{INF}$), the midpoint of the anterior surface of the C3 body (C3, routine location); and the midpoint of the anterior surface of the C4 body (C4). The $C2_{INF}$ force application location corresponds to that observed with the Airtraq videolaryngoscope.[16,20] Four intubation force magnitudes were studied: 24.4 N, 48.8 N (routine magnitude), 73.2 N, and 97.6 N, corresponding to 50, 100, 150, and 200% of the routine force magnitude. In a study of patients who were predicted to be easy to intubate, Macintosh intubation force magnitude was 48.8 ± 15.8 N (mean ± SD), with the greatest individual patient force magnitude equal to 70.9 N.[20] In a different intubation study, with the utilization of manual in-line stabilization, pressures applied by a Macintosh blade were two-fold greater than without the use of manual in-line stabilization.[4] In a previous cadaver intubation study, Macintosh intubation force magnitude was 47.1 ± 20.5 N, with the greatest individual cadaver Macintosh force magnitude equaling 93.6 N.[21] Thus, 97.6 N (twice the routine value) appears to approximate the maximum amount of force that anesthesiologists can apply with a conventional direct (Macintosh) laryngoscope. Finally, three laryngoscope force directions were studied: 50 degrees, 70 degrees (routine direction), and 90 degrees from the body's coronal plane. The 90-degree

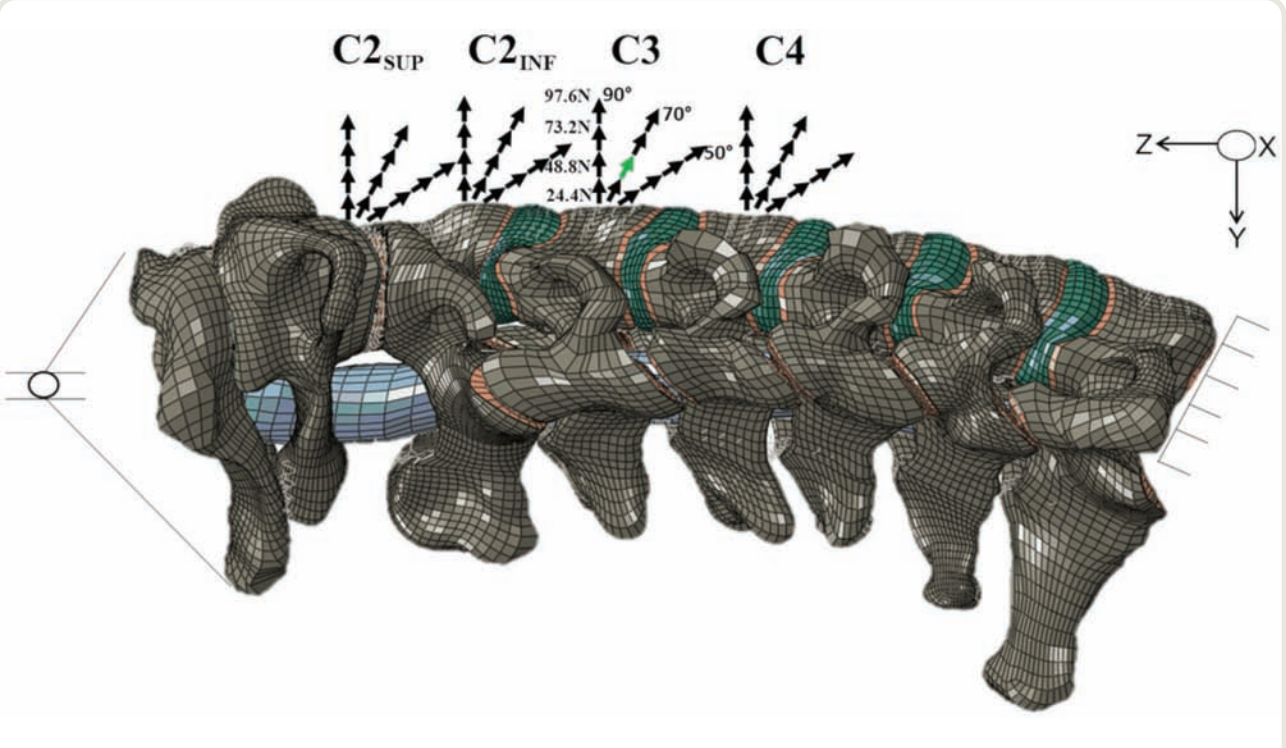

Fig. 1. Finite element model of the human cervical spine and spinal cord, external sagittal view. For clarity, the caudal portion of the occiput is shown without showing the skull. The spinal cord (*blue cylinder*) is seen within the spinal canal between the occiput–C1 and C1–C2. The inferior surface of the C7 vertebral body was fixed in all directions. The occiput was allowed to rotate around the sagittal (*X*) axis in all simulations and translate in the axial (*Z*) direction. Four laryngoscope force application locations were studied: the superior half of the anterior surface of the C2 vertebral body ($C2_{SUP}$), the inferior half of the anterior surface of the C2 body ($C2_{INF}$), the midpoint of the anterior surface of the C3 body (routine location, shown in *green*), and the midpoint of the anterior surface of the C4 body. Four intubation force magnitudes were studied: 24.4 N, 48.8 N (routine force, shown in *green*), 73.2 N, and 97.6 N. Three laryngoscope force directions were studied: 50 degrees, 70 degrees (routine direction, shown in *green*), and 90 degrees from the body's coronal plane.

force direction corresponds to that observed with the Airtraq videolaryngoscope.[16,20] Thus, in total, 48 simulations were conducted, consisting of all combinations of laryngoscope force application location (n = 4), magnitude (n = 4), and direction (n = 3). The resultant spine motion and cord strain values represent quasistatic values corresponding to the maximum values occurring during tracheal intubation.

Measuring Cervical Spine Intervertebral Motion Characteristics

In all simulations, the occiput was allowed to rotate and translate cranially and caudally, whereas the caudal surface of the C7 vertebral body was kinematically constrained to restrict all motion (see Discussion, Limitations). In all simulations, the cervical spine was considered to start at a neutral position, with the degrees of intervertebral rotation (flexion and extension) and anterior–posterior translation (subluxation) defined as zero. Segmental intervertebral rotation and translation at each of seven intervertebral segments were calculated. Rotation was measured as the difference in rotation between reference nodes kinematically attached to adjacent vertebrae and was independent of translation. Intervertebral extension was represented by positive values and flexion by negative values. Translation was measured as the difference in anterior–posterior displacement of the centers of rotation of the two adjacent vertebrae. This method decreases the effect of intervertebral rotation on measures of translation. In a given intervertebral segment, translation of the cranial vertebral body posterior to the caudal vertebral body was defined as being posterior subluxation and is represented with positive values. Conversely, translation of the cranial vertebral body anterior to the caudal vertebral body of a segment was defined as anterior and is represented with negative values.

Measuring Cervical Spinal Cord Strain and Selection of Potentially Injurious Strain Thresholds

Because strain quantitates tissue deformation (*e.g.*, change in length or width) as a ratio of the initial/final value of the parameter, strain is dimensionless. We utilized the logarithmic strain method to calculate strain, strain = $\ln(L/L_0)$, where L is the final length, and L_0 is the initial length. Studies show that accounting for strain in multiple simultaneous planes has a larger observed correlation with tissue injury than strain in any single plane.[13,22] Thus, we used two strain measures that each incorporate the overall three-dimensional strain field: (1) maximum principal strain (tensile strain, analogous to stretch, represented by positive values) and (2) minimum principal strain (analogous to compression, represented by negative values; see Supplemental Digital Content 1 [Finite Element Model Development, Material Properties, Calculations, and Limitations; http://links.lww.com/ALN/C740]). In animal spinal cord injury models, these two strains had the largest observed correlations with tissue injury.[13,14]

Based on a recent experimental study of cervical cord injury in nonhuman primates,[14] we defined two strain values as thresholds for potential cord injury. The maximum principal strains resulting in a 50% cord injury measured histologically 14 to 17 weeks after insult were 0.26 to 0.31 for gray and white matter, respectively.[14] In the same study, the 50% injury values for minimum principal strains were –0.38 to –0.42 for gray and white matter, respectively. Because 50% injury strain values are too great to use as clinical safety thresholds, we defined 50% of these values as *potentially* injurious, specifically 0.14 for maximum principal strain (stretch) and –0.20 for minimum principal strain (compression; see Discussion).

Statistical Analysis

Because model cervical spine anatomy was derived from a single adult human subject[23] and mean material property data inputs were utilized to define the model, the model does not simulate the inherent variation across the human population. In addition, the model does not include random error from experimental measurements. The absence of these variations produces deterministic (*i.e.*, single-valued) motion and strain values. Thus, model predictions for motion and strain are functionally equivalent to population mean values (see Discussion, Limitations). All values for cervical spine motions were rounded to a single decimal before analysis.

Results

Cervical Intervertebral Motion

Figure 2 (A and B) shows the complete data set of predicted intervertebral rotations (extension and flexion) and anterior–posterior translations (subluxation) at the 7 cervical intervertebral segments, each under all (48) modeled tracheal intubation force conditions. Table 1 summarizes model maximum values for intervertebral rotation and translation and the specific force conditions that resulted in these motions.[24–30] Among the 14 combinations of motion (n = 2; rotation and translation) and intervertebral segment (n = 7), all maximum values occurred with the maximum force magnitude (97.6 N). Other intubation force characteristics (location, direction) causing maximum motions differed among motions and segments. To address our first question, table 1 also shows maximum physiologic values for intervertebral motion reported among seven clinical voluntary range of motion studies.[24–30] Maximum values for intervertebral rotation and translation predicted by the model did not meaningfully exceed physiologically normal maximum values measured during voluntary cervical flexion and extension (for additional details and discussion see Supplemental Digital Content 2 [Clinical Studies of Voluntary Cervical Intervertebral Motion; http://links.lww.com/ALN/C741]).

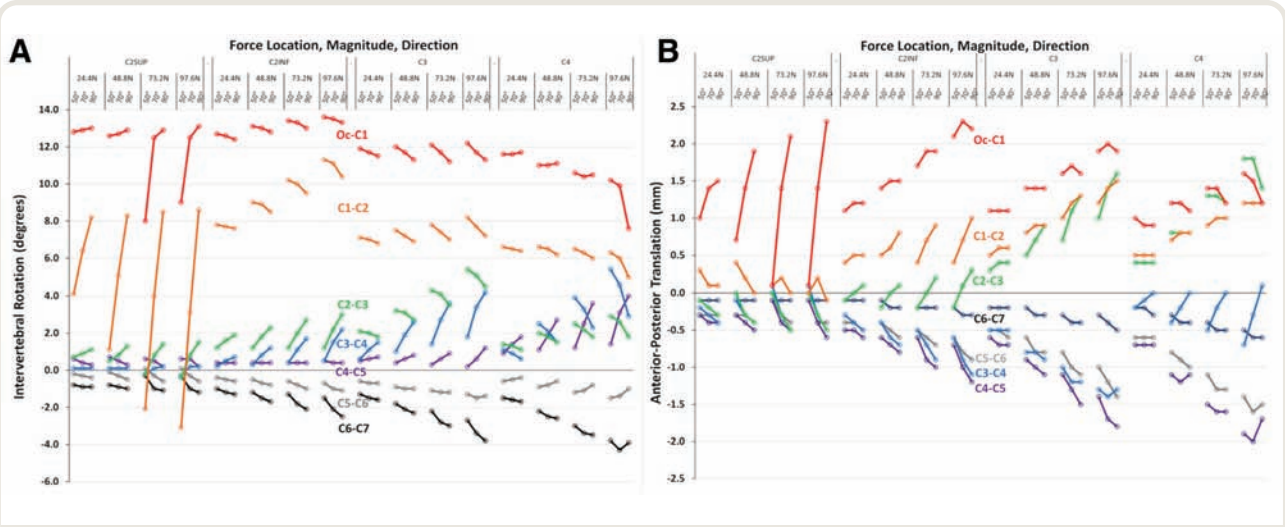

Fig. 2. Segmental intervertebral rotation (*A*) and anterior–posterior translation (*B*) at each of seven cervical segments (occiput–C1 through C6–C7), each under 48 different intubation force conditions consisting of four locations ($C2_{SUP}$, $C2_{INF}$, C3, and C4), four magnitudes (24.4, 48.8, 73.2, and 97.6 N), and three directions (50, 70, and 90 degrees). The values for each segment are color-coded (*e.g.*, occiput–C1 is *red*, C1–C2 is *orange*, and so forth). Positive rotation values indicate extension, and negative rotation values indicate flexion. Positive translation values indicate that the cranial vertebral body of the segment moves posterior to the caudal vertebral body, and negative translation values indicate the cranial vertebral body moves anterior to the caudal vertebral body.

Table 1 also summarizes model values for rotation and translation under routine intubation conditions. Among the 7 segments, the differences between maximum and routine values for rotation and translation were 3.5 degrees or less and 1.1 mm or less, respectively. Thus, the predicted differences between maximum intervertebral motions during intubation and those occurring during a routine intubation are quantitatively small.

Cervical Cord Strain

Although our second aim pertained only to maximum (peak) values of strain present in *any* portion of the cord, the model predicted cord strain to be spatially heterogeneous, with peak strains present in different regions of the cord depending on the location of applied force. Figure 3 shows the distribution of spinal cord strains at each of the four force application locations. Maximum principal (tensile) strain (stretch) was very low in most of the cord. However, there were foci of increased maximum principal strain in the anterior cord. In addition, there were smaller foci of greater (peak) tensile strain in the posterior cord at C1–C2 that were present at mid-C3 when force was applied at C4. Similarly, minimum principal strain (compression) was very low in most of the cord. A focus of increased (peak) compressive strain was present in the posterior cord at C1–C2 with the two most cephalad force application locations ($C2_{SUP}$ and $C2_{INF}$) and was present at mid-C3 with the two most caudal force locations (C3 and C4).

Specifically addressing our second aim, some tracheal intubation conditions *did* result in potentially injurious cord strains. Figure 4 shows peak maximum and minimum principal strain under all (48) intubation force conditions. Peak maximum principal strain (stretch) did not exceed the potential injury threshold (0.14) in any modeled intubation force condition (0 of 48). The peak values for maximum principal strain were insensitive to force magnitude. In contrast, peak minimum principal strain (compression) exceeded the potential injury threshold (–0.20) in 3 of 48 conditions, all with force applied at C4 with the greatest force magnitude (97.6 N). Peak values for minimum principal strain were sensitive to force magnitude; compressive strains increased markedly when force magnitude exceeded 24.4 N. Although peak compressive strains did not exceed the potential injury threshold when force was applied at the routine location (C3), compressive strains were close to the potential injury threshold with force magnitudes of 48.8 N or greater (see Discussion).

Discussion

Clinical Implications and Applications

In the presence of an intact (stable) spine, are there tracheal intubation conditions in which cervical intervertebral motions exceed physiologically normal maximum values? The model predicted that the answer is no. Model predictions for intervertebral rotation (flexion/extension) and translation (subluxation) did not exceed the range of voluntary motion reported in the clinical studies. This was so even with the maximum modeled force magnitude, 97.6 N, which approximates the greatest amount of force anesthesiologists can apply with a conventional direct laryngoscope.

Table 1. Intervertebral Rotation and Translation Predicted by the Model under Maximum and Routine Intubation Force Conditions and Maximum Physiologically Normal Values Reported in the Literature

		Intervertebral Segment						
Variable	**Value**	**Occiput–C1**	**C1–C2**	**C2–C3**	**C3–C4**	**C4–C5**	**C5–C6**	**C6–C7**
Rotation (degrees)	Model maximum	13.6	11.3	5.4	5.4	4.0	–1.5	–4.3
	Physiologic maximum*	14.2	8.3	9.3	11.3	13.3	–9.7	–12.5
	Model routine	11.7	7.2	3.1	1.9	0.6	–1.0	–2.1
Translation (mm)	Model maximum	2.3	1.5	1.8	–1.4	–2.0	–1.6	–0.6
	Physiologic maximum*	1.7	0.8	0.9	–1.2	–1.2	–1.3	–0.9
	Model routine	1.4	0.9	0.7	–0.8	–1.0	–0.8	–0.3
Intubation force conditions: location, magnitude (N), direction (degrees)	Model maximum rotation	$C2_{INF}$ 97.6 N 50	$C2_{INF}$ 97.6 N 50	C3 97.6 N 50	C4 97.6 N 50	C4 97.6 N 90	C3 97.6 N 70 / C4 97.6 N 50	C4 97.6 N 70
	Model maximum translation	$C2_{SUP}$ 97.6 N 90 / $C2_{SUP}$ 97.6 N 70	C3 97.6 N 90	C4 97.6 N 50 / C4 97.6 N 70	C3 97.6 N 70	C4 97.6 N 70	C4 97.6 N 70	C4 97.6 N 70 / C4 97.6 N 90
	Model routine	C3 48.8 N 70	C3 48.8 N 70	C3 48.8 N 70	C3 48.8 N 70	C3 48.8 N 70	C3 48.8 N 70	C3 48.8 N 70

Model rotation and translation values are analogous to group mean values. Physiologic maximum values are group mean values. For rotation, extension is represented with positive values and flexion is represented with negative values. For translation, translation of the superior vertebral body posterior to the inferior vertebral body is defined as posterior translation and is represented with positive values; translation of the superior vertebral body anterior to the inferior vertebral body is defined as anterior and is represented with negative values. See Materials and Methods for an explanation of intubation force conditions and notation. All force conditions are reported when there was more than one set of force conditions that resulted in equal maximum values for segmental motion.

*The values are the greatest mean values reported among seven clinical voluntary range of motion studies.[24–30] These studies and their results are reviewed and discussed in greater detail in Supplemental Digital Content 2 (Clinical Studies of Voluntary Cervical Intervertebral Motion; http://links.lww.com/ALN/C741).

In our models, we included two intubation force locations that may, in fact, not be clinically achievable: one very cephalad ($C2_{SUP}$) and one very caudad (C4). However, this only serves to reinforce the conclusions of this study. We modeled conditions that might truly be one in a million, and still it was practically impossible for tracheal intubation to cause an intact cervical spine to move beyond the maximum motions that occur voluntarily. This is the expected behavior of a stable cervical spine.

The second question was whether in the presence of an intact cervical spine there are tracheal intubation conditions in which potentially injurious cervical cord strains can occur? Importantly, for this second question, we obtained a different answer. The model predicted that the answer is yes, *conditionally*. Notably, under force conditions approximating a routine intubation using a Macintosh blade, peak strains did *not* exceed estimated potential cord injury thresholds for maximum and minimum principal strains. This is an expected result because if injurious cord strains occurred during routine direct laryngoscopy and intubation, intubation-related cervical cord injury would be commonplace, which it is not. In fact, even when intubation force magnitude was twice the routine value (97.6 N instead of 48.8 N), when force was applied at the routine (C3) location, compressive strain did not exceed the potential injury threshold. Again, this is consistent with clinical experience, because even with a difficult intubation, cord injury is rare. However, when maximum force was applied in a location that was more caudal than is routine (*i.e.*, force applied at C4), predicted compressive cord strains exceeded a potentially injurious value. Admittedly, it is difficult to imagine how, with any current laryngoscope, it would be helpful or even possible to apply such high force below the level of the glottis. Thus, in patients who have an intact cervical spine, it might appear to be practically impossible for the cervical cord to experience injurious strain during tracheal intubation.

There is, however, one critically important caveat. The caveat is that model predictions of whether or not injurious cord strains occur during tracheal intubation depend entirely on the levels of cord strain that cause injury. Strain values that cause cord injury in patients are not currently known. The potential strain injury thresholds used in this study are estimates (see Discussion, Limitations, and Supplemental Content 1 [Finite Element Model Development, Material Properties, Calculations, and Limitations; http://links.lww.com/ALN/C740]). Logically, if a patient's strain injury thresholds were less than our estimated injury thresholds

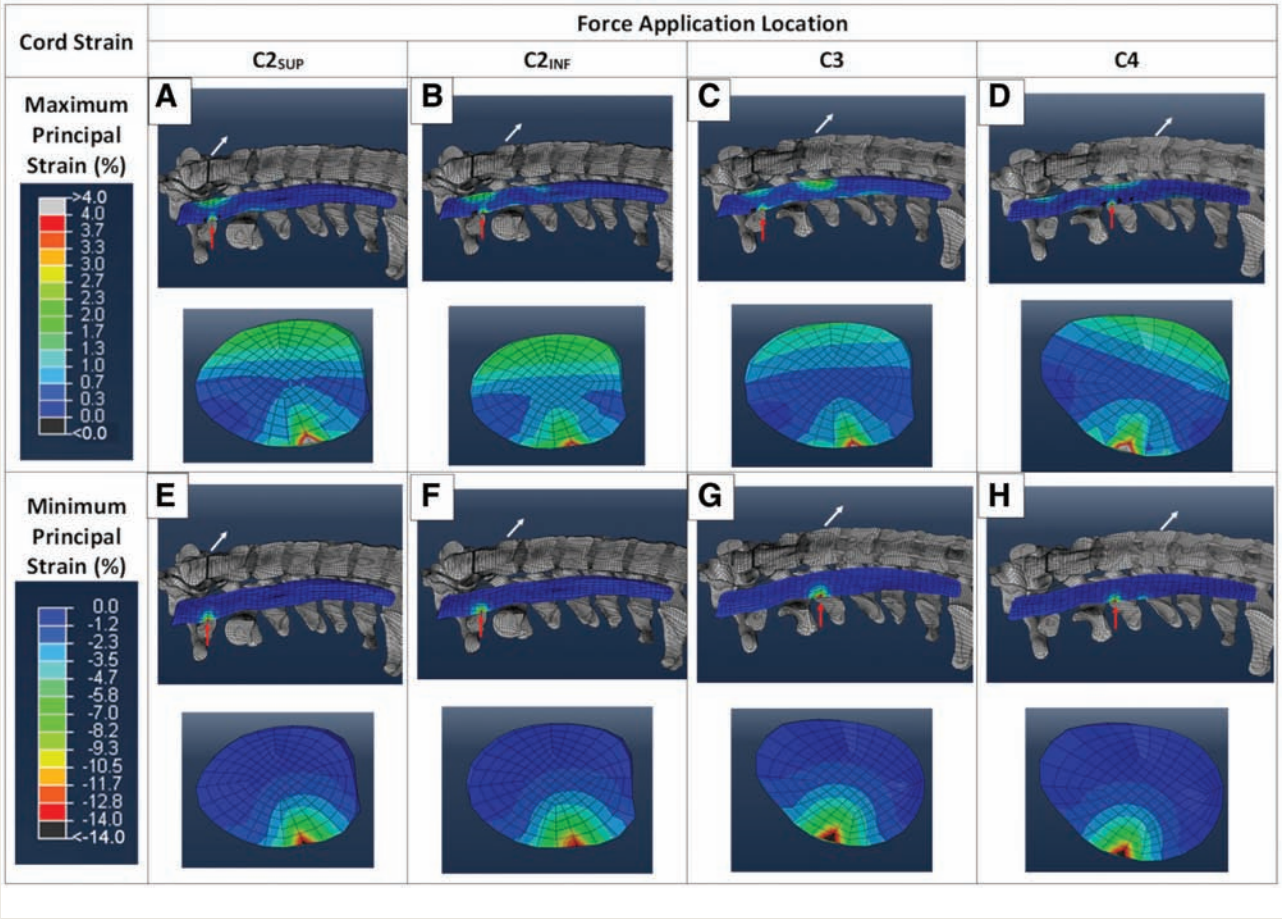

Fig. 3. Cervical spinal cord strain distributions. Using routine values for intubation force magnitude (48.8 N) and direction (70 degrees), the regional distribution of maximum principal strain (stretch) in sagittal and transverse sections of the cervical spinal cord at four force application locations are shown in (*A*) through (*D*). In the sagittal views, the *white arrows* show the locations and directions of the applied forces, and the *red arrows* show the locations of peak cord strain. At each force location, the transverse view of the cord corresponds to the location of the peak cord strain (*red arrows*). (*E*) through (*H*) show the regional distributions of minimum principal strain (compression), using the same conventions.

(*i.e.*, less than normal), strain-related cord injury could occur during *routine* intubation conditions. In other words, cord injury could occur even with normal intubation force and in the absence of pathologic cervical spine motion. In fact, there are several observations that suggest cervical cord injury does, in fact, occur in patients by this mechanism. First, in animal models, acute electrophysiologic responses (*e.g.*, evoked potentials) serve as an indicator of neural sensitivity to acute cord strain.[9,31] Second, in a study of 38 patients who had chronic cervical spondylotic myelopathy, spinal cord evoked potential (N13) amplitudes decreased when patients were placed in 20 degrees of head/neck extension.[32] Decreased evoked potential amplitudes with extension were not associated with cervical spine stability but were associated with measures of preexisting cervical cord compression.[32] These observations suggest that patients who have spondylotic myelopathy may have less tolerance to acute increases in cord strain, even in the absence of instability. Third, in a closed claims study, 11 of 37 patients who experienced perioperative cervical cord injury did so while undergoing a noncervical spine procedure and with an apparently *stable* cervical spine.[2] Most of these 11 patients had preoperatively unrecognized severe cervical spondylosis. Fourth, there are more than 20 case reports describing patients with severe cervical spondylosis and who, in the absence of a difficult intubation, suffered intraoperative cervical cord injury during noncervical spine surgery[33–35] (for additional references and discussion, see Supplemental Digital Content 3 [Case Reports of Perioperative Cervical Spinal Cord Injury in Patients with Cervical Spondylosis; http://links.lww.com/ALN/C742]). Accordingly, we hypothesize that patients who have severe cervical spondylosis have less tolerance to acute cord strain and consequently have greater potential to experience

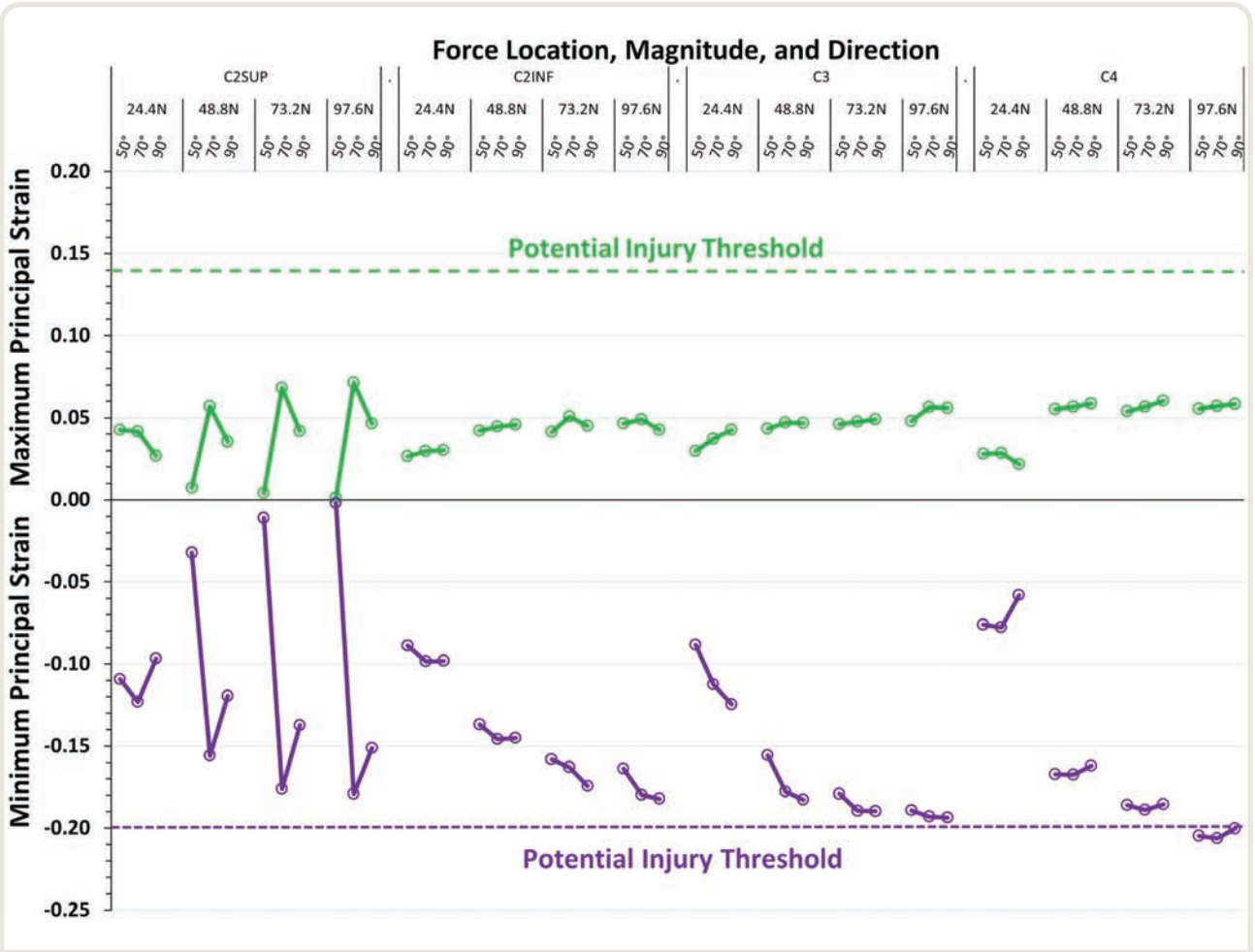

Fig. 4. Peak spinal cord strain values as determined by intubation force location, magnitude, and direction. The figure shows the peak values of maximum principal strain (stretch, *green points and lines*) and minimum principal strain (compression, *purple points and lines*) present at any location in the cervical spinal cord under 48 different intubation force conditions consisting of four locations ($C2_{SUP}$, $C2_{INF}$, C3, and C4), four magnitudes (24.4, 48.8, 73.2, and 97.6 N), and three directions (50, 70, and 90 degrees). Potential cord injury thresholds are shown as *color-matched dashed lines*. Three values of minimum principal strain exceed the potential injury threshold (–0.20), each with force applied at C4 with maximum force magnitude.

potentially injurious cord strain during an otherwise routine (normal force) intubation. Figure 4 shows that peak compressive strains increase markedly and approach the potential injury threshold when force magnitude exceeds 24.4 N, which is half the value applied during a routine intubation with a Macintosh blade. Thus, in patients who may have increased susceptibility to strain-related cord injury, we hypothesize that low-force laryngoscopy[20] may confer less risk of strain-related cervical cord injury.

Intubation-related Cervical Cord Injury

The findings of this study suggest that the approach to preventing intubation-related cervical cord injury should be reconsidered. The model suggests that cervical cord injury from tracheal intubation is not directly related to the *motion* of the cervical spine but instead by the resultant spinal cord deformation, *i.e.*, *strain*. This mechanism of injury would apply regardless of whether the cervical spine is intact (stable) or injured (unstable). We suggest that airway management of patients who have disease of the cervical spine or cord should no longer exclusively focus on minimizing cervical *spine motion*. Instead, an additional, more mechanistically oriented goal, should be to minimize cervical *cord strain*.

Limitations

As previously reported, when compared to patients, the current model appears to underestimate intubation-related extension at C3–C4 and C4–C5 by 2 or 3 degrees.[16] This may be caused by the imposed kinematic constraint of the C7 vertebral body. Although the difference between observed and predicted motion is small at these two segments, we cannot estimate how much this difference

might affect model values for cord strains in the more caudal regions of the cervical cord. In a future version of the model, inclusion of the first thoracic (T1) vertebral segment will permit C7–T1 motion, and this may increase subaxial segmental motion.

Because model anatomy was derived from a single adult human subject and because mean material property data were utilized to define the model, the lack of geometric and material property variation produces deterministic (*i.e.*, single-valued) motion and strain values. Accordingly, the current model does not simulate the inherent variation across the human population but instead represents an anthropometrical mean, *i.e.*, an "average" patient. In the future, to account for variation in geometry and material properties across the general population, probabilistic methods will be dovetailed with the current model. With probabilistic analyses, model parameters (anatomy, material properties) are not defined by a single value but are sampled from a distribution that represents the population's variation, and the model is solved many times to develop a distribution of output variables.[36]

The values used to definite potential strain injury thresholds—50% of 50% cord injury values observed in nonhuman primates (see Materials and Methods)—are unavoidably speculative. In living humans, injurious cord strain values are not currently known. A recent magnetic resonance imaging study of nine healthy volunteers reported *in vivo* maximum and minimum principal strains in sustained extension (without pain or symptoms) were approximately 0.12 and –0.14, respectively.[37] Thus, potential strain injury thresholds used in our simulations (0.14 for maximum and –0.20 for minimum principal strains, respectively) were greater than cord strains that appear to be *non*-injurious in healthy asymptomatic patients. Thus, potential injury thresholds used in this study do not appear to be too low and, as a result, do not appear to greatly overestimate the potential for intubation-related cord injury.

The current model does not include an explicit representation of spinal cord gray and white matter. These tissues may[38,39] or may not[40] have different primary biomechanical properties, and the rostral–caudal alignment of axonal fibers in the spinal cord white matter provides a direction-specific mechanical response.[39] Gray matter may have lesser strain tolerances than white matter,[10–12,14,41] although the difference is small (10 to 20%). Thus, spinal cord strain fields[42,43] and regional (intracord) susceptibility to strain injury are certain to be more complex than are represented in the current version of our model. For additional discussion of model limitations see Supplemental Content 1 (Finite Element Model Development, Material Properties, Calculations, and Limitations; http://links.lww.com/ALN/C740).

Conclusions

In the presence of an intact cervical spine, computational modeling predicted that intervertebral motions during tracheal intubation did not exceed normal physiologic (voluntary) maximum values, even under high-force conditions. In contrast, under nonroutine high-force conditions, the model predicted that potentially injurious cervical cord strains could occur. In patients who have less than normal tolerance to acute cord strain (e.g., patients with cervical myelopathy), cord strains occurring during routine tracheal intubation conditions could approach potentially injurious values. In such patients, low-force laryngoscopy may reduce the risk of intubation-related (i.e., strain-related) cervical cord injury.

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Competing Interests

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ANESTHESIOLOGY

Respiratory Drive in Patients with Sepsis and Septic Shock: Modulation by High-flow Nasal Cannula

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Increases in respiratory drive and effort in critically ill patients may place the patient at higher risk for respiratory failure and intubation.
- The authors have previously shown that respiratory drive and effort are significantly increased in patients with pulmonary infection and that support by high-flow nasal cannula significantly reduces this increase relative to low-flow oxygen therapy.
- Whether respiratory drive is increased and the effect of high-flow nasal cannula in patients with extrapulmonary sepsis remain unknown.

What This Article Tells Us That Is New

- Respiratory drive and effort and dynamic lung compliance were evaluated in 25 nonintubated patients with extrapulmonary sepsis or septic shock using arterial blood gases, esophageal pressure monitoring, and electrical impedance tomography at baseline with low flow nasal oxygen therapy during high-flow nasal cannula support and again with low-flow nasal oxygen therapy. Patient comfort was evaluated using a 10-point visual analog scale at each step.
- High-flow nasal oxygen therapy significantly reduced elevated respiratory drive and effort.
- There was no correlation between patient perceived comfort and measures of drive and effort.
- The impact of the findings from this physiologic study on patient outcome remain to be determined.

ABSTRACT

Background: Experimental and pilot clinical data suggest that spontaneously breathing patients with sepsis and septic shock may present increased respiratory drive and effort, even in the absence of pulmonary infection. The study hypothesis was that respiratory drive and effort may be increased in septic patients and correlated with extrapulmonary determinant and that high-flow nasal cannula may modulate drive and effort.

Methods: Twenty-five nonintubated patients with extrapulmonary sepsis or septic shock were enrolled. Each patient underwent three consecutive steps: low-flow oxygen at baseline, high-flow nasal cannula, and then low-flow oxygen again. Arterial blood gases, esophageal pressure, and electrical impedance tomography data were recorded toward the end of each step. Respiratory effort was measured as the negative swing of esophageal pressure (ΔP_{es}); drive was quantified as the change in esophageal pressure during the first 500 ms from start of inspiration ($P_{0.5}$). Dynamic lung compliance was calculated as the tidal volume measured by electrical impedance tomography, divided by ΔP_{es}. The results are presented as medians [25th to 75th percentile].

Results: Thirteen patients (52%) were in septic shock. The Sequential Organ Failure Assessment score was 5 [4 to 9]. During low-flow oxygen at baseline, respiratory drive and effort were elevated and significantly correlated with arterial lactate ($r = 0.46$, $P = 0.034$) and inversely with dynamic lung compliance ($r = –0.735$, $P < 0.001$). Noninvasive support by high-flow nasal cannula induced a significant decrease of respiratory drive ($P_{0.5}$: 6.0 [4.4 to 9.0] *vs.* 4.3 [3.5 to 6.6] *vs.* 6.6 [4.9 to 10.7] cm H_2O, $P < 0.001$) and effort (ΔP_{es}: 8.0 [6.0 to 11.5] *vs.* 5.5 [4.5 to 8.0] *vs.* 7.5 [6.0 to 12.6] cm H_2O, $P < 0.001$). Oxygenation and arterial carbon dioxide levels remained stable during all study phases.

Conclusions: Patients with sepsis and septic shock of extrapulmonary origin present elevated respiratory drive and effort, which can be effectively reduced by high-flow nasal cannula.

(ANESTHESIOLOGY 2021; 135:1066–75)

Sepsis and septic shock are deadly syndromes characterized by intense acute inflammatory reaction.[1] Mediators produced at the site of infection are poured into systemic circulation and activate amplification pathways within and between peripheral target organs.[2]

Proinflammatory stimuli to the central nervous system trigger an increase in body temperature.[3] Activation of the sympathetic response and release of stress hormones increase the cardiovascular tone.[4] These responses alter the metabolic demands of the organism, increasing carbon dioxide

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production.[5,6] A compensatory increase of the respiratory drive will be the price to pay to eliminate sepsis-induced excess of carbon dioxide through adequate minute ventilation.[7]

Metabolic acidosis due to poor peripheral perfusion, lactate production, impaired renal function, and altered plasma buffers will further increase minute ventilation to compensate for systemic acidosis.[8] Moreover, spontaneously breathing septic patients often present with respiratory alkalosis, because arterial carbon dioxide levels fall below the compensatory value. This is likely due to further activation of the respiratory drive by inflammatory stimuli targeting central and peripheral chemosensors and generating exaggerated breathing response.[9]

Although there is scant data, if any, on human subjects,[10] the authors reasoned that activation of the above-mentioned mechanisms (*i.e.*, increased metabolic activity, metabolic acidosis, inflammatory mediators) could lead to increased respiratory drive, resulting in excessive inspiratory effort in sepsis and septic shock patients, even in the absence of pulmonary infection.

Relevant clinical consequences of increased respiratory drive during sepsis and septic shock could be many: increased muscular effort poses the risk of diaphragm fatigue and pump failure[11]; higher inspiratory transpulmonary pressure may lead to patient self-inflicted lung injury in lungs already "hit" by soluble inflammatory mediators[12]; the increase in oxygen consumption by the respiratory muscles could further impair the delivery/consumption imbalance and precipitate cardiovascular failure.[13] Two large clinical studies already showed extremely high mortality of spontaneously breathing septic patients intubated during their intensive care unit (ICU) stay *versus* those patients who were never intubated.[14,15] All these data generate the hypothesis that modulation of respiratory drive and effort might represent a relevant physiologic goal in spontaneously breathing patients with sepsis and septic shock in the ICU.

In patients with acute hypoxemic respiratory failure, high-flow nasal cannula improves clinical outcomes through multiple physiologic mechanisms (*e.g.*, decreased effort, dead space wash-out, increased alveolar F_{IO_2}, and improved comfort).[16–18] Even though these mechanisms may also be beneficial in patients with increased drive caused by extrapulmonary causes, they have not been evaluated in patients with sepsis and septic shock without pneumonia. The aim of this study was to measure respiratory drive and effort in these patients and to assess the physiologic effects of high-flow nasal cannula. The study hypothesis was that respiratory drive and effort may be increased in septic patients and correlated with extrapulmonary determinants (*e.g.*, metabolic acidosis) and that high-flow nasal cannula may modulate drive and effort.

Materials and Methods

Patient Population

Between March 2019 and November 2020, 25 nonintubated patients admitted to 3 ICUs in Italy with a diagnosis of sepsis or septic shock were enrolled. Sepsis and septic shock were defined according to the Sepsis-3 consensus guidelines.[1] The exclusion criteria were diagnosis of pneumonia, severe chronic obstructive pulmonary disease, contraindication to the use of an esophageal balloon catheter, and encephalopathy with a Glasgow coma scale score of less than 12.

This study was approved by the ethical committees of each participating center (promoting and coordinating center: Maggiore Policlinico Hospital, Milan, Italy; reference No. 193_2019bis). Written informed consent was obtained from all participants before enrollment. The study was planned and conducted according to ethics and transparence guidelines following the Declaration of Helsinki. Because this was an explorative physiologic study, the methods used were not registered on a public server before its completion, as for other similar studies in this field.[17–20]

Clinical Data

After enrollment, the following characteristics were recorded: age, height, weight, body mass index, length of stay in the ICU before inclusion, oxygenation under clinical respiratory support (*i.e.*, Pa_{O_2}/F_{IO_2} ratio), clinical severity assessed by SAPS II and Sequential Organ Failure Assessment (SOFA) scores, plasma lactate and C-reactive protein levels, and use of vasopressors.

Monitoring

An esophageal balloon catheter (Cooper Surgical, USA) was inserted through the nose, inflated following the manufacturer's recommendations, and secured. Appropriate positioning was confirmed by insertion depth, presence of cardiac artifacts, and convincing inspiratory swings. The esophageal pressure (P_{es}) signal was recorded intermittently with a dedicated acquisition system at a 100-Hz sample rate and analyzed offline.

An electrical impedance tomography belt was placed between the fourth and fifth intercostal space and connected to its recording device. The acquisition sample rate was set at 50 Hz. The electrical impedance tomography data were continuously acquired and analyzed offline with dedicated software. Detailed information about the devices and software used in each center is available in the Supplemental Digital Content (table A1, http://links.lww.com/ALN/C699).

Study Protocol

Patients were kept in a semirecumbent position without sedation. Adequate analgesia was checked before the start of the protocol (visual analog scale [VAS] of 3 or lower). A calm environment was ensured around the patients throughout the study. Each patient underwent 3 consecutive 30-min steps:

1) Low-flow oxygen–baseline, with no support or low-flow oxygenation device to maintain peripheral oxygen saturation (Spo_2) at greater than 94%
2) High-flow nasal cannula, with flow 50 l/min, temperature 34 to 37°C and Fio_2 to maintain Spo_2 at greater than 94%
3) Low-flow oxygen–end, same support and settings as during the low-flow oxygen–baseline step.

During Steps 1 and 3, low-flow oxygen support was delivered through nasal cannula or standard nonocclusive facemask, according to the clinical practice of each center (Supplemental Digital Content, table A2, http://links.lww.com/ALN/C699). In Step 2, high-flow nasal cannula was provided through a dedicated system (Airvo 2, Fisher & Paykel Healthcare, New Zealand).

Toward the end of each step, the following was recorded: respiratory rate (RR), Spo_2, mean arterial pressure, and heart rate. Then a 3-min recording of the P_{es} waveform was stored, and arterial blood gas was measured. During the high-flow nasal cannula step, the Fio_2 was assessed directly by the device, while the Fio_2 during the two low-flow oxygen steps was calculated as follows: [21 + (O_2 flow in l/min × 3)]%.[21]

The ratio of oxygen saturation was computed as the Spo_2/Fio_2 ratio divided by RR.[22] Patients were asked to rate the comfort related to each respiratory support by VAS, ranging between 0 (extreme discomfort) to 10 (very comfortable).

Esophageal Pressure

Data from esophageal pressure waveforms from 10 consecutive representative breaths were computed offline from recordings performed at the end of each step. All tracings were analyzed by two independent observers. In four patients, tracings were discarded due to poor quality of the waveforms (Supplemental Digital Content, fig. A1a and A1b, http://links.lww.com/ALN/C699).

Respiratory effort was assessed by maximal amplitude of P_{es} change during negative inspiratory swing (ΔP_{es}). An estimate of the metabolic work of breathing was calculated as the esophageal pressure-time product per minute (Supplemental Digital Content, fig. A2, http://links.lww.com/ALN/C699)[17].

Electrical Impedance Tomography

Offline analysis of electrical impedance tomography data allowed the calculation of tidal volume (V_T) by measuring the average tidal impedance variation (10 representative breaths recorded at the end of each step) and then converting arbitrary units into milliliters based on a calibration factor derived from a similar population of ICU patients from a previous study.[18] Supplemental information about this calibration process is provided in the Supplemental Digital Content (http://links.lww.com/ALN/C699).

Minute ventilation was computed as the product of V_T × RR. Dynamic compliance of the lung was calculated as the ratio of $V_T/\Delta P_{es}$, as previously described.[17] Lung homogeneity was assessed by the ratio between tidal impedance variation in the ventral and dorsal regions ($V_{T\text{-}NDEP/DEP}$).[17,18]

Respiratory Drive

Respiratory drive was measured by three P_{es} and electrical impedance tomography–based measures: the inspiratory esophageal pressure change during the first 500 ms from the start of inspiration ($P_{0.5}$)[23]; the slope of the inspiratory negative P_{es} swing from the start of inspiration to the minimum pressure ($\Delta P_{es}/\Delta t$); and the mean inspiratory flow, calculated as the ratio between V_T and the inspiratory time (V_T/Ti).[24] Through the use of these indexes, the authors aimed to assess the two dimensions of drive: the intensity ($P_{0.5}$ and $\Delta P_{es}/\Delta t$) and the amplitude (V_T/Ti).

Statistical Analysis

All results are presented as median [interquartile range] or number (%). Distribution normality was checked for each variable using the D'Agostino–Pearson test. Based on previous studies, sample size calculation (n = 20) was performed by hypothesizing a change of ΔP_{es} of 2.5±3 cm H_2O between study Steps 1 and 2,[17,18] with a two-tailed type I error of 5% and statistical power of 80%. Because we predicted a feasibility for ΔP_{es} measurement of 80%, sample size was increased to 25 patients.

Comparisons of physiologic variables between the three study steps were preplanned and performed by using one-way repeated measures ANOVA on rank. *Post hoc* comparisons between the low-flow oxygen–baseline and the two following steps were performed by Dunnett's test.

Correlations between ΔP_{es} and selected physiologic variables were performed by Spearman's correlation. To further identify independent determinants of respiratory effort, we performed a multiple linear regression including the two factors significantly associated with ΔP_{es} at Spearman's correlation (*i.e.*, $\Delta P_{es}/V_T$ and arterial lactate) and adjusted for age, body mass index, and SOFA score. Spearman's correlations were also used to assess the relationship between comfort scale (VAS), ΔP_{es}, and $P_{0.5}$.

The association between ΔP_{es} and measures of respiratory drive was assessed by linear regression, pooling data from all three study steps (n = 63). Measurements were assumed to be independent across individuals.

Given the amount of physiologic data that we measured in adjunct to esophageal pressure, all 25 patients were analyzed for main outcomes. Then we repeated the analyses only in the subgroup of patients with high-quality waveforms of esophageal pressure (n = 21). Finally, we performed a *post hoc* sensitivity analysis (*i.e.*, subgroup analysis) on nonhypoxemic patients (*i.e.*, patients with Pao_2/Fio_2 ratios of greater than 200 mmHg upon enrollment, n = 21)

to avoid overlap with results from our previous study.[17] For all analyses, a two-tailed *P* value of less than 0.05 was considered significant. Statistical analysis was performed using SPSS (SPSS Statistics, USA) and Prism (GraphPad version 9.0, USA).

Results

Twenty-five patients were enrolled in this study. The main characteristics of the study population are described in table 1. The median age was 69 [interquartile range, 54 to 79] yr old. Seventeen patients (68%) were enrolled within 24 h from admission, with a median ICU stay before enrollment of 1 [0 to 2] day. The median SOFA score was 5 [4 to 9], and 13 patients (52%) were in septic shock (table 1).

As mentioned above, esophageal data were missing for four patients, because of poor quality of the recorded waveforms. Arterial blood gas analysis was not available for one patient during the low-flow oxygen–baseline step for technical reasons. There were no other missing data.

Respiratory effort assessed by ΔP_{es} and was elevated during low-flow oxygen–baseline and low-flow oxygen–end phases and significantly decreased during the high-flow nasal cannula phase, in comparison to both low-flow oxygen steps (ANOVA $P < 0.001$; table 2; fig. 1A). Support by high-flow nasal cannula was also associated with a decrease of respiratory drive: all three variables that were measured as surrogate of central drive ($P_{0.5}$, $\Delta P_{es}/\Delta t$, and V_T/Ti) significantly fell during high-flow nasal cannula ($P < 0.01$ for all; table 2; fig. 1B). Of note, high-flow nasal cannula modulated respiratory drive and effort even in patients with relatively normal values during the first low-flow oxygen step (fig. 1). The absolute changes in respiratory effort and drive between study phases were so relevant that they may be considered clinically significant (table 2).

Electrical impedance tomography allowed noninvasive assessment of minute ventilation and dynamic lung compliance ($V_T/\Delta P_{es}$; table 2; fig. 1C). During high-flow nasal cannula, minute ventilation decreased ($P = 0.080$) with unchanged arterial carbon dioxide levels ($P = 0.151$), and the $V_T/\Delta P_{es}$ ratio improved ($P = 0.003$). Lung homogeneity assessed by electrical impedance tomography with the $V_{NDEP/DEP}$ ratio improved ($P = 0.080$) as well (table 2).

As expected by study protocol, there was no difference between the three phases in terms of Spo_2 ($P = 0.335$), and the Pao_2/Fio_2 ratio did not change either ($P = 0.160$; table 2). Hemodynamics remained stable during high-flow nasal cannula (table 2). All the main study comparisons presented in table 2 were reanalyzed in the subgroups of nonhypoxemic patients and those with high-quality esophageal pressure tracings (n = 21 for both, see "Materials and Methods" above), leading to similar results (Supplemental Digital Content, tables A3 and A4, http://links.lww.com/ALN/C699).

Table 1. Patients' Main Characteristics

Characteristics	All Patients (n = 25)
Age, yr	69 [54 to 79]
Female (%)	15 (60)
Height, cm	170 [160 to 173]
Body mass index, kg/m^2	24.2 [21.6 to 27.1]
ICU days before enrollment	1 [0 to 2]
SOFA score	5 [4 to 9]
SAPS II score at ICU admission	37 [31 to 46]
C-reactive protein, mg/l	19 [13 to 35]
Patients with septic shock (%)	13 (52)
Plasma lactate in septic shock patients, mmol/l	2.9 [2.4 to 4.7]
Plasma lactate in patients with sepsis, mmol/l	1.2 [0.9 to 3.3]
Etiology (%)	
Abdominal	15 (60)
Urinary	7 (28)
Other	3 (12)

ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment score.

Although maybe relevant only for hypoxemic patients, the authors measured the ratio of oxygen saturation, which increased during the high-flow nasal cannula phase (low-flow oxygen–baseline 11.7 [9.4 to 17.1] *vs.* high-flow nasal cannula 18.5 [15.6 to 25.6] *vs.* low-flow oxygen–end 14.8 [11.9 to 19.4]; $P < 0.001$). High-flow nasal cannula was well tolerated: comfort assessed by the VAS scale did not differ between the three phases (low-flow oxygen–baseline 8 [7 to 9] *vs.* high-flow nasal cannula 8 [7 to 9] *vs.* low-flow oxygen–end 8 [8 to 9]; $P = 0.119$). Of note, there was no correlation between ΔP_{es}, $P_{0.5}$, and the comfort VAS during the low-flow oxygen–baseline step (Supplemental Digital Content, fig. A3, http://links.lww.com/ALN/C699).

To explore the main determinants of increased inspiratory effort during sepsis and septic shock, the authors evaluated the correlation between ΔP_{es} assessed within the low-flow oxygen–baseline phase and physiologic respiratory stimuli measured at the bedside. Figure 2 shows all the correlations: ΔP_{es} was significantly associated with arterial lactate and inversely with the $V_T/\Delta P_{es}$ ratio ($r = 0.46$, $P = 0.034$ and $r = -0.76$, $P < 0.001$, respectively). Interestingly, altered arterial blood gases (O_2 and carbon dioxide levels), sepsis severity (SOFA score), and biomarker of inflammation (C-reactive protein) did not correlate with respiratory effort. In the multivariate model adjusted for clinical confounders (see the "Materials and Methods" above), both arterial lactate (β-coefficient: 1.70 [95% CI 0.53 to 2.87], $r^2 = 0.41$, $P = 0.012$) and the $V_T/\Delta P_{es}$ ratio (β-coefficient: –0.05 [–0.08 to –0.02], $r^2 = 0.39$, $P = 0.012$) were independently correlated with ΔP_{es}.

The correlation between drive and effort may be lost in the presence of neuromuscular insufficiency, but in the current study performed early after admission, the correlation between $P_{0.5}$ and ΔP_{es} was statistically significant ($r = 0.95$; $P < 0.001$; fig. 3). Significant correlations existed

Table 2. Physiologic Effects of High-flow Nasal Cannula in Spontaneously Breathing Patients with Sepsis and Septic Shock

	Low-flow Oxygen–Baseline	High-flow Nasal Cannula	Low-flow Oxygen–End	ANOVA *P* Value
Respiratory effort				
ΔP_{es}, cm H_2O	8.0 [6.0 to 11.5]	5.5 [4.5 to 8.0]*	7.5 [6.0 to 12.6]	**< 0.001**
P_{es} time product, cm $H_2O \cdot s \cdot min^{-1}$	224 [184 to 300]	140 [84 to 192]*	210 [174 to 275]	**< 0.001**
Respiratory drive				
$P_{0.5}$, cm H_2O	6.0 [4.4 to 9.0]	4.3 [3.5 to 6.6]*	6.6 [4.9 to 10.7]	**< 0.001**
$\Delta P_{es}/\Delta t$, cm $H_2O \cdot s^{-1}$	9.0 [5.4 to 13.0]	5.7 [4.6 to 8.8]*	10.0 [6.2 to 14.2]	**< 0.001**
V_T/T_i, ml $\cdot s^{-1}$	534 [473 to 668]	489 [424 to 593]†	533 [420 to 611]	**0.003**
Lung volumes by electrical impedance tomography				
V_T, ml	512 [391 to 695]	584 [421 to 733]	519 [403 to 635]	0.958
Respiratory rate, min^{-1}	23 [20 to 27]	20 [14 to 24]*	22 [20 to 25]	**0.002**
Minute ventilation, l $\cdot min^{-1}$	11.95 [9.72 to 14.70]	10.49 [8.73 to 14.28]	11.51 [8.17 to 14.06]	0.080
$V_T/\Delta P_{es}$, ml $\cdot$ cm H_2O^{-1}	63 [36 to 105]	83 [71 to 144]*	65 [41 to 114]	**0.003**
$V_{T\text{-}NDEP/DEP}$	1.21 [0.84 to 1.54]	1.15 [0.78 to 1.48]	1.27 [0.86 to 1.52]	0.080
Gas exchange				
pH	7.43 [7.41 to 7.46]	7.44 [7.39 to 7.47]	7.43 [7.41 to 7.47]	0.663
$Paco_2$, mmHg	33.8 [30.9 to 41.3]	33.9 [29.9 to 39.1]	34.1 [32.1 to 41.2]	0.151
Pao_2/Fio_2, mmHg	257 [228 to 331]	329 [280 to 367]	308 [246, 356]	0.160
Sao_2, %	96.0 [93.8 to 96.5]	96 [93.8 to 96.0]	96.0 [95.0 to 96.4]	0.335
Hemodynamics				
Mean arterial pressure, mmHg	83 [71 to 97]	80 [71 to 92]	76 [69 to 94]	0.130
Heart rate, beats/min	94 [81 to 118]	101 [84 to 113]	94 [78 to 115]	0.319

The values are from Dunnett's *post hoc* tests. Boldface refers to the statistically significant ANOVA *P* values (with a threshold of 0.05).

*$P < 0.005$ from low-flow oxygen–baseline; †$P < 0.05$ from low-flow oxygen–baseline.

Fio_2, inspired dioxygen fraction; ΔP_{es}, negative esophageal pressure swing; RR, respiratory rate; Sao_2, arterial dioxygen saturation; T_i, inspiratory time; V_T, tidal volume; $V_{T\text{-}NDEP/DEP}$, nondependent on dependent regions tidal volume ratio.

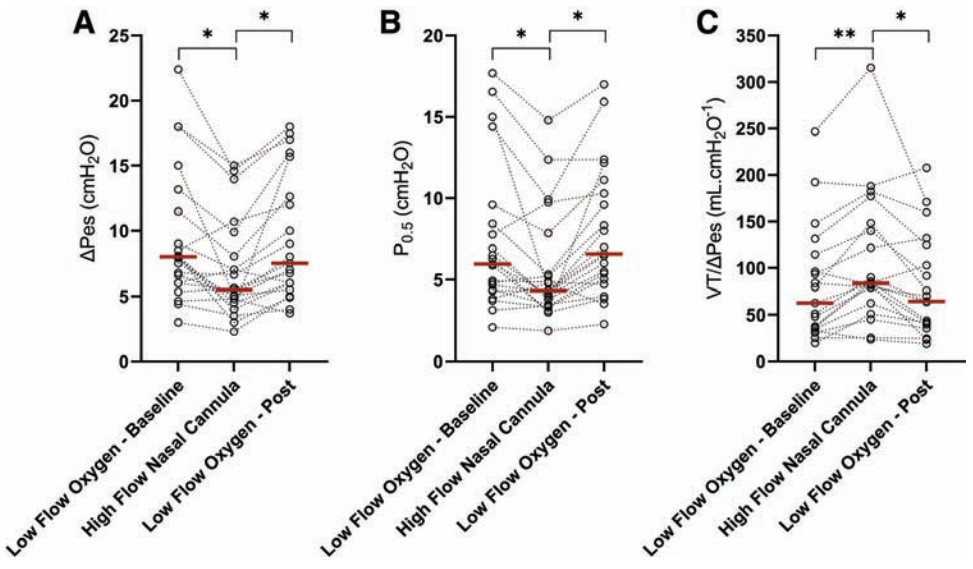

Figure 1. Effects of high-flow nasal cannula on negative esophageal pressure swing (patient's effort: ΔP_{es}, *A*); ΔP_{es} at 500 ms from the start of effort (patient's drive: $P_{0.5}$, *B*); and dynamic lung compliance ($V_T/\Delta P_{es}$, *C*). *Red bars* indicate median value. *P* values for the ANOVA test are reported in table 2. *Post hoc* Dunnett's *P* values: *$P < 0.005$; **$P < 0.05$.

also between ΔP_{es} and $\Delta P_{es}/\Delta t$, whereas correlation with mean inspiratory flow was poorer (Supplemental Digital Content, fig. A4, http://links.lww.com/ALN/C699). ΔP_{es} during the high-flow nasal cannula phase improved more in patients with higher baseline RR and ΔP_{es}, with a linear relationship between these variables and the ΔP_{es}

improvement (Supplemental Digital Content, fig. A5, http://links.lww.com/ALN/C699).

Discussion

The main findings of the study can be summarized as follows: respiratory drive and effort are increased in patients with sepsis and septic shock of extrapulmonary origin, and noninvasive support by high-flow nasal cannula modulates them effectively; higher plasma lactate level and lower dynamic lung compliance are associated with more intense respiratory effort; respiratory drive and effort are tightly correlated early after admission to the ICU; and higher inspiratory effort and respiratory rate during low-flow oxygen are associated with more effective modulation of effort by high-flow nasal cannula. This study confirmed the hypothesis of increased respiratory effort in patients with sepsis and septic shock in comparison to controls. The median for ΔP_{es} of 8.0 cm H_2O measured in septic patients is clearly higher than 3.2 cm H_2O measured in recent series on healthy adults.[25] In addition, more than 75% of septic patients had pressure-time product values above the physiologic upper threshold of 150 cm $H_2O \cdot s \cdot min^{-1}$.[26] Experimental and pilot clinical data showed that, during sepsis, multiple mechanisms could lead to increased respiratory drive and effort.[10,27]

Askanazi *et al.*[5] showed that infusion of catecholamines and stress hormones (which are hallmark mediators of the systemic septic syndrome) increase the O_2 consumption and carbon dioxide production in healthy subjects, leading to a compensatory increase of minute ventilation. Metabolic acidosis is highly prevalent in sepsis and septic shock; the etiology is multifactorial, and the severity of the acidosis is correlated with the outcome.[28] Metabolic acidosis is accompanied by respiratory compensation and hyperventilation to clear carbon dioxide, if the patient is able to manage that.[8,10]

Tang *et al.*[9] showed that an intravenous challenge with 50 mg/kg endotoxin in healthy rats increases the minute ventilation by 144% within 5 h and that tachypnea is prevented by vagotomy, suggesting that hyperventilation is mediated by lung vagal afferents. Interestingly, in that study, the effects of endotoxin were independent from alterations of gas exchange.[9] Similarly, Huxtable *et al.*[29] described increased respiratory rates in rats treated with lipopolysaccharide and hypothesized a direct action on the brainstem centers. Finally, the study findings may resemble experimental human data by Doorduin *et al.*[30]: Lipopolysaccharides infused in healthy humans induced an increase in diaphragmatic strength, which might explain the tight correlation with drive.

In summary, metabolic demands, acidosis, and inflammation increase the respiratory drive and, if muscular function is preserved, the effort in septic patients.[10,31] The close correlation between drive and effort that we describe likely suggests that the muscular function in the patient population was not impaired, and higher drive directly produced

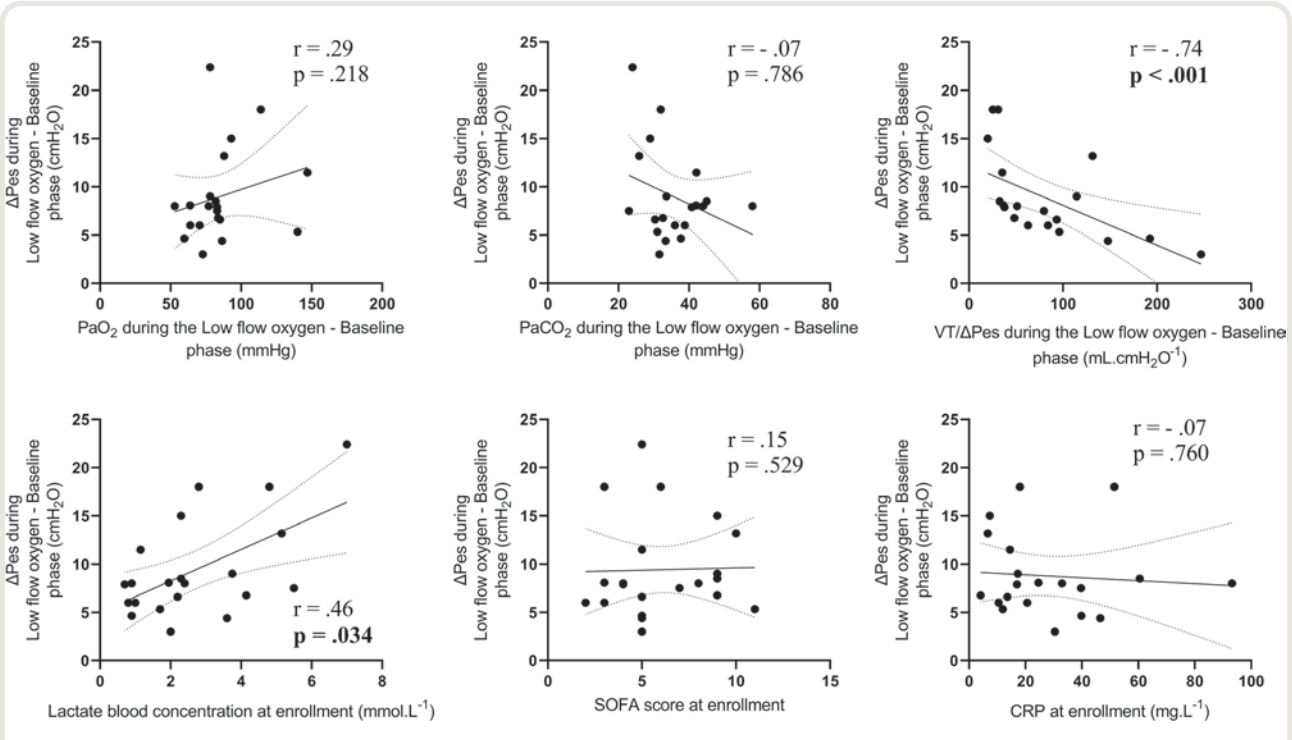

Figure 2. Correlations between physiologic determinants of inspiratory effort *versus* ΔP_{es} during the low-flow oxygen–baseline step. Spearman's correlation was computed for each variable. r and *p* values are reported in the figure for each variable.

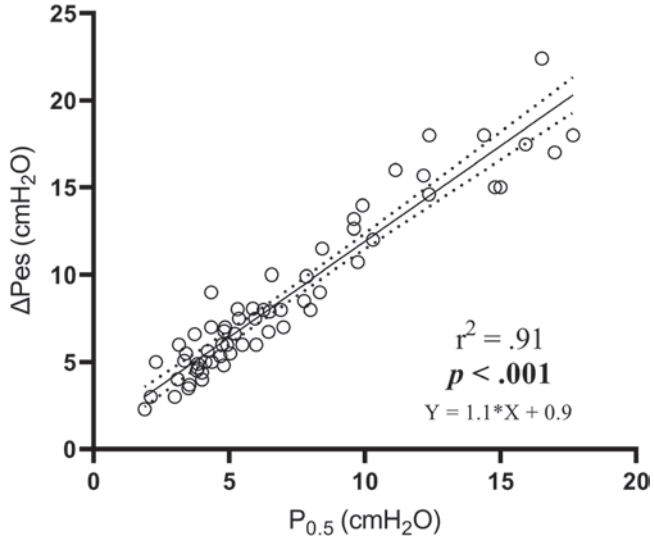

Figure 3. Dunnett's *post hoc* tests: *$P < 0.05$ from low-flow oxygen–baseline; †$P < 0.005$ from low-flow oxygen–baseline. Data from all three study steps were gathered. Linear regression values are provided with 95% CIs and equation.

an increase in ventilation. Previous clinical study confirmed a more rapid and shallow breathing pattern in intubated septic patients during weaning, which is a quite different setting in comparison with the current data.[27] Septic patients may be considered at risk of increased respiratory drive and effort, even when their lungs are not the primary site of infection.

To further describe the correlation between determinants of drive and the respiratory effort in the study population, the authors correlated markers of each mechanism with ΔP_{es}. Plasma lactate and dynamic lung compliance were the only factors showing an association. Lactate is one of the main determinants of cerebrospinal fluid acidosis, which directly stimulates the respiratory centers[32]; however, they are also correlated with the overall severity of sepsis, and a simple noncausal association cannot be excluded.[33] Dynamic compliance may be a more sensitive indicator of the impairment in lung function than gas exchange, and although patients with pneumonia were excluded from the study, initial lung injury caused by circulating mediators and/or high lung stress may have already been at play to increase respiratory drive and effort.

In our population, there was no association between the respiratory drive and effort and the comfort perceived by the patient, making this measure unsuitable as a marker of increased transpulmonary pressure. This finding likely highlights the very complex interaction between acute respiratory failure and comfort: other determinants like mucosal dryness, pain, psychologic stress, and fear might become predominant over more specific mechanisms such as increased respiratory load. Similar lack of linear correlation between respiratory pattern and comfort was already described in patients with acute exacerbation of chronic obstructive pulmonary disease.[34]

Previously published data on patients with acute respiratory hypoxemic failure (including only patients with Pao_2/Fio_2 of less than 200, 87% with pneumonia) already showed a decrease in respiratory effort by noninvasive support with high-flow nasal cannula.[17] In the current study, only 4 patients (16%) had Pao_2/Fio_2 of less than 200, and pneumonia was an exclusion criterion. Despite different settings and minimum overlap with previous study, high-flow nasal cannula modulated both the intensity and the amplitude of respiratory drive of septic patients, and this likely decreased the instantaneous per-breath effort (ΔP_{es}), as well as the surrogate index of longer term work of breathing (pressure-time product). The most probable mechanisms leading to beneficial effects of high-flow nasal cannula in septic patients may have been washout of the dead space, compensating excessive carbon dioxide production, and some expiratory positive pressure effect, improving dynamic lung compliance.[17,18] Regardless of the mechanism used for the same clinical condition, by application of high-flow nasal cannula, the muscles of septic patients may have to bear less work of breathing, and their lungs may be subject to decreased lung stress.

The potential clinical impact of the authors' findings is correlated with the risk of worse clinical outcome in spontaneously breathing septic patients intubated during their ICU stay. In a *post hoc* analysis of data from a large randomized clinical trial on 776 septic shock patients, Delbove *et al.*[14] described significantly lower mortality in patients admitted to the ICU and never requiring intubation *versus* those intubated during their ICU stay. Later on, the

prospective INTUBATIC study performed by Darreau *et al.*[15] enrolled 859 spontaneously breathing patients with septic shock admitted to the ICU: in-hospital mortality was 46.9% in patients intubated within 8 h *versus* 41.2% in patients intubated between 8 and 72 h and 13.1% in patients who were never intubated. Interestingly, in that study, use of accessory muscles (likely indicating strong inspiratory effort) and higher respiratory rate characterized patients who ended up intubated *versus* those who were never intubated. Respiratory effort and rate are the same factors that, in the current study, correlated with larger reduction of effort by high-flow nasal cannula. However, the primary endpoint of the current study was physiologic.

This study presents some limitations. First, findings should be generalized with caution because of the limited number of patients enrolled and given the heterogeneous nature of sepsis. However, the sample size is larger than previous physiologic studies on the same topic.[17,18,20,27] Second, esophageal pressure measurements were performed without calibration according to the method described by Baydur *et al.*,[35] but the current study used objective criteria to evaluate the quality of online measures (insertion depth, cardiac artifacts, amplitude of negative P_{es} swings). Third, electrical impedance tomography was calibrated by a factor derived from another patient population with similar characteristics (adult nonintubated critically ill patients),[18] for whom synchronized spirometry and electrical impedance tomography data were collected; although the factor may not be as accurate for this population, the relative effects between study steps should be reliable. Fourth, the authors did not assess the differential role of the diaphragm *versus* accessory inspiratory and expiratory muscles (*e.g.*, by ultrasonography)[36] as the origin of increased effort. Of note, experimental studies in dogs exposed to endotoxin showed homogeneous activation of all the inspiratory muscles.[37,38] In a cohort of intubated septic patients, use of accessory muscles measured by ultrasonography was verified in the majority of cases.[36] These findings generate the hypothesis that both the diaphragm and the accessory muscles may generate increased effort in septic patients, and their differential role deserves further exploration. Fifth, the correlation between ΔP_{es} and dynamic lung compliance ($V_T/\Delta P_{es}$) may suffer by some degree of mathematical coupling. However, we present it given the sound physiologic background linking respiratory mechanics and effort.[39] Sixth, the three measures of respiratory drive may have been influenced by respiratory muscle strength and/or respiratory system compliance, and conclusions regarding the impact of high-flow nasal cannula on respiratory drive in septic patients should be taken with caution. Finally, both sepsis and septic shock patients were enrolled in this study, which may have introduced some heterogeneity; the authors wanted to explore a spectrum of severity to analyze correlations between clinical and biochemical factors and respiratory drive and effort.

Conclusions

High-flow nasal cannula modulates effectively elevated respiratory drive and effort in patients with sepsis and septic shock of extrapulmonary etiology. Higher lactatemia and lower dynamic lung compliance characterize patients with stronger inspiratory effort. Higher respiratory rate and effort during low-flow oxygen may predict larger modulation of effort by high-flow nasal cannula. The study findings generate the hypothesis that noninvasive respiratory support by high-flow nasal cannula in septic patients without pneumonia might reduce the risks of increased inspiratory effort.

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Competing Interests

Dr. Mauri received personal fees from Drager (Lubeck, Germany), Fisher & Paykel Healthcare (Auckland, New Zealand), Mindray (Nanshan, China), and BBraun (Melsungen, Germany), all outside of the submitted work. Dr. Pesenti received personal fees from Fresenius (Bad Homburg vor der Höhe, Germany), Getinge (Getinge, Sweden), and Baxter (Deerfield, Illinois), all outside the submitted work. The other authors declare no competing interests.

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ANESTHESIOLOGY

Treatments Associated with Lower Mortality among Critically Ill COVID-19 Patients: A Retrospective Cohort Study

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- While the treatment of critically ill COVID-19 patients has improved, mortality rates remain high

What This Article Tells Us That Is New

- In a retrospective cohort consisting of 2,070 critically ill COVID-19 patients treated in six hospitals, multivariable regression analysis showed lower in-hospital mortality associated with apixaban, aspirin, or enoxaparin treatment
- Propensity score–matching analyses demonstrated lower mortality for patients receiving apixaban (27% [96 of 360] *vs.* 37% [133 of 360]), aspirin (26% [121 of 473] *vs.* 30% [140 of 473]), or enoxaparin (25% [87 of 347) *vs.* 34% [117 of 347]) compared to matched controls

ABSTRACT

Background: Mortality in critically ill COVID-19 patients remains high. Although randomized controlled trials must continue to definitively evaluate treatments, further hypothesis-generating efforts to identify candidate treatments are required. This study's hypothesis was that certain treatments are associated with lower COVID-19 mortality.

Methods: This was a 1-yr retrospective cohort study involving all COVID-19 patients admitted to intensive care units in six hospitals affiliated with Yale New Haven Health System from February 13, 2020, to March 4, 2021. The exposures were any COVID-19–related pharmacologic and organ support treatments. The outcome was in-hospital mortality.

Results: This study analyzed 2,070 patients after excluding 23 patients who died within 24 h after intensive care unit admission and 3 patients who remained hospitalized on the last day of data censoring. The in-hospital mortality was 29% (593 of 2,070). Of 23 treatments analyzed, apixaban (hazard ratio, 0.42; 95% CI, 0.363 to 0.48; corrected CI, 0.336 to 0.52) and aspirin (hazard ratio, 0.72; 95% CI, 0.60 to 0.87; corrected CI, 0.54 to 0.96) were associated with lower mortality based on the multivariable analysis with multiple testing correction. Propensity score–matching analysis showed an association between apixaban treatment and lower mortality (with *vs.* without apixaban, 27% [96 of 360] *vs.* 37% [133 of 360]; hazard ratio, 0.48; 95% CI, 0.337 to 0.69) and an association between aspirin treatment and lower mortality (with *vs.* without aspirin, 26% [121 of 473] *vs.* 30% [140 of 473]; hazard ratio, 0.57; 95% CI, 0.41 to 0.78). Enoxaparin showed similar associations based on the multivariable analysis (hazard ratio, 0.82; 95% CI, 0.69 to 0.97; corrected CI, 0.61 to 1.05) and propensity score–matching analysis (with *vs.* without enoxaparin, 25% [87 of 347] *vs.* 34% [117 of 347]; hazard ratio, 0.53; 95% CI, 0.367 to 0.77).

Conclusions: Consistent with the known hypercoagulability in severe COVID-19, the use of apixaban, enoxaparin, or aspirin was independently associated with lower mortality in critically ill COVID-19 patients.

(ANESTHESIOLOGY 2021; 135:1076–90)

A particular challenge of COVID-19 treatment is the high mortality, especially among critically ill patients. Although the mortality rate was estimated to be ~50% among critically ill COVID-19 patients in the early stage of the pandemic,[1] a study performed at a later stage of the pandemic showed a downward trend of mortality rates from ~44% to ~19%.[2] Effective treatments might be one factor responsible for this decline. Continuous efforts in discovering effective treatments are needed and have been ongoing as evidenced by the recent trials exploring the effectiveness of therapeutic *versus* prophylactic anticoagulation in hospitalized and critically ill patients.[3–5] With the passing of the COVID-19 pandemic's first anniversary and the surge of the Delta variant, a look back at the data accumulated over 1 yr provides an opportunity to identify potentially effective treatments. Such an approach could corroborate established treatments or generate hypotheses for future investigations.

This retrospective cohort study hypothesized that certain treatments would be associated with lower mortality in patients

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treated in intensive care units (ICUs) for COVID-19–related complications. Our objective was to identify the treatments associated with lower COVID-19 mortality based on multivariable analysis. The reproducibility of the associations identified by multivariable analysis was evaluated by propensity score–matching analysis. This study was based on all COVID-19 patients treated in the ICUs in hospitals affiliated with Yale New Haven Health System headquartered in New Haven, Connecticut.

Materials and Methods

Study Design

Yale University's Human Subject Protection Program initially approved this retrospective cohort study and waived informed consent on May 6, 2020 (institutional review board protocol no. 2000028070). The reporting of this study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Setting

This study was based on all patients diagnosed with COVID-19 secondary to a SARS-CoV-2 infection and treated for COVID-19–related complications in the ICUs of six hospitals affiliated with Yale New Haven Health System (*i.e.*, Yale New Haven Hospital, Saint Raphael Campus, Greenwich Hospital, Bridgeport Hospital, Lawrence + Memorial Hospital, and Westerly Hospital). The study period was from February 13, 2020, when the first COVID-19 patient was admitted to the ICU at Yale, to March 4, 2021, when the COVID-19 ICU admission significantly declined. We included all COVID-19 patients admitted to Yale's ICUs during the study period to reflect the experience of treating critically ill COVID-19 patients throughout the first pandemic year.

Study Population

Inclusion criteria for this study included an age of 18 yr or older, a diagnosis of COVID-19 (based on real-time reverse transcription–polymerase chain reaction assay targeting three regions of the SARS-CoV-2 genome, namely orf1ab, spike [S] gene, and nucleocapsid [N] gene), and treatment in one of Yale New Haven Health System's ICUs at any time during the study period. COVID-19 patients who required organ support therapies or intensive monitoring and care were eligible for ICU admission at Yale. No patients were admitted to ICU purely for isolation. The respiratory criteria for ICU admission varied over time: when there were sufficient ICU resources, patients requiring noninvasive ventilation or invasive mechanical ventilation were admitted to the ICU; however, during the case surge, when ICU resources were inadequate, only patients requiring invasive mechanical ventilation were admitted to the ICU. Exclusion criteria for this study were death within 24 h after ICU admission, age of less than 18 yr, and continued hospitalization on the last day of data censoring. Patient care was per the institutional protocols customized for COVID-19 patients and continuously updated based on the evolving evidence.

Variables

The primary outcome was in-hospital mortality, defined as all-cause death that occurred during a patient's hospitalization. Patients were regarded as survivors if they were discharged alive from the hospital or as nonsurvivors if they died during hospitalization. We included patients who were admitted to Yale's ICUs up to March 4, 2021. The relevant information of those patients who remained hospitalized on March 4, 2021, was updated based on the electronic medical records on June 1, 2021 (*i.e.*, the last day of data censoring).

The treatments in this study were any COVID-19–related pharmacologic or organ support intervention instituted during a patient's hospitalization. The pharmacologic treatments included (1) antiviral drugs (*e.g.*, remdesivir and hydroxychloroquine); (2) anticoagulants (*e.g.*, enoxaparin, heparin, and apixaban); (3) antiplatelet agents (*e.g.*, aspirin, clopidogrel, and ticagrelor); (4) steroids (*e.g.*, dexamethasone, methylprednisolone, and hydrocortisone); (5) immunomodulators (*e.g.*, tocilizumab); (6) immunosuppressants (*e.g.*, tacrolimus); (7) vasopressors (*e.g.*, norepinephrine, epinephrine, and dopamine); and (8) uncategorized drugs (*e.g.*, azithromycin, convalescent plasma, and famotidine). Information on drug dose, timing, and duration of treatment was collected. The organ support therapies included (1) conventional oxygen therapy delivered using a regular nasal cannula or face mask; (2) high-flow nasal cannula; 3) bilevel positive airway pressure ventilation; (4) continuous positive airway pressure ventilation; (5) invasive mechanical ventilation; (6) continuous venovenous hemofiltration; and (7) extracorporeal membrane oxygenation.

The potential confounders were as follows: (1) the known risk factors for COVID-19 mortality (age, sex, and hypertension); (2) the severity of the acute illness during the first 24 h after ICU admission (Sequential Organ Failure Assessment score, Glasgow Coma Scale score, and invasive mechanical ventilation); (3) the various phases during the first pandemic year, *i.e.*, the first phase (February 1, 2020, to May 31, 2020), the second phase (June 1, 2020, to August 31, 2020), the third phase (September 1, 2020, to November 30, 2020), and the fourth phase (December 1, 2020, to March 4, 2021), with each patient assigned to a phase based on their ICU admission date; (4) the demographics and comorbidities; and (5) the laboratory results and vital signs during the first 24 h after ICU admission.

Data Sources and Measurement

The measurements of all variables of interest were conducted in routine patient care guided by the institutional protocols customized for COVID-19 patients and continuously updated based on the evolving evidence. Patient data were extracted from the electronic medical records by the Joint Data Analytics Team at the Yale Center for Clinical Investigation. This team centralizes and coordinates clinical

and research analytics and reporting across the Yale New Haven Health System and Yale School of Medicine.

Bias

Efforts were made to minimize selection bias. Our study analyzed all adult COVID-19 patients admitted to the ICUs in six hospitals affiliated with Yale New Haven Health System at any time during the study period. Yale New Haven Health System covers a significant portion of Connecticut and provides a mixture of different levels of care to state residents. As all our patients were treated in hospital settings, missing data were minimized because of standardized electronic methods for data capture and recording. All variables of interest were measured using the same methods across the healthcare system.

Study Size

No statistical power calculation was conducted before the study because we planned to include all COVID-19 patients who had been treated in Yale New Haven Health System's ICUs throughout the entire first pandemic year. The sample size was based on the available cases.

Quantitative Variables

We used original quantitative data collected from electronic medical records, including demographic characteristics, laboratory results, vital signs, drug doses, and treatment timing and duration. We removed data outside of the 0.5 to 99.5 percentile range for vital signs, considering that some of these measurements could be artifacts or outliers.

Statistical Methods

Continuous data are presented as means and SD or median and interquartile range, depending on the normality of distribution, assessed using histograms and Q-Q plots. Categorical data are presented as numbers and percentages. Missing data were not imputed.

Our objective was to identify treatments associated with lower mortality using a multivariable Cox proportional-hazards model. The variables entering the multivariable analysis included all COVID-19–related treatments and the potential confounders described above under "Variables." Only those treatments that were used in at least 5% of patients were included in the analysis. Demographics, comorbidities, laboratory results, and vital signs with a *P* value less than 0.25 in univariate analyses were included in the multivariable analysis. If two variables had an absolute Pearson's or Spearman's rank correlation coefficient greater than 0.5, we included only one variable to avoid collinearity. We excluded variables that had missing data for more than 10% of the patients. Multiple testing correction was performed using the Bonferroni method to reduce the chance of type I errors at the two-sided 0.05 α level. The hypotheses for all COVID-19–related treatments were considered as a family; therefore, the raw *P* value for each treatment was multiplied by the number of treatments being analyzed to derive the corrected *P* value. The association was estimated using hazard ratios and reported with 95% CIs. To account for clustering within hospitals, we used robust sandwich estimators to compute standard errors for the hazard ratios.[6]

We used propensity score–matching analysis to evaluate the reproducibility of the association identified by the multivariable analysis. We divided patients into two cohorts: one cohort received the treatment, and the other cohort did not, with these two cohorts balanced at the baseline level using propensity score matching. The propensity score model included the demographic characteristics, comorbidities, pandemic phase, severity of acute illness (during the first 24 h after ICU admission), laboratory results (during the first 24 h after ICU admission), and vital signs (during the first 24 h after ICU admission). The matched pairs were identified using a one-to-one nearest neighbor caliper of 0 to 0.1 width. The balance between matched pairs was assessed using a standardized 10% difference. Survival was estimated using the product-limit Kaplan–Meier estimator, and the log-rank statistic was used to compare the survival curves. A stratified Cox proportional-hazards model was used in the analysis of the matched pairs.

We additionally explored the factors that could have modified the association identified by the multivariable analysis and evaluated by the propensity score–matching analysis. The method of analysis depended on the characteristics of the treatment associated with lower COVID-19 mortality. If a drug was associated with lowering mortality significantly, we presented the relevant data by dividing the patients into subgroups with different drug doses when feasible. When feasible, we also split the matched pairs derived from the propensity score matching into subgroups with different drug doses to explore the potential factors that might have modified the association.

A data analysis and statistical plan was written and filed with a private entity (institutional review board) before the data were accessed. During the peer-review process, significant modifications were requested and implemented. No minimum clinically meaningful effect size was defined before data access. The propensity score-matched analyses were planned *post hoc*. For a two-tailed hypothesis test, the significance level for each general hypothesis was 0.05. All analyses were performed in R software (version 3.5.3, R Foundation for Statistical Computing, Austria), with packages including sqldf, dplyr, sandwich, survival, survminer, arsenal, mltools, MatchIt, stddiff, and tableone.

Results

Study Population

From February 13, 2020, to March 4, 2021 (1 yr and 3 weeks), a total of 2,096 patients were treated for COVID-19–related complications in Yale New Haven Health System's ICUs (fig. 1). We excluded 23 patients who died within 24 h after ICU admission and 3 patients who remained hospitalized on the last day of data censoring. The final analysis involved 2,070 patients, including 856 (41%) patients admitted to

ICU during the first phase, 138 (6.7%) patients during the second phase, 400 (19.3%) patients during the third phase, and 676 (32.7%) patients during the fourth phase (fig. S1 in Supplemental Digital Content, http://links.lww.com/ALN/C693). The study population had a mean age of 65 yr (SD, 16 yr; N = 2,070) and a male patient percentage of 58.8% (1,218 of 2,070; table 1 and table S1 in Supplemental Digital Content, http://links.lww.com/ALN/C693).

Descriptive Data

The potential COVID-19–related treatments are presented in table S2 in Supplemental Digital Content (http://links.lww.com/ALN/C693), with most treatments given to less than 5% of the study population. The treatments included in the multivariable analysis are presented in table 2. The potential confounders included in the multivariable analysis are presented in table S3 in Supplemental Digital Content (http://links.lww.com/ALN/C693).

Outcome Data

A total of 593 patients died during hospitalization, and 1,477 patients were discharged from the hospital alive. The all-cause in-hospital mortality was 28.6% (593 of 2,070). The mortality was 31.8% (272 of 856) during the first pandemic phase, 10.1% (14 of 138) during the second pandemic phase, 26.8% (107 of 400) during the third pandemic phase, and 29.6% (200 of 676) during the fourth pandemic phase. The median hospital stay was 16 days (interquartile range, 10 to 27), and the median ICU stay was 6 days (interquartile range, 2 to 13).

Treatments Associated with Lower Mortality

The following treatments were associated with lower mortality based on the multivariable analysis: atazanavir (hazard ratio, 0.58; 95% CI, 0.393 to 0.89; $P = 0.006$), enoxaparin (hazard ratio, 0.82; 95% CI, 0.69 to 0.97; $P = 0.021$), heparin (hazard ratio, 0.79; 95% CI, 0.66 to 0.95; $P = 0.011$), apixaban (hazard ratio, 0.42; 95% CI, 0.363 to 0.48; $P < 0.001$), aspirin (hazard ratio, 0.72; 95% CI, 0.60 to 0.87; $P < 0.001$), famotidine (hazard ratio, 0.364; 95% CI, 0.174 to 0.76; $P = 0.008$), and conventional oxygen therapy (hazard ratio, 0.51; 95% CI, 0.327 to 0.81; $P = 0.004$; table 2). The results of the 23 hypotheses, corresponding to all treatments included in the multivariable analysis, were corrected using the Bonferroni method. After multiple testing correction, only apixaban (corrected CI, 0.336 to 0.52; corrected $P < 0.001$) and aspirin (corrected CI, 0.54 to 0.96; corrected $P = 0.010$) remained significantly associated with lower mortality. The results of the univariate analyses are presented in table S4 in Supplemental Digital Content (http://links.lww.com/ALN/C693).

Propensity Score–matching Analysis for Apixaban

The association between apixaban and mortality was further evaluated using propensity score–matching analysis as this association remained significant after the multivariable analysis with multiple testing correction. The propensity score matching generated two well balanced cohorts: one comprising 360 patients who received apixaban treatment and the other comprising 360 patients who never received apixaban treatment (table 3 and table S5 in Supplemental Digital Content, http://links.lww.com/ALN/C693). The mortality was 26.7% (96 of 360) in patients treated with apixaban and 36.9% (133 of 360) in patients not treated with apixaban. Apixaban treatment had a significant association with lower mortality (hazard ratio, 0.48; 95% CI, 0.337 to 0.69; $P < 0.001$), reflecting a 52% lower mortality risk in apixaban-treated patients compared to patients never treated with apixaban. The respective survival probabilities

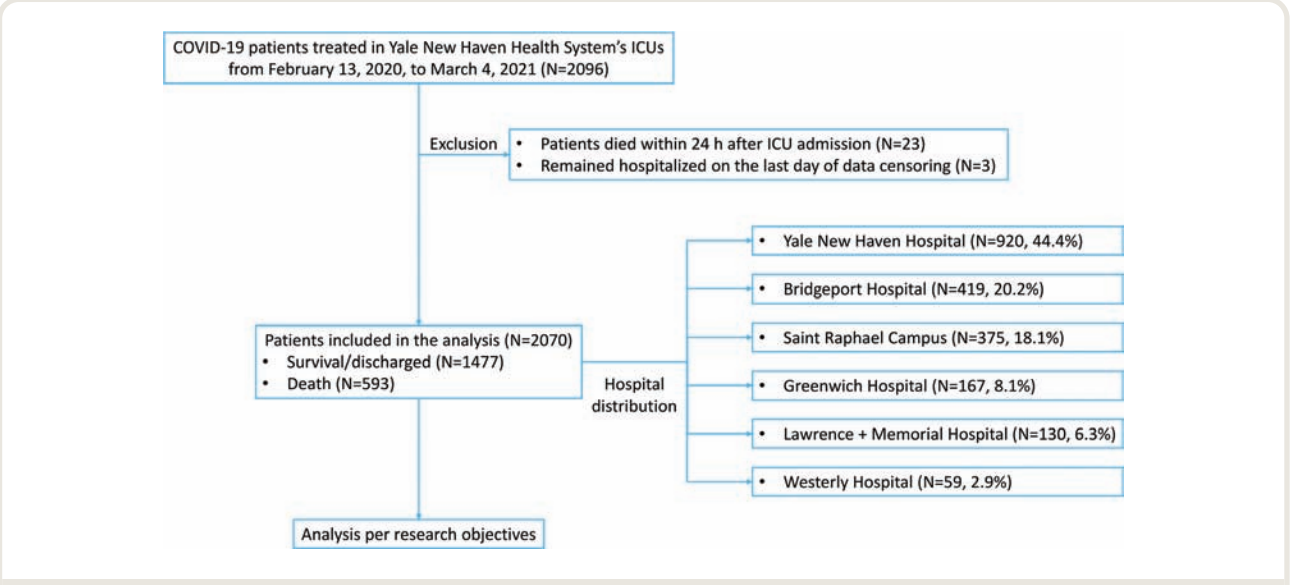

Fig. 1. Patients and analyses. ICU, intensive care unit.

Table 1. Baseline Characteristics (N = 2,070)

Categories and Variables	Mean ± SD and Median [Interquartile Range] and Number of Patients (%)
Demographics	
Age, yr	65 ± 16
Sex (male)	1,218 (58.8%)
Body mass index, kg/m²*	29 [24–35]
Never smoking†	882 (46.6%)
Comorbidities	
Myocardial infarction	381 (18.4%)
Congestive heart failure	665 (32.1%)
Peripheral vascular disease	512 (24.7%)
Cerebrovascular disease	539 (26.0%)
Dementia	283 (13.7%)
Chronic obstructive pulmonary disease	749 (36.2%)
Rheumatic disease	141 (6.8%)
Peptic ulcer disease	142 (6.9%)
Liver disease	347 (16.8%)
Diabetes	935 (45.2%)
Paraplegia	127 (6.1%)
Renal disease	619 (29.9%)
Malignancy	377 (18.2%)
Metastatic cancer	201 (9.7%)
Human immunodeficiency virus infection	28 (1.4%)
Hypertension	1,549 (74.8%)
Hyperlipidemia	1,263 (61.0%)
Anxiety	532 (25.7%)
Depression	542 (26.2%)
Immunosuppression	18 (0.9%)
Asthma	430 (20.8%)
Number of comorbidities, number	4 [2–7]
Charlson Comorbidity Index, points	3 [1–6]
Severity of acute illness during the first 24 h after ICU admission	
Sequential Organ Failure Assessment score‡	6 [4–9]
Glasgow Coma Scale score§	15 [14–15]
Invasive mechanical ventilation	541 (26.1%)

Refer to table S1 in Supplemental Digital Content (http://links.lww.com/ALN/C693) for laboratory results and vital signs acquired during the first 24 h after ICU admission.

*Data were missing in 9 patients. †Data were missing in 177 patients. ‡Data were missing in 114 patients. §Data were missing in 927 patients.

ICU, intensive care unit.

of patients who received and did not receive apixaban treatment are presented in figure 2A. An additional stratified multivariable Cox regression analysis based on the matched cohorts also showed a significant association between apixaban treatment and lower mortality (hazard ratio, 0.388; 95% CI, 0.254 to 0.59; $P < 0.001$), with the covariates including enoxaparin, aspirin, and dexamethasone.

Propensity Score–matching Analysis for Enoxaparin

Enoxaparin was the anticoagulant of choice for hospitalized COVID-19 patients during this pandemic. In total, 72.7% of our patients received enoxaparin, whereas only 19.7% received apixaban. The multivariable analysis suggested an association between enoxaparin treatment and lower mortality, although this association was no longer significant after multiple testing correction (table 2). This result might be due to overcorrection. To further explore this association, we used propensity score–matching analysis to estimate the association between enoxaparin and mortality.

The propensity score matching generated two well balanced cohorts: one comprising 347 patients who received enoxaparin treatment and the other comprising 347 patients who never received enoxaparin treatment (table 4 and table S6 in Supplemental Digital Content, http://links.lww.com/ALN/C693). The mortality was 25.1% (87 of 347) in patients treated with enoxaparin and 33.7% (117 of 347) in patients never treated with enoxaparin. Enoxaparin treatment had a significant association with lower mortality (hazard ratio, 0.53; 95% CI, 0.367 to 0.77; $P < 0.001$), reflecting a 47% lower mortality risk in enoxaparin-treated patients compared to patients never treated with enoxaparin. The respective survival probabilities of patients who received and did not receive enoxaparin are presented in figure 2B. An additional stratified multivariable Cox regression analysis based on the matched cohorts also showed a significant association between enoxaparin treatment and lower mortality (hazard ratio, 0.55; 95% CI, 0.373 to 0.81; $P = 0.002$), with the covariates including apixaban, aspirin, and dexamethasone.

Propensity Score–matching Analysis for Aspirin

The association between aspirin and mortality was further evaluated using propensity score–matching analysis because this association remained significant after the multivariable analysis with multiple testing correction. The propensity score matching generated two well balanced cohorts: one comprising 473 patients who received aspirin treatment and the other comprising 473 patients who never received aspirin treatment (table 5 and table S7 in Supplemental Digital Content, http://links.lww.com/ALN/C693). The mortality was 25.6% (121 of 473) in patients treated with aspirin and 29.6% (140 of 473) in patients not treated with aspirin. Aspirin treatment had a significant association with lower mortality (hazard ratio, 0.57; 95% CI, 0.41 to 0.78; $P < 0.001$), reflecting a 43% lower mortality risk in aspirin-treated patients compared to patients never treated with aspirin. The respective survival probabilities of patients who received and did not receive aspirin treatment are presented in figure 2C. An additional stratified multivariable Cox regression analysis based on the matched cohorts also showed a significant association between aspirin treatment and lower mortality (hazard ratio, 0.61; 95% CI, 0.43 to 0.86; $P = 0.005$), with the covariates including apixaban, enoxaparin, and dexamethasone.

Exploratory Analysis

Association Modification by Apixaban Dose. Apixaban was administered in two different doses: a prophylactic dose (2.5 or 5 mg two times daily) in 80% (328 of 408) of patients and a therapeutic dose (10 mg two times daily) in 20% (80 of

Table 2. Association between Treatment and Mortality Based on Multivariable Analysis (N = 1,656)

Categories and Treatments	Number of Patients (%)*	Multiple Testing Uncorrected		Multiple Testing Corrected†	
		Hazard Ratio [95% CI]	*P* Value	Hazard Ratio [Corrected CI]	*P* Value
Antiviral drugs					
Remdesivir	991 (47.9)	1.06 [0.71–1.58]	0.770	1.06 [0.57–1.98]	> 0.999
Hydroxychloroquine	706 (34.1)	0.98 [0.64–1.52]	0.935	0.98 [0.50–1.94]	> 0.999
Atazanavir	162 (7.8)	0.58 [0.393–0.89]	0.006	0.58 [0.315–1.07]	0.138
Anticoagulants					
Enoxaparin	1,504 (72.7)	0.82 [0.69–0.97]	0.021	0.82 [0.61–1.05]	0.483
Heparin	1,086 (52.5)	0.79 [0.66–0.95]	0.011	0.79 [0.59–1.05]	0.253
Apixaban	408 (19.7)	0.42 [0.363–0.48]	< 0.001	0.42 [0.336–0.52]	< 0.001
Antiplatelet drugs					
Aspirin	1,355 (65.5)	0.72 [0.60–0.87]	< 0.001	0.72 [0.54–0.96]	0.010
Clopidogrel	181 (8.7)	0.88 [0.53–1.44]	0.610	0.88 [0.40–1.91]	> 0.999
Steroids					
Dexamethasone	831 (40.1)	1.13 [0.70–1.83]	0.603	1.13 [0.54–2.39]	> 0.999
Methylprednisolone	561 (27.1)	0.91 [0.81–1.03]	0.123	0.91 [0.76–1.09]	> 0.999
Hydrocortisone	264 (12.8)	1.29 [1.02–1.62]	0.030	1.29 [0.89–1.88]	0.690
Immunomodulators					
Tocilizumab	925 (44.7)	1.03 [0.86–1.23]	0.738	1.03 [0.78–1.37]	> 0.999
Vasopressors					
Norepinephrine	890 (43.0)	1.38 [1.07–1.77]	0.012	1.38 [0.93–2.04]	0.276
Epinephrine	178 (8.6)	1.62 [1.37–1.92]	< 0.001	1.62 [1.24–2.11]	< 0.001
Uncategorized drugs					
Azithromycin	327 (15.8)	0.78 [0.55–1.10]	0.156	0.78 [0.46–1.33]	> 0.999
Convalescent plasma	317 (15.3)	0.90 [0.77–1.05]	0.193	0.90 [0.71–1.15]	> 0.999
Famotidine	132 (6.4)	0.364 [0.174–0.76]	0.008	0.364 [0.114–1.15]	0.184
Organ support therapies					
Conventional oxygen therapy	1,898 (91.7)	0.51 [0.327–0.81]	0.004	0.51 [0.253–1.05]	0.092
High-flow nasal cannula	1,070 (51.7)	0.81 [0.61–1.08]	0.146	0.81 [0.52–1.26]	> 0.999
Bilevel positive airway pressure ventilation	473 (22.9)	1.45 [0.98–2.15]	0.066	1.45 [0.78–2.68]	> 0.999
Continuous positive airway pressure ventilation	234 (11.3)	0.83 [0.68–1.02]	0.076	0.83 [0.61–1.14]	> 0.999
Invasive mechanical ventilation	888 (42.9)	1.01 [0.91–1.13]	0.791	1.01 [0.86–1.20]	> 0.999
Continuous veno-venous hemofiltration	116 (5.6)	1.26 [0.89–1.77]	0.194	1.26 [0.73–2.15]	> 0.999

All treatments included in this table were entered into a multivariable regression model simultaneously. The multivariable model included the following variables: all treatments listed in this table and all potential confounders listed under "Multivariable Analysis" in table S3 in Supplemental Digital Content (http://links.lww.com/ALN/C693). Refer to table S4 in Supplemental Digital Content (http://links.lww.com/ALN/C693) for the results of the association between each treatment and mortality based on univariate analysis. Refer to table S3 in Supplemental Digital Content (http://links.lww.com/ALN/C693) for the results of the associations between each potential confounder and mortality based on univariate and multivariable analysis.

*The denominator for percentage calculation was 2,070. †The CI of hazard ratio and *P* value were corrected for multiple testing using the Bonferroni method. The 23 hypotheses for all treatments included in this table were regarded as one family. The corrected *P* value is equal to the uncorrected *P* value multiplied by 23.

408) of patients (table S8 in Supplemental Digital Content, http://links.lww.com/ALN/C693). The 360 matched pairs based on apixaban treatment were split into two subgroups: one subgroup had patients treated with prophylactic apixaban *versus* matched patients never treated with apixaban (N, 287 *vs*. 287), whereas the other subgroup had patients treated with therapeutic apixaban *versus* matched patients never treated with apixaban (N, 73 *vs*. 73; table S9 in Supplemental Digital Content, http://links.lww.com/ALN/C693). Prophylactic apixaban was associated with lower mortality (30.7% *vs*. 38.0%; hazard ratio, 0.50; 95% CI, 0.340 to 0.73; $P < 0.001$), whereas therapeutic apixaban was not associated with lower mortality (11.0% *vs*. 32.9%; hazard ratio, 0.385; 95% CI, 0.137 to 1.08; $P = 0.069$).

Association Modification by Enoxaparin Dose. Enoxaparin was administered in two different doses: a prophylactic dose (40 mg one time daily or 0.5 mg/kg two times daily) in 79.3% (1,192 of 1,504) of patients and a therapeutic dose (1 mg/kg two times daily) in 20.7% (312 of 1,504) of patients (table S10 in Supplemental Digital Content, http://links.lww.com/ALN/C693). The 347 matched pairs per enoxaparin treatment were split into two subgroups: one subgroup had patients treated with prophylactic enoxaparin *versus* matched patients never treated with enoxaparin (N, 289 *vs*. 289), whereas the other subgroup had patients treated with therapeutic enoxaparin *versus* matched patients never treated with enoxaparin (N, 58 *vs*. 58; table S11 in Supplemental Digital Content, http://links.lww.com/ALN/C693). Prophylactic and therapeutic enoxaparin were both associated with lower mortality (25.6% *vs.* 31.8%; hazard ratio, 0.65; 95% CI, 0.43 to 0.97; $P = 0.036$ and 22.4% *vs.* 43.1%; hazard ratio, 0.191; 95% CI, 0.066 to 0.55; $P = 0.002$, respectively).

Table 3. Cohort Characteristics before and after Propensity Score Matching Based on Apixaban Treatment

Categories and Treatments	Before Propensity Score Matching			After Propensity Score Matching		
	Apixaban Used (N = 408)*	Apixaban Not Used (N = 1,662)*	Standardized Difference	Apixaban Used (N = 360)*	Apixaban Not Used (N = 360)*	Standardized Difference
Demographics						
Age, yr	70 ± 12	64 ± 16	0.454	70 ± 12	70 ± 14	0.001
Sex (male)	248 (60.8%)	970 (58.4%)	0.049	216 (60.0%)	205 (56.9%)	0.062
Body mass index, kg/m^2	29 [24–34]	29 [25–35]	0.078	29 [24–34]	28 [24–34]	0.039
Never smoking	144 (37.6%)	738 (48.9%)	0.229	134 (37.2%)	136 (37.8%)	0.011
Hospital						
Yale New Haven Hospital	173 (42.4%)	747 (44.9%)	0.147	156 (43.3%)	156 (43.3%)	0.056
Bridgeport Hospital	72 (17.6%)	347 (20.9%)		64 (17.8%)	67 (18.6%)	
Saint Raphael Campus	32 (7.8%)	135 (8.1%)		20 (5.6%)	22 (6.1%)	
Greenwich Hospital	28 (6.9%)	102 (6.1%)		24 (6.7%)	20 (5.6%)	
Lawrence + Memorial Hospital	87 (21.3%)	288 (17.3%)		80 (22.2%)	80 (22.2%)	
Westerly Hospital	16 (3.9%)	43 (2.6%)		16 (4.4%)	15 (4.2%)	
Comorbidities						
Myocardial infarction	118 (28.9%)	263 (15.8%)	0.318	109 (30.3%)	105 (29.2%)	0.024
Congestive heart failure	199 (48.8%)	466 (28.0%)	0.436	184 (51.1%)	181 (50.3%)	0.017
Peripheral vascular disease	141 (34.6%)	371 (22.3%)	0.274	130 (36.1%)	121 (33.6%)	0.052
Cerebrovascular disease	137 (33.6%)	402 (24.2%)	0.208	121 (33.6%)	125 (34.7%)	0.023
Dementia	57 (14.0%)	226 (13.6%)	0.011	50 (13.9%)	53 (14.7%)	0.024
COPD	178 (43.6%)	571 (34.4%)	0.191	165 (45.8%)	168 (46.7%)	0.017
Rheumatic disease	40 (9.8%)	101 (6.1%)	0.138	38 (10.6%)	36 (10.0%)	0.018
Peptic ulcer disease	28 (6.9%)	114 (6.9%)	< 0.001	25 (6.9%)	22 (6.1%)	0.034
Liver disease	77 (18.9%)	270 (16.2%)	0.069	66 (18.3%)	72 (20.0%)	0.042
Diabetes	206 (50.5%)	729 (43.9%)	0.133	190 (52.8%)	184 (51.1%)	0.033
Paraplegia	30 (7.4%)	97 (5.8%)	0.061	28 (7.8%)	27 (7.5%)	0.010
Renal disease	178 (43.6%)	441 (26.5%)	0.364	164 (45.6%)	165 (45.8%)	0.006
Malignancy	91 (22.3%)	286 (17.2%)	0.128	86 (23.9%)	83 (23.1%)	0.020
Metastatic cancer	48 (11.8%)	153 (9.2%)	0.084	48 (13.3%)	44 (12.2%)	0.033
HIV infection	6 (1.5%)	22 (1.3%)	0.013	6 (1.7%)	5 (1.4%)	0.023
Hypertension	334 (81.9%)	1,215 (73.1%)	0.211	304 (84.4%)	308 (85.6%)	0.031
Hyperlipidemia	292 (71.6%)	971 (58.4%)	0.278	270 (75.0%)	262 (72.8%)	0.051
Anxiety	100 (24.5%)	432 (26.0%)	0.034	87 (24.2%)	91 (25.3%)	0.026
Depression	119 (29.2%)	423 (25.5%)	0.083	110 (30.6%)	107 (29.7%)	0.018
Immunosuppression	3 (0.7%)	15 (0.9%)	0.019	3 (0.8%)	2 (0.6%)	0.033
Asthma	94 (23.0%)	336 (20.2%)	0.069	88 (24.4%)	85 (23.6%)	0.020
Number of comorbidities, number	6 [3–8]	4 [2–6]	0.420	6 [4–8]	6 [3–8]	0.025
Charlson Comorbidity Index, points	4 [2–7]	2 [1–5]	0.368	5 [2–7]	4 [2–7]	0.029
Severity of acute illness during the first 24 h after ICU admission						
SOFA score	7 [5–9]	6 [4–9]	0.187	7 [5–9]	6 [5–9]	0.018
Glasgow Coma Scale score	15 [14–15]	15 [14–15]	0.012	15 [14–15]	15 [14–15]	0.009
Invasive mechanical ventilation	106 (26.0%)	435 (26.2%)	0.004	91 (25.3%)	94 (26.1%)	0.019
Pandemic phase†						
First phase	168 (41.2%)	688 (41.4%)	0.121	136 (37.8%)	127 (35.3%)	0.053
Second phase	19 (4.7%)	119 (7.2%)		17 (4.7%)	17 (4.7%)	
Third phase	88 (21.6%)	312 (18.8%)		83 (23.1%)	87 (24.2%)	
Fourth phase	133 (32.6%)	543 (32.7%)		124 (34.4%)	129 (35.8%)	

Refer to table S5 in Supplemental Digital Content (http://links.lww.com/ALN/C693) for laboratory results and vital signs before and after propensity score matching per apixaban treatment.

*Data are expressed as mean ± SD, median [interquartile range], or number (%). †The World Health Organization declared the COVID-19 outbreak a global pandemic on March 11, 2020. Accordingly, we divided the first year of the pandemic into four stages: the first phase from February 1, 2020, to May 31, 2020 (including the early cases happened before March 11, 2020); the second phase from June 1, 2020, to August 31, 2020; the third phase from September 1, 2020, to November 30, 2020; and the fourth phase from December 1, 2020, to March 11, 2021. We divided the pandemic into different phases to account for the chronological effect of different treatments.

COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment.

Association Modification by Aspirin Dose. Aspirin was administered in two different doses: a low dose (81 mg one time daily) in 89.2% (1,209 of 1,355) of patients and a high dose (300/325 mg one time daily) in 10.8% (146 of 1,355) of patients (table S12 in Supplemental Digital Content, http://links.lww.com/ALN/C693). The 473 matched pairs based on aspirin treatment were split into two subgroups: one subgroup had patients treated with low-dose aspirin *versus* matched patients never treated with aspirin (N, 422 *vs.* 422), whereas the other subgroup had patients

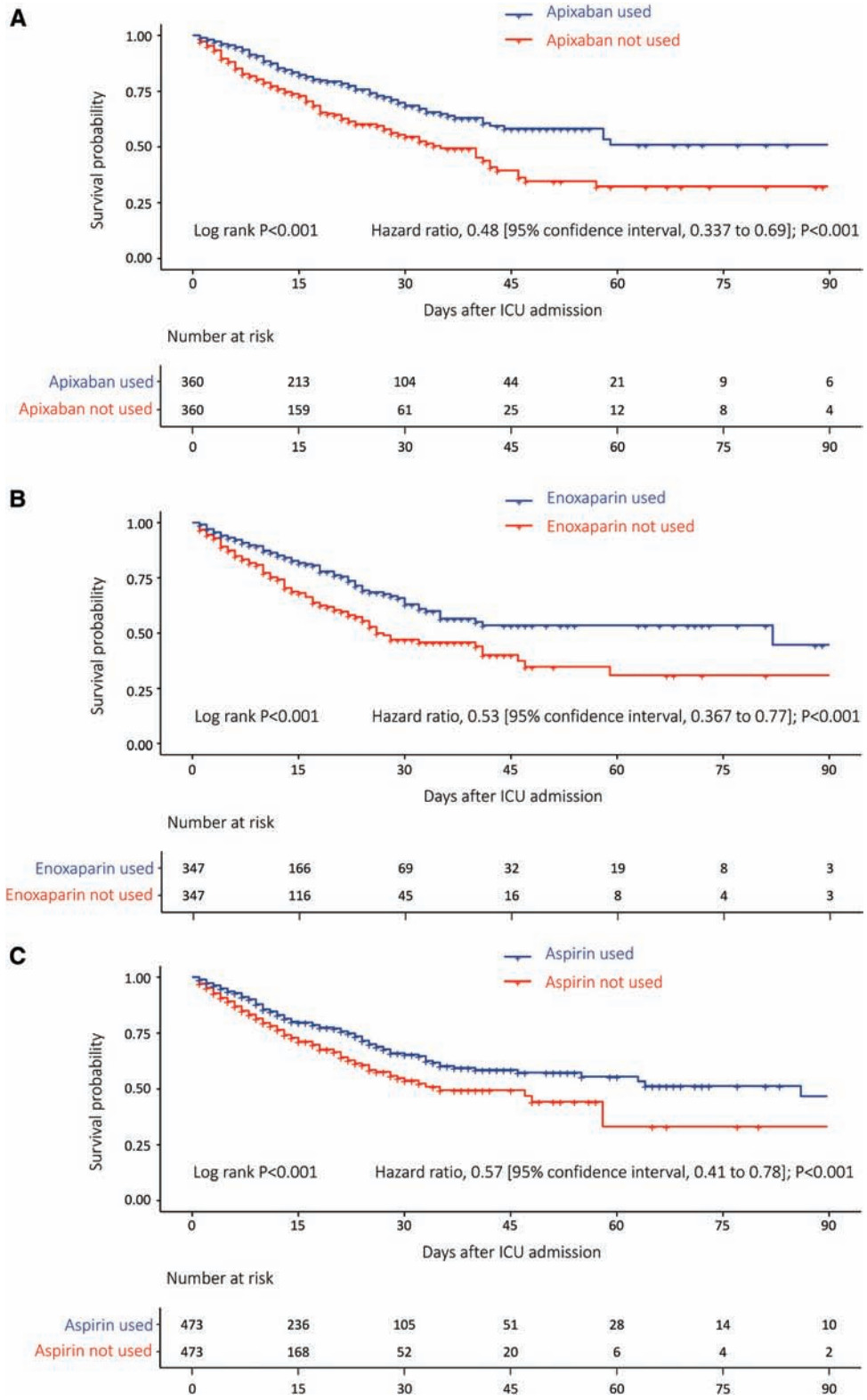

Fig. 2. Survival probability for patients treated and not treated with apixaban (*A*), enoxaparin (*B*), and aspirin (*C*). The patients are matched using propensity score matching. ICU, intensive care unit.

Table 4. Cohort Characteristics before and after Propensity Score Matching Based on Enoxaparin Treatment

Categories and Treatments	Before Propensity Score Matching			After Propensity Score Matching		
	Enoxaparin Used (N = 1,504)*	Enoxaparin Not Used (N = 566)*	Standardized Difference	Enoxaparin Used (N = 347)*	Enoxaparin Not Used (N = 347)*	Standardized Difference
Demographics						
Age, yr	64 ± 16	68 ± 18	0.214	69 ± 16	68 ± 15	0.086
Sex (male)	904 (60.1%)	314 (55.5%)	0.094	186 (53.6%)	189 (54.5%)	0.017
Body mass index, kg/m^2	29 [25–35]	29 [24–35]	0.018	28 [24–35]	29 [24–35]	0.064
Never smoking	665 (48.9%)	217 (40.7%)	0.165	135 (38.9%)	141 (40.6%)	0.035
Hospital						
Yale New Haven Hospital	643 (42.8%)	277 (48.9%)	0.332	173 (49.9%)	173 (49.9%)	0.022
Bridgeport Hospital	279 (18.6%)	140 (24.7%)		79 (22.8%)	80 (23.1%)	
Saint Raphael Campus	146 (9.7%)	21 (3.7%)		17 (4.9%)	16 (4.6%)	
Greenwich Hospital	107 (7.1%)	23 (4.1%)		13 (3.7%)	14 (4.0%)	
Lawrence + Memorial Hospital	280 (18.6%)	95 (16.8%)		56 (16.1%)	55 (15.9%)	
Westerly Hospital	49 (3.3%)	10 (1.8%)		9 (2.6%)	9 (2.6%)	
Comorbidities						
Myocardial infarction	208 (13.8%)	173 (30.6%)	0.411	96 (27.7%)	94 (27.1%)	0.013
Congestive heart failure	375 (24.9%)	290 (51.2%)	0.563	167 (48.1%)	157 (45.2%)	0.058
Peripheral vascular disease	299 (19.9%)	213 (37.6%)	0.400	127 (36.6%)	115 (33.1%)	0.073
Cerebrovascular disease	328 (21.8%)	211 (37.3%)	0.344	124 (35.7%)	121 (34.9%)	0.018
Dementia	196 (13.0%)	87 (15.4%)	0.067	55 (15.9%)	48 (13.8%)	0.057
COPD	482 (32.0%)	267 (47.2%)	0.313	157 (45.2%)	164 (47.3%)	0.040
Rheumatic disease	90 (6.0%)	51 (9.0%)	0.115	23 (6.6%)	30 (8.6%)	0.076
Peptic ulcer disease	89 (5.9%)	53 (9.4%)	0.13	29 (8.4%)	31 (8.9%)	0.021
Liver disease	243 (16.2%)	104 (18.4%)	0.059	62 (17.9%)	64 (18.4%)	0.015
Diabetes	627 (41.7%)	308 (54.4%)	0.257	174 (50.1%)	179 (51.6%)	0.029
Paraplegia	74 (4.9%)	53 (9.4%)	0.173	27 (7.8%)	25 (7.2%)	0.022
Renal disease	322 (21.4%)	297 (52.5%)	0.68	150 (43.2%)	146 (42.1%)	0.023
Malignancy	253 (16.8%)	124 (21.9%)	0.129	87 (25.1%)	83 (23.9%)	0.027
Metastatic cancer	130 (8.6%)	71 (12.5%)	0.127	46 (13.3%)	45 (13.0%)	0.009
HIV infection	19 (1.3%)	9 (1.6%)	0.028	6 (1.7%)	5 (1.4%)	0.023
Hypertension	1,058 (70.3%)	491 (86.7%)	0.408	299 (86.2%)	295 (85.0%)	0.033
Hyperlipidemia	859 (57.1%)	404 (71.4%)	0.301	245 (70.6%)	246 (70.9%)	0.006
Anxiety	364 (24.2%)	168 (29.7%)	0.124	104 (30.0%)	108 (31.1%)	0.025
Depression	353 (23.5%)	189 (33.4%)	0.221	107 (30.8%)	112 (32.3%)	0.031
Immunosuppression	13 (0.9%)	5 (0.9%)	0.002	7 (2.0%)	5 (1.4%)	0.044
Asthma	282 (18.8%)	148 (26.1%)	0.178	82 (23.6%)	90 (25.9%)	0.053
Number of comorbidities, number	4 [2–6]	6 [4–8]	0.665	6 [3–8]	5 [3–8]	0.019
Charlson Comorbidity Index, points	2 [1–5]	5 [2–7]	0.623	4 [2–7]	4 [2–7]	0.033
Severity of acute illness during the first 24 h after ICU admission						
SOFA score	6 [4–8]	7 [4–10]	0.208	6 [4–9]	6 [4–9]	0.008
Glasgow Coma Scale score	15 [14–15]	15 [14–15]	0.055	15 [14–15]	15 [14–15]	0.048
Invasive mechanical ventilation	401 (26.7%)	140 (24.7%)	0.044	79 (22.8%)	83 (23.9%)	0.027
Pandemic phase†						
First phase	659 (43.8%)	197 (34.8%)	0.227	103 (29.7%)	108 (31.1%)	0.046
Second phase	83 (5.5%)	55 (9.7%)		33 (9.5%)	31 (8.9%)	
Third phase	291 (19.3%)	109 (19.3%)		79 (22.8%)	74 (21.3%)	
Fourth phase	471 (31.3%)	205 (36.2%)		132 (38.0%)	134 (38.6%)	

Refer to table S6 in Supplemental Digital Content (http://links.lww.com/ALN/C693) for laboratory results and vital signs before and after propensity score matching per enoxaparin treatment.

*Data are expressed as mean ± SD, median [interquartile range], or number (%). †The World Health Organization declared the COVID-19 outbreak a global pandemic on March 11, 2020. Accordingly, we divided the first year of the pandemic into four stages: the first phase from February 1, 2020, to May 31, 2020 (including the early cases happened before March 11, 2020); the second phase from June 1, 2020, to August 31, 2020; the third phase from September 1, 2020, to November 30, 2020; and the fourth phase from December 1, 2020, to March 11, 2021. We divided the pandemic into different phases to account for the chronological effect of different treatments.

COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment.

treated with high-dose aspirin *versus* matched patients never treated with aspirin (N, 51 *vs.* 51; table S13 in Supplemental Digital Content, http://links.lww.com/ALN/C693). Low-dose aspirin was associated with lower mortality (24.6% *vs.* 30.6%; hazard ratio, 0.53; 95% CI, 0.375 to 0.74; $P < 0.001$), whereas high-dose aspirin was not associated with lower mortality (33.3% *vs.* 21.6%; hazard ratio, 1.14; 95% CI, 0.41 to 3.15; $P = 0.796$).

Table 5. Cohort Characteristics before and after Propensity Score Matching Based on Aspirin Treatment

Categories and Treatments	Before Propensity Score Matching			After Propensity Score Matching		
	Aspirin Used (N = 1,355)*	Aspirin Not Used (N = 715)*	Standardized Difference	Aspirin Used (N = 473)*	Aspirin Not Used (N = 473)*	Standardized Difference
Demographics						
Age, yr	67 ± 14	62 ± 18	0.272	64 ± 16	64 ± 18	0.007
Sex (male)	810 (59.8%)	408 (57.1%)	0.055	273 (57.7%)	260 (55.0%)	0.055
Body mass index, kg/m^2	29 [25–35]	28 [24–35]	0.041	28 [24–34]	28 [24–35]	0.044
Never smoking	555 (44.7%)	327 (50.2%)	0.109	213 (45.0%)	228 (48.2%)	0.064
Hospital						
Yale New Haven Hospital	612 (45.2%)	308 (43.1%)	0.240	214 (45.2%)	205 (43.3%)	0.089
Bridgeport Hospital	242 (17.9%)	177 (24.8%)		106 (22.4%)	102 (21.6%)	
Saint Raphael Campus	97 (7.2%)	70 (9.8%)		34 (7.2%)	39 (8.2%)	
Greenwich Hospital	97 (7.2%)	33 (4.6%)		17 (3.6%)	24 (5.1%)	
Lawrence + Memorial Hospital	262 (19.3%)	113 (15.8%)		88 (18.6%)	90 (19.0%)	
Westerly Hospital	45 (3.3%)	14 (2.0%)		14 (3.0%)	13 (2.7%)	
Comorbidities						
Myocardial infarction	299 (22.1%)	82 (11.5%)	0.287	69 (14.6%)	66 (14.0%)	0.018
Congestive heart failure	472 (34.8%)	193 (27.0%)	0.170	150 (31.7%)	147 (31.1%)	0.014
Peripheral vascular disease	364 (26.9%)	148 (20.7%)	0.145	130 (27.5%)	118 (24.9%)	0.058
Cerebrovascular disease	378 (27.9%)	161 (22.5%)	0.124	133 (28.1%)	118 (24.9%)	0.072
Dementia	174 (12.8%)	109 (15.2%)	0.069	72 (15.2%)	75 (15.9%)	0.018
COPD	501 (37.0%)	248 (34.7%)	0.048	186 (39.3%)	183 (38.7%)	0.013
Rheumatic disease	93 (6.9%)	48 (6.7%)	0.006	37 (7.8%)	34 (7.2%)	0.024
Peptic ulcer disease	83 (6.1%)	59 (8.3%)	0.082	38 (8.0%)	41 (8.7%)	0.023
Liver disease	216 (15.9%)	131 (18.3%)	0.063	83 (17.5%)	88 (18.6%)	0.027
Diabetes	640 (47.2%)	295 (41.3%)	0.120	212 (44.8%)	215 (45.5%)	0.013
Paraplegia	84 (6.2%)	43 (6.0%)	0.008	32 (6.8%)	31 (6.6%)	0.008
Renal disease	441 (32.5%)	178 (24.9%)	0.170	155 (32.8%)	134 (28.3%)	0.096
Malignancy	240 (17.7%)	137 (19.2%)	0.037	114 (24.1%)	101 (21.4%)	0.066
Metastatic cancer	117 (8.6%)	84 (11.7%)	0.103	52 (11.0%)	55 (11.6%)	0.020
HIV infection	15 (1.1%)	13 (1.8%)	0.059	10 (2.1%)	11 (2.3%)	0.014
Hypertension	1,049 (77.4%)	500 (69.9%)	0.171	370 (78.2%)	362 (76.5%)	0.040
Hyperlipidemia	893 (65.9%)	370 (51.7%)	0.291	296 (62.6%)	286 (60.5%)	0.043
Anxiety	350 (25.8%)	182 (25.5%)	0.009	138 (29.2%)	138 (29.2%)	< 0.001
Depression	365 (26.9%)	177 (24.8%)	0.050	141 (29.8%)	135 (28.5%)	0.028
Immunosuppression	16 (1.2%)	2 (0.3%)	0.106	3 (0.6%)	2 (0.4%)	0.029
Asthma	277 (20.4%)	153 (21.4%)	0.024	109 (23.0%)	113 (23.9%)	0.020
Number of comorbidities, number	4 [2–7]	4 [2–6]	0.181	4 [2–7]	4 [2–7]	0.048
Charlson Comorbidity Index, points	3 [1–6]	2 [1–6]	0.069	3 [1–6]	3 [1–6]	0.038
Severity of acute illness during the first 24 h after ICU admission						
SOFA score	6 [4–9]	6 [4–9]	0.030	6 [4–9]	6 [4–9]	0.051
Glasgow Coma Scale score	15 [14–15]	15 [14–15]	0.130	15 [14–15]	15 [14–15]	0.057
Invasive mechanical ventilation	326 (24.1%)	215 (30.1%)	0.136	125 (26.4%)	122 (25.8%)	0.014
Pandemic phase†						
First phase	400 (29.5%)	456 (63.8%)	0.808	250 (52.9%)	249 (52.6%)	0.010
Second phase	77 (5.7%)	61 (8.5%)		41 (8.7%)	42 (8.9%)	
Third phase	326 (24.1%)	74 (10.3%)		65 (13.7%)	66 (14.0%)	
Fourth phase	552 (40.7%)	124 (17.3%)		117 (24.7%)	116 (24.5%)	

Refer to table S7 in Supplemental Digital Content (http://links.lww.com/ALN/C693) for laboratory results and vital signs before and after propensity score matching per aspirin treatment.

*Data are expressed as mean ± SD, median [interquartile range], or number (%). †The World Health Organization declared the COVID-19 outbreak a global pandemic on March 11, 2020. Accordingly, we divided the first year of the pandemic into four stages: the first phase from February 1, 2020, to May 31, 2020 (including the early cases happened before March 11, 2020); the second phase from June 1, 2020, to August 31, 2020; the third phase from September 1, 2020, to November 30, 2020; and the fourth phase from December 1, 2020, to March 11, 2021. We divided the pandemic into different phases to account for the chronological effect of different treatments.

COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment.

Discussion

Key Results

This retrospective cohort study examined 2,070 patients treated for COVID-19–related complications in the ICUs in six hospitals affiliated with one healthcare system throughout the first pandemic year. The results suggested that among the multiple COVID-19–related treatments, anticoagulants (i.e., apixaban and enoxaparin) and antiplatelet therapy (i.e., aspirin) were associated with lower in-hospital mortality. Analyses based on propensity score matching suggested that patients

treated with apixaban were associated with a 52% lower mortality risk than patients who never received apixaban, patients treated with enoxaparin were associated with a 47% lower mortality risk compared to patients who never received enoxaparin, and patients treated with aspirin were associated with a 43% lower mortality risk compared to patients who never received aspirin. It is worth noting that patients treated with apixaban were older and had more comorbidities than patients who never received apixaban treatment in our study population. Moreover, therapeutic anticoagulants were used for imaging-confirmed venous thromboembolism (i.e., patients were likely sicker). Nevertheless, we still observed an association between apixaban/enoxaparin/aspirin and lower mortality among critically ill COVID-19 patients.

Interpretation

Although abundant treatments were applied to our patients throughout the first pandemic year, our study finds that apixaban, enoxaparin, and aspirin, rather than the previously reported treatments like remdesivir,[7,8] dexamethasone,[9] hydroxychloroquine,[10] convalescent plasma,[11] and famotidine,[12] are associated with lower COVID-19 mortality. In hospitalized COVID-19 patients, four different meta-analyses indicated that venous thromboembolism occurred in 24 to 31% of patients, pulmonary embolism occurred in 12 to 19%, and deep venous thrombosis occurred in 12 to 20%.[13–16] The incidence of venous thromboembolism was much higher in COVID-19 patients admitted to the ICU than those hospitalized on the ward (30% *vs.* 13%).[16] Patients with severe COVID-19 had an almost four-fold increased risk of venous thromboembolism compared to patients with nonsevere COVID-19.[14] Therefore, the existing evidence advocates a more proactive strategy of systemic anticoagulation therapy in hospitalized COVID-19 patients.

Several studies examined the use of systemic anticoagulants in hospitalized COVID-19 patients.[17,18] A retrospective cohort study involving 4,389 hospitalized COVID-19 patients showed that therapeutic and prophylactic anticoagulation is associated with lower mortality when compared to no anticoagulation therapy.[19] However, that study did not distinguish different anticoagulants and was not explicitly investigating critically ill patients. Another retrospective cohort study involving 3,625 hospitalized COVID-19 patients showed that the prophylactic use of apixaban or enoxaparin was associated with lower in-hospital mortality.[20] The study also showed that apixaban's therapeutic use was associated with lower mortality, although it was not more beneficial than prophylactic use. However, that study was only based on propensity score–matching analysis and only considered the last anticoagulant order in the first 48 h after hospital admission. Therefore, it did not control the confounding exerted by other COVID-19–related treatments, unlike the multivariable analysis used in our study, and it could not tell what would have happened if an anticoagulant had been given after the first 48 h of hospital admission. Moreover, the study involved all hospitalized patients, including patients requiring ICU-level care, and covered a short period (from March 1, 2020, to April 26, 2020; less than 2 months during the early stage of the pandemic); therefore, it may provide a different insight compared to our study, which focuses on ICU patients and spans the entire first pandemic year.

Three international trials compared the effectiveness of therapeutic-dose anticoagulation with heparin *versus* usual pharmacologic thromboprophylaxis.[3,4] These trials discontinued the enrollment of noncritically ill patients (defined as an absence of critical care-level organ support at enrollment) because of therapeutic anticoagulation's superiority in reducing the need for organ support over 21 days.[3] These trials also discontinued the enrollment of critically ill patients because of therapeutic anticoagulation's futility in reducing the need for organ support over 21 days.[4] These trials did not find an in-hospital mortality difference between different anticoagulation treatments.[3,4] A separate multicenter trial performed in hospitalized COVID-19 patients with elevated D-dimer did not find a difference between therapeutic and prophylactic anticoagulation.[5] However, the result of this trial is challenging to interpret because the primary outcome was defined as a hierarchical composite of time to death, duration of hospitalization, or duration of supplemental oxygen use over 30 days.[5] This trial also did not find a mortality difference between different anticoagulation treatments. Overall, the available evidence showed no mortality difference between therapeutic and prophylactic anticoagulation among hospitalized and critically ill COVID-19 patients. The discrepancy in the results of nonmortality outcome measures among these studies remains to be reconciled.

Although lacking in some details, the current anticoagulation recommendations have primarily focused on the use of enoxaparin.[18] Our findings support this practice. However, our important finding is the robust association between the use of apixaban and lower mortality in critically ill COVID-19 patients, which is consistent with early cohort studies suggesting an association between apixaban treatment and lower mortality in hospitalized COVID-19 patients.[20,21] As a commonly used direct factor Xa inhibitor, apixaban has anticoagulant, anti-inflammatory, and antiviral effects.[22] A previous virology investigation suggested that the inhibition of coagulation factor Xa–mediated cleavage and the subsequent activation of the viral spike protein leads to an impaired fusion of the viral envelope with host cells and, consequently, reduces the infectivity of the SARS virus.[23] This finding offers a mechanism that could explain our observed associations. We note that we did not find an association between the use of rivaroxaban (with a mechanism similar to apixaban) and mortality. The reasons for this finding remain to be elucidated but may be related to the small number of patients who received rivaroxaban treatment (3.4%, 70 of 2,070) in our study population. It should also be noted that the concurrent use of direct oral anticoagulants, including apixaban and antiviral drugs in COVID-19

patients, can lead to an alarming increase in plasma anticoagulant levels and may increase the risk of bleeding.[24]

The association between aspirin treatment and lower COVID-19 mortality identified by our study is consistent with the literature based on large patient cohorts.[25–28] This association was also corroborated by meta-analyses.[29]

Limitations

This study has several limitations. First, although this cohort study is based on data collected from electronic medical records for all patients treated within a predefined time window across a relatively homogeneous healthcare system, there may still be imprecise information and patient selection bias, especially considering the dramatic toll on the healthcare system caused by the pandemic. Second, our study may be limited by confounding by indication as a retrospective cohort study. Although multivariable analysis and analysis based on propensity score matching were performed, residual bias and a lack of control for unmeasured confounders may still exist. Third, there is a possibility of an immortal time bias or other similar biases related to ignoring differences in timing before treatment because certain medications were not administered until a particular time in the disease course. Fourth, caution is needed when interpreting the data concerning the comparisons of prophylactic and therapeutic anticoagulants with their counterparts because these analyses were not powered to differentiate between different drug doses. Fifth, we conducted a complete case analysis and chose not to impute missing data. Although other approaches dealing with missing data were possible, we excluded patients from specific analyses if the data were missing. Last, as a study based on the experiences of the first pandemic year, the results may not be entirely applicable to future cases, for reasons that include viral mutation, different vulnerable populations, vaccination rates, and the evolution of our knowledge of and measures for treating the disease.

Conclusions

We performed a retrospective cohort study involving all patients treated in a healthcare system's ICUs for COVID-19–related complications throughout the first pandemic year to explore the treatments associated with lower mortality. Consistent with the known hypercoagulability in severe COVID-19, our study showed that the use of apixaban, enoxaparin, or aspirin was independently associated with lower mortality among critically ill COVID-19 patients. The reproducibility of this finding and the ideal dose, timing, and duration of treatment require further elucidation in future studies.

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Competing Interests

Dr. Meng received consulting fees from Edwards Lifesciences, Irvine, California. The other authors declare no competing interests.

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

For Future Journalist Edward Gilbert Abbott, Ether Day Was No "Puff Piece"

The significance of Ether Day could not be overstated for surgical patient and future journalist Edward Gilbert Abbott (*above*, artwork by Michael Edens). Orphaned at age seven with limited financial resources, Abbott suffered from a congenital mass below his jaw. He was admitted to the Massachusetts General Hospital in October 1846 for evaluation. Without the looming demonstration of surgical etherization, this young patient, who was not gravely ill, would have been an unlikely operative candidate for surgeon John Collins Warren, M.D. From the moment Abbott drew his first breath through Morton's ether inhaler, his life was changed. Though neither fame nor fortune followed his lengthy recovery, the 21-year-old renewed his zeal for life. Abbott was apprenticed to a printer and pursued a successful career as a journalist for *The Boston Herald* and *The Boston Daily Bee*. In 1850, he married and started a family with fellow New Englander, Mary Dunbar Fuller. Sadly, these auspicious years would not last, and in 1855, he expired from tuberculosis. Nevertheless, Abbott's ether inhalation was historic, and Ether Day—October 16, 1846—would transform not only his own life, but also surgical practice forever.

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ANESTHESIOLOGY

Preoperative Paravertebral Block and Chronic Pain after Breast Cancer Surgery: A Double-blind Randomized Trial

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Chronic pain after breast surgery is common, both causing suffering and limiting function.
- Previous studies suggest that paravertebral blocks may prevent chronic pain after breast surgery, but the data are limited.

What This Article Tells Us That Is New

- More than 350 study participants undergoing mastectomy were randomized to either paravertebral blocks with ropivacaine or saline injections. Both groups received multimodal analgesia.
- Although paravertebral block using ropivacaine had a small analgesic effect in the immediate postoperative period, no differences in pain 3, 6, and 12 months after surgery were detected.

ABSTRACT

Background: The effectiveness of paravertebral block in preventing chronic pain after breast surgery remains controversial. The primary hypothesis of this study was that paravertebral block reduces the incidence of chronic pain 3 months after breast cancer surgery.

Methods: In this prospective, multicenter, randomized, double-blind, parallel-group, placebo-controlled study, 380 women undergoing partial or complete mastectomy with or without lymph node dissection were randomized to receive preoperative paravertebral block with either 0.35 ml/kg 0.75% ropivacaine (paravertebral group) or saline (control group). Systemic multimodal analgesia was administered in both groups. The primary endpoint was the incidence of chronic pain with a visual analogue scale (VAS) score greater than or equal to 3 out of 10, 3 months after surgery. The secondary outcomes were acute pain, analgesic consumption, nausea and vomiting, chronic pain at 6 and 12 months, neuropathic pain, pain interference, anxiety, and depression.

Results: Overall, 178 patients received ropivacaine, and 174 received saline. At 3 months, chronic pain was reported in 93 of 178 (52.2%) and 83 of 174 (47.7%) patients in the paravertebral and control groups, respectively (odds ratio, 1.20 [95% CI, 0.79 to 1.82], $P = 0.394$). At 6 and 12 months, chronic pain occurred in 104 of 178 (58.4%) *versus* 79 of 174 (45.4%) and 105 of 178 (59.0%) *versus* 93 of 174 (53.4%) patients in the paravertebral and control groups, respectively. Greater acute postoperative pain was observed in the control group 0 to 2 h (area under the receiver operating characteristics curve at rest, 4.3 ± 2.8 *vs.* 2.9 ± 2.8 VAS score units × hours, $P < 0.001$) and when maximal in this interval (3.8 ± 2.1 *vs.* 2.5 ± 2.5, $P < 0.001$) but not during any other interval. Postoperative morphine use was 73% less in the paravertebral group (odds ratio, 0.272 [95% CI, 0.171 to 0.429]; $P < 0.001$).

Conclusions: Paravertebral block did not reduce the incidence of chronic pain after breast surgery. Paravertebral block did result in less immediate postoperative pain, but there were no other significant differences in postoperative outcomes.

(ANESTHESIOLOGY 2021; 135:1091–103)

Chronic pain after breast cancer surgery is frequent and an important healthcare priority because of its effect on quality of life. Although the association between the severity of acute pain after surgery and the likelihood of chronic pain is known, their causal relationship has not been clarified. We previously showed that wound infiltration with ropivacaine did not reduce the incidence or severity of pain after breast surgery.[1] Thus, other authors have used paravertebral block rather than infiltration to improve pain control after breast surgery. One recent, single-center, double-blind study including 172 patients with similar outcomes to our study showed that ultrasound-guided multilevel paravertebral block lowered the incidence of chronic pain 3 months (35% *vs.* 51% of patients) and 6 months (22% *vs.* 37%) after partial mastectomy with or without axillary lymph node dissection. Another recent study including 2,132 patients from 13 hospitals evaluated the recurrence of breast cancer after regional or general anesthesia, with the incidence of chronic pain as a secondary outcome.[2] Incisional pain was identical in the two groups at 6 months (52% in each group) and 1 yr (27% *vs.* 28%). A Cochrane review on chronic pain also found that paravertebral block reduced chronic pain after breast surgery

This article is featured in "This Month in Anesthesiology," page A1. This article has a visual abstract available in the online version.

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but graded the evidence as low.[3] Another recent review and meta-analysis[4] concluded that the data on chronic pain for paravertebral block are too scarce to be conclusive. The quality of evidence was considered to be low, mainly due to a lack of adequate blinding. Nonetheless, although the existing evidence is weak and conflicting, there is increasing interest in the role of paravertebral block in preventing chronic pain after breast cancer surgery.[3,4]

Therefore, this prospective, multicenter, randomized, double-blind, parallel-group, placebo-controlled study in a large homogenous population evaluated the effect of paravertebral block with ropivacaine on acute and chronic pain as well as on comorbidities, such as anxiety and depression, after complete or partial mastectomy with or without axillary or sentinel lymph node dissection for cancer.

The primary hypothesis of this study was that preoperative ultrasound-guided paravertebral block reduces the incidence of chronic pain. The primary endpoint was the incidence of chronic pain greater than or equal to 3 out of 10 on a 0 to 10 visual analogue scale (VAS) 3 months after breast surgery. The secondary outcomes were acute postoperative pain at rest or during mobilization, the extent of sensory blockade, complications of paravertebral block, the consumption of analgesics, and nausea and vomiting every 30 min for 2 h in the postanesthesia care unit (PACU) and every 6 h for 48 h after surgery. Chronic pain was also evaluated 6 months and 1 yr after surgery.

Materials and Methods

Study Design and Number of Participants

This large, prospective, randomized (1:1), multicenter (four cancer centers), double-blind, parallel-group, placebo-controlled trial was approved by the institutional review board (Institut Curie, Saint-Cloud, France) of the study ethics review committee (Hospital Ambroise Paré, Boulogne, France) and was registered in ClinicalTrials.gov (NCT02408393), Aline Albi-Feldzer, April 2015. The trial was conducted in accordance with the original protocol with minor changes. Following the recommendations of the French Society of Anesthesiologists (Paris, France), preoperative blood tests were performed if necessary, depending on clinical status rather than systematically in each patient.

The number of patients in the study was determined using the Casagrande and Pike formula.[5] Based on previous results,[1] the expected effect size was calculated to detect a 50% incidence reduction in chronic pain (30% to 15% of patients) 3 months after surgery. With a bilateral α risk of 5% and 90% power, 179 patients were needed per group, for a total of 358. To account for loss to follow-up or consent withdrawals, the number of patients was increased to 391.

Inclusion and Randomization

Three hundred ninety-one women aged 18 to 85 yr with an American Society of Anesthesiologists (Schaumburg, Illinois) Physical Status of I, II, or III who were admitted for mastectomy with or without axillary lymph node or sentinel lymph node dissection or partial mastectomy (sparing the skin, areola, and nipple) with axillary lymph node dissection were included in the study. The study was explained by an anesthesiologist during the preoperative consultation.

The exclusion criteria included male sex; a life expectancy less than 2 yr; active malignant disease; pregnant or breastfeeding women; bilateral surgery; ipsilateral breast surgery in the past 3 yr; preoperative chronic pain; allergy to local anesthetics, steroids, or morphine; a reported history of substance abuse; local skin inflammation at the puncture area; and an inability to comply with the protocol for any reason.

All patients gave written informed consent, and enrollment ceased when the target sample size was reached.

The research assistant checked for eligibility and informed consent and then enrolled the participants. The statistician generated the allocation sequence on a computer. The patients were randomly allocated (1:1) into two groups using a Web site random number generator with Tenalea software (Netherlands Cancer Institute, The Netherlands). Randomization was stratified by center and the type of surgery: partial mastectomy with axillary lymph node dissection, and mastectomy with or without axillary lymph node dissection or sentinel lymph node dissection.

The results of the randomization were given to the pharmacist, who prepared a syringe with ropivacaine or normal saline solution (0.35 ml/kg) within 24 h before surgery. The syringe was sealed in a sterile envelope and sent to the PACU. The nurse opened the sequentially numbered envelope containing the syringe with the solution.

The paravertebral group received 0.35 ml/kg ropivacaine 0.75% in the paravertebral space without exceeding a total volume of 30 ml. The control group also received an equal volume of saline (0.35 ml/kg) in the paravertebral space. All attending anesthesiologists, patients, nurses, and data collectors were blinded to the group assignment.

Procedure

No premedication was given before surgery.

In the preoperative holding area located in the PACU, standard monitoring included electrocardiography, pulse oximetry, capnography, and noninvasive blood pressure monitoring. Oxygen (2 $l \cdot min^{-1}$) was delivered through nasal prongs.

The patients were placed in the lateral position on the opposite side from surgery, and remifentanil administration was started with an IV targeted effect-site concentration objective to reach a concentration of 2 $ng \cdot ml^{-1}$.

The second thoracic paravertebral space (T2) was scanned by ultrasonography (Model Alpinion E-cube i7 [Alpinion Medical Systems, Korea]) with a 2- to 5-MHz ultrasound probe (linear array L3-8H). The probe was positioned on the transverse plane against the spinal

process. Under aseptic conditions, a 22-gauge 80-mm needle (SonoTAP [Pajunk, Germany]) was advanced in an "in-plane" direction toward the paravertebral space, immediately above the pleura and below the costotransverse ligament. The position of the needle was confirmed by the descent of the pleura when injecting 2 to 3 ml of saline solution for hydrolocalization.

Then, 0.35 ml · kg^{-1} ropivacaine 0.75% was injected with intermittent negative aspiration tests every 5 ml, without exceeding a total of 30 ml or an equivalent volume of saline.

Immediately after the paravertebral block injection procedure was completed in the preoperative holding area, the intensity of pain from the procedure was evaluated with a VAS, the remifentanil injection was discontinued, and the patients were transferred to the operating room 30 min later. Then, 20 min after the procedure, the dermatome block level to temperature was measured by another anesthesiologist to map the spread of blocked dermatomes. An ice cube was placed in the finger of a disposable plastic glove and used to perform the cold sensation test. Patients were given a reference cold sensation at the third cervical dermatome before each measurement. The blocked area was tested between the midaxillary and midclavicular lines from the fourth thoracic dermatome in the cranial and caudal directions, and the sensation in each dermatome on the blocked side was compared to the reference sensation. Persistence of any cold sensation was considered to be an absence of sensory block. The peak sensory cephalad block and caudal block levels were assessed, and then the number of blocked dermatomes was recorded.

The patient was positioned on the operating table and fitted with monitors, including a Bispectral Index. Then, general anesthesia was induced with an IV bolus of propofol (2.5 mg · kg^{-1}) that was administered when the IV remifentanil targeted effect-site concentration reached 4 ng · ml^{-1}. If necessary, cisatracurium besilate (0.1 mg/kg) or atracurium (0.05 mg/kg) was injected to facilitate insertion of the tracheal tube, or a second-generation laryngeal mask (Ambu, Denmark) was secured in the pharynx. Volume-controlled mechanical ventilation was initiated using 6 ml · kg^{-1} of predicted body weight tidal volume, 5 cm H_2O of positive end expiratory pressure, and a 40% inspired oxygen concentration.

Anesthesia was maintained with inhaled sevorane (1 to 2% end-expiratory concentration) or desflurane (3 to 4% end-expiratory concentration) combined with nitrous oxide (50%) and IV remifentanil using a targeted effect-site concentration ranging from 2 to 4 ng · ml^{-1}. The inhaled sevorane or desflurane concentrations and remifentanil effect-site targets were continuously adapted to the monitor (40 < Bispectral Index < 60, and hemodynamics, respectively) outputs. The patient was extubated at the end of surgery after reversal of the neuromuscular block, if necessary.

Antiemetic prophylaxis and postoperative pain prevention were systematically provided with an IV injection of 8 mg dexamethasone on induction, and paracetamol (1,000 mg), ketoprofen (100 mg), and omeprazole (40 mg) 60 min before surgery was expected to be completed. The laryngeal mask or tracheal tube was removed in the operating room, and the patients were transferred to the PACU.

The postoperative intensity of pain at rest and during ipsilateral anterior arm and shoulder elevation was measured upon arrival in the PACU, every 30 min for the first 2 postoperative hours, then every 6 h of the hospital stay, using a VAS ranging from 0 (no pain at all) to 10 (worst imaginable pain). In the presence of a VAS score greater than 3/10 at rest in the PACU, rescue IV morphine was titrated using 2-mg boluses administered every 5 min (no upper limit of dosage). The patients remained in the PACU until the VAS score was less than or equal to 3.

The surgical patients systematically received oral ketoprofen (100 mg) every 12 h. If more analgesia was needed, the first-line treatment was oral paracetamol (1,000 mg) every 6 h when the VAS score was greater than 3, and the second-line treatment was oral tramadol (100 mg) twice a day. In the case of postoperative nausea and vomiting, ondansetron (4 mg) and droperidol (1.25 mg) were given every 8 h IV on demand.

Outcomes

The primary objective of this study was to evaluate the effect of ultrasound-guided single-injection paravertebral block with ropivacaine on the incidence of chronic pain at the surgical site 3 months after major breast surgery. Chronic pain was defined as pain at the surgical site greater than or equal to 3 out of 10 on item 5 of the Brief Pain Inventory (item 5: "Please rate your pain by circling the one number that best describes your pain on the average in the past 24 h, no pain = 0, worst pain = 10"). The Brief Pain Inventory[6] is a multidimensional pain assessment tool that measures pain severity and interference (0 to 10). Pain severity was measured by four items: worst pain, least pain, average pain in the last 24 h, and pain now. The seven interference items (sleep disturbances, general activity, mood, work, relations with others, walking, and enjoyment of life) were assessed on a 0 to 10 scale, with 0 being "did not interfere" and 10 being "interfered completely."

The following early secondary endpoints were evaluated: distribution of a diminished cold sensation (ice cube test) 15 min and 24 h after the paravertebral injection, acute pain assessed with a VAS (no pain = 0, worst pain = 10) at rest and mobilization every 30 min for 2 h in the PACU and every 6 h for 48 h, satisfaction with the quality of acute pain management, any episodes of paravertebral block–related complications, postoperative nausea and vomiting, total morphine and analgesic consumption for 48 h, and immediate complications or side effects.

Late secondary endpoints were also evaluated: chronic pain according to item 5 of the Brief Pain Inventory and other parameters of the Brief Pain Inventory at 6 months and 12 months; pain characterized with the Douleur Neuropathique 4 score at 3, 6, and 12 months and the Hospital Anxiety Depression Scale questionnaire; and any episodes of late complications, side effects, or paravertebral block–related complications.

Three subscale scores that can be generated with the Brief Pain Inventory were added to the analysis[7,8]: the average score of all seven items of the Brief Pain Inventory (Brief Pain Inventory—Pain Interference Total Score), physical interference (the average score of work, general activity, and walking from the Brief Pain Inventory), and affective interference (the average score of relations with others, enjoyment of life, and mood from the Brief Pain Inventory). The sleep item was excluded from the physical interference scale because the multidimensional scaling analysis revealed that the pain interference items clustered into two groups and that the sleep item was separated from those two clusters. Thus, according to the Brief Pain Inventory manual, the average score of work, general activity, and walking from the Brief Pain Inventory subscale is recommended.

Questionnaires at 3, 6, and 12 months were sent by mail, and patients were contacted by telephone 3, 6, and 12 months after surgery if they did not return the questionnaires.

Statistical Analysis

The intent-to-treat population was defined as all randomized patients, but 28 patients withdrew their consent before surgery. Therefore, these patients were excluded from the intent-to-treat population. Some patients did not receive the entire assigned treatment (fig. 1) but remained in the intent-to-treat population and were excluded from the per-protocol population, which only included patients who received a paravertebral injection. The demographic and clinical characteristics of the patients are described. Nominal (type of surgery, treatments, complications) and ordinal (American Society of Anesthesiologists Physical Status) data are presented as numbers and percentages, excluding missing data. Ratio-scaled quantitative data (age and postoperative treatment doses) are presented as mean ± SD. The interval scaled data (VAS score during injection) and the ratio scaled data of remifentanil doses are presented as median with interquartile range. Comparisons between the two groups were only performed for the dose of remifentanil and pain during injection in the paravertebral space. In these two cases, due to nonhomogeneous variances, data were presented as median with interquartile range instead of mean ± SD. The Mann–Whitney U test was used because we compared only two groups, the control and the paravertebral group.

The incidence of pain 3 months after surgery greater than or equal to 3 on the VAS for item 5 of the Brief Pain Inventory (primary endpoint) was expressed as a percentage with the 95% CI according to the treatment group in the intent-to-treat population. A Pearson chi-square test was performed to compare the results of the Brief Pain Inventory at 3 months, and the odds ratio was estimated using logistic regression and presented with the 95% CI. Missing values for the primary endpoint in the intent-to-treat population were considered to be failures, *i.e.*, the presence of chronic pain at 3 months. Sensitivity analyses were performed on the per-protocol population. Missing values were successively considered, as in the intent-to-treat population, as failures, completed by multiple imputations of the analysis or excluded. Data imputation was computed from the table 1 variables using multiple imputation by chained equations. Five imputations resulted in five complete datasets. Then the results obtained for each dataset were pooled in a global imputation result. All analyses for the primary endpoint were performed without stratification for the randomization strata (site and type of surgery).

Post hoc exploratory subgroup analyses of the primary endpoint were performed. The subgroup results according to the treatment arm were assessed by logistic regression models and presented in the form of a forest plot with odds ratios and interaction *P* values. The secondary outcomes were analyzed in the per-protocol population. Postoperative pain over time (VAS score) was plotted for each patient, and the area under the receiver operating characteristics curve (AUC) was then estimated for each patient. The mean AUCs were compared according to the randomization arm using two independent samples *t* tests. The difference in perioperative opioid requirements was assessed with a logistic regression model with 0 for patients who did not receive morphine and 1 for those who received morphine. Blocked dermatomes and answers to the Brief Pain Inventory, Hospital Anxiety Depression Scale, and Douleur Neuropathique 4 questionnaires are represented using bar plots and histograms. Comparisons between the two groups for blocked dermatomes at 15 min and 24 h were performed with Pearson chi-square tests.

All tests were two-tailed, and $P < 0.05$ was considered to be significant. All analyses were performed using R software (version 4.0.2; R Core Team, Austria).

Results

We screened 391 patients for participation in this study from March 27, 2015, to June 3, 2018. Eleven of these patients did not meet the inclusion criteria, resulting in 380 randomized patients. Twenty-eight of these patients withdrew their consent after randomization and before surgery. Randomization was performed the day before surgery. Eighteen patients changed their minds after randomization and before surgery mainly due to fear of the paravertebral block and ineffectiveness of the saline injection. The type of surgery changed in 10 patients, and they withdrew their consent. Therefore, the final population in the intent-to-treat population analysis included 352 patients. Fifteen of

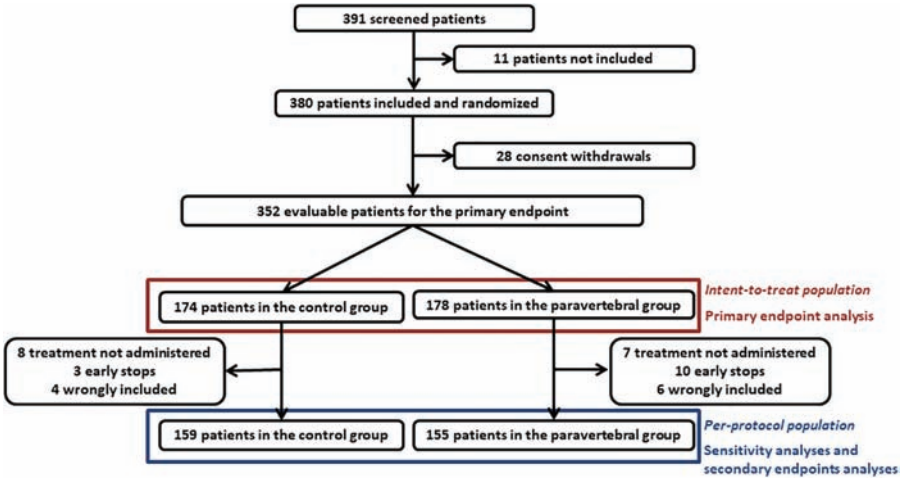

Fig. 1. Flowchart. Control group: thoracic paravertebral block with saline.

these patients were excluded from the paravertebral group and 23 from the placebo group due to a breach in protocol. Thus, the 314 remaining patients received treatment, completed the study, and constituted the per-protocol population (fig. 1). The population characteristics, treatments, and complications in each arm are described in table 1. The characteristics were similar between the two arms, particularly in average age (58 yr).

The primary endpoint of this trial was the incidence of chronic pain greater than or equal to 3 on a 0 to 10 scale for item 5 of the Brief Pain Inventory 3 months after breast surgery. Patients were considered to have pain if the pain score was greater than or equal to 3 and to be pain-free if the score was less than 3 for the fifth item of the Brief Pain Inventory. In the intent-to-treat population, there were 93 of 178 (52.2%) and 83 of 174 (47.7%) patients in the paravertebral block and control groups with pain greater than or equal to 3 on the Brief Pain Inventory 3 months after surgery, respectively. The associated odds ratio, with the control group as a reference, was 1.20 (95% CI, 0.79 to 1.82; $P = 0.394$). In this analysis, any missing data for the fifth item of the Brief Pain Inventory at 3 months (43 of 174 patients in the control group and 46 of 178 in the paravertebral group) was considered to be a failure, and thus was considered to be pain (table 2). Sensitivity analyses were then performed in the per-protocol population; the missing values of Brief Pain Inventory (32 of 159 patients in the control and 33 of 155 in the paravertebral group) were successively considered as failures, completed by multiple imputations of the analysis, or excluded, as described above. The same results were obtained as in the intent-to-treat analysis (table 2).

In all situations, the results obtained were similar and led to the same conclusion: there was no difference between the control group and paravertebral group in pain at 3 months according to the Brief Pain Inventory. There was also no difference for secondary outcomes at 6 and 12 months. Chronic pain was reported in 104 of 178 (58.4%) patients in the paravertebral group and 79 of 174 (45.4%) in the control group at 6 months and in 105 of 178 (59.0%) and 93 of 174 (53.4%) at 12 months (fig. 2). Subgroup analyses were performed to detect any subgroups with a beneficial effect. The results are shown in a forest plot (fig. 3). Paravertebral block with ropivacaine tended to have a beneficial effect on pain at 3 months in patients who underwent partial mastectomy but was associated with more pain in patients who underwent mastectomy, although the difference is not statistically significant.

Evaluations of the blocked dermatomes were performed with the ice test at 15 min and 24 h. At 15 min, there were significantly more patients with at least one blocked dermatome in the paravertebral group than in the control group (84.8% [95% CI, 77.7 to 90.3] *vs.* 43.7% [95% CI, 35.4 to 52.2]; $P < 0.001$). Although still observed between the two arms at 24 h, the difference was less marked (78.2% [95% CI, 69.9 to 85.1] *vs.* 64.9% [95% CI, 56.1 to 73.0]; $P = 0.019$) (fig. 4). Ninety-two percent of the patients in the paravertebral group experienced loss of cold sensation either 15 min or 24 h after the injection, which persisted in 78% of patients after 24 h, with a reduction in the lower dermatome blockade from the sixth thoracic intercostal nerve to the fifth (fig. 4).

Acute postoperative pain was measured every 30 min in the PACU for the first 2 h and then every 6 h for 48 h. The VAS scores were plotted for each patient at each time point, and the profile of pain scores was determined for each patient. From surgery to 48 h after surgery, the profile of pain scores was very similar between the two groups at rest and during mobilization. AUCs were determined for each

Table 1. Demographic and Clinical Characteristics of the Intent-to-treat Population

	Control Group (n = 174)		Paravertebral Group (n = 178)	
Quantitative data	n (missing values) mean ± SD or median (interquartile range)		n (missing values) mean ± SD or median (interquartile range)	
Nominal and ordinal data	n (%)		n (%)	
Demographics				
Age, yr, mean ± SD	174 (0)	58 ± 13	178 (0)	58 ± 14
Body mass index, kg/m²				
< 25		94 (54.3)		85 (47.8)
≥ 25		79 (45.7)		93 (52.3)
Missing values		1		0
ASA Physical Status				
1		27 (15.6)		32 (18.0)
2		137 (79.2)		140 (78.7)
3		9 (5.2)		6 (3.4)
Missing values		1		0
Surgical information				
Type of surgery				
Mastectomy		6 (3.5)		11 (6.2)
Mastectomy + axillary lymph node dissection		73 (42.2)		70 (39.3)
Mastectomy + sentinel lymph node dissection		68 (39.3)		74 (41.6)
Partial mastectomy + axillary lymph node dissection		25 (14.5)		23 (12.9)
Partial mastectomy + sentinel lymph node dissection		1 (0.6)		0 (0)
Missing values		1		0
Intraoperative variables				
Remifentanil during surgery (maintenance dose)				
No		4 (2.4)		3 (1.8)
Yes		161 (97.6)		163 (98.2)
Missing values		9		12
Total dose of remifentanil, µg,* median (interquartile range)	150 (24)	344 (245–434)	135 (43)	276 (210–384)
Pain during injection, VAS score,† median (interquartile range)	150 (24)	6 (3–7)	145 (33)	2 (0–4)
Postoperative treatments				
Intravenous morphine titration				
No		49 (30.1)		101 (61.2)
Yes		114 (69.9)		64 (38.8)
Missing values		11		13
Dose of morphine, mg, mean ± SD	111 (3)	6 ± 3	63 (1)	6 ± 3
Tramadol during the 48 h after surgery				
No		139 (79.9)		142 (79.8)
Yes		35 (20.1)		36 (20.2)
Total dose of tramadol during the 48 h after surgery, mg, mean ± SD	35 (0)	150 ± 100	36 (0)	150 ± 100
Paracetamol during the 48 h after surgery				
No		64 (36.8)		79 (44.4)
Yes		110 (63.2)		99 (55.6)
Total dose of paracetamol during the 48 h after surgery, g, mean ± SD	110 (0)	3 ± 2	99	3 ± 2
Ketoprofen during the 48 h after surgery				
No		32 (18.4)		39 (21.9)
Yes		142 (81.6)		139 (78.1)
Total dose of ketoprofen during the 48 h after surgery, mg, mean ± SD	142 (32)	300 ± 150	139 (39)	300 ± 100
Postoperative complications				
Immediate complications				
No		155 (93.4)		160 (94.1)
Claude Bernard Horner syndrome		1 (0.6)		9 (5.3)
Pain during injection with feeling of pressure in the thorax and chest		10 (6.0)		0 (0)
Motor blockade in the arm of the operated side		0 (0)		1 (0.6)
Missing values		8		8
Complications during the first 48 h				
No		161 (95.8)		162 (96.4)
Hematoma of the surgical site		4 (2.4)		2 (1.2)
Hematoma of the surgical site with necessity of surgery		2 (1.2)		1 (0.6)
Pain at the paravertebral block puncture site		0 (0)		1 (0.6)
Pain at the surgical drain		1 (0.6)		2 (1.2)
Missing values		6		10
Nausea and/or vomiting immediately after the injection				
No		157 (90.2)		166 (93.3)
Yes		17 (9.8)		12 (6.7)
Nausea and/or vomiting in the first 48 h				
No		161 (92.5)		167 (93.8)
Yes		13 (7.5)		11 (6.2)

Nominal (type of surgery, treatments, complications) and ordinal (ASA Physical Status) data are presented as numbers and percentages, excluding missing data. Ratio-scaled quantitative data (age and postoperative treatment doses) are presented as mean ± SD. The interval scaled data (VAS score during injection) and the ratio-scaled data of remifentanil doses are presented as median with interquartile range. Comparisons between the two groups were only performed for the dose of remifentanil and pain during injection in the paravertebral space. In these two cases, due to nonhomogeneous variances, data were presented as median with interquartile range instead of mean ± SD. The Mann–Whitney U test was performed because we compared only two groups, the control group and the paravertebral group.

*Mann–Whitney U test: $P < 0.01$. †Mann–Whitney U test: $P < 0.001$.

ASA, American Society of Anesthesiologists; VAS, visual analogue scale.

Table 2. Results of the Primary Outcome Analysis and Sensitivity Analyses

Population	Class	Control Group, n (%)	Paravertebral Group, n (%)	Odds Ratio (95% CI)	*P* Value
Intent-to-treat		174	178		
Missing data considered as failures for item 5 of Brief Pain Inventory: VAS score < or ≥ 3	Score < 3	91/174 (52.3%)	85/178 (47.8%)	1.20 (0.79–1.82)	*P* = 0.394
	Score ≥ 3	83/174 (47.7%)	93/178 (52.2%)		
Per-protocol		159	155		
Missing data considered as failures for item 5 of Brief Pain Inventory: VAS score < or ≥ 3	Score < 3	89/159 (56.0%)	80/155 (51.6%)	1.19 (0.76–1.86)	*P* = 0.438
	Score ≥ 3	70/159 (44.0%)	75/155 (48.4%)		
Per-protocol		159	155		
Missing data were treated by multiple imputations, item 5 of Brief Pain Inventory: VAS score < or ≥ 3	Score < 3	110/159 (69.2%)	101/155 (65.2%)	1.18 (0.98–1.42)	*P* = 0.142
	Score ≥ 3	49/159 (30.8%)	54/155 (34.8%)		
Per-protocol		127	122		
Missing data for Brief Pain Inventory were excluded, item 5 of Brief Pain Inventory: VAS score < or ≥ 3	Score < 3	89/127 (70.1%)	80/122 (65.6%)	1.23 (0.72–2.10)	*P* = 0.447
	Score ≥ 3	38/127 (29.9%)	42/122 (34.4%)		

The main analysis, as specified in the protocol, is supposed to for the intent-to-treat population and consider all patients even if there are missing data. For the primary outcome analysis, missing values for the fifth item of the Brief Pain Inventory (43 of 174 patients in the control group and 46 of 178 in the paravertebral group) were considered as failures, *i.e.*, pain equal to or higher than 3 for the fifth item of the Brief Pain Inventory. Sensitivity analyses were performed on the per-protocol population with missing values (32 of 159 patients in the control group and 33 of 155 in the paravertebral group). In the first case, missing values were considered, as in the intent-to-treat population, as failures. In the second case, missing values were completed by multiple imputations of the analysis. In the third case, the missing values were excluded. In all situations, the results obtained were similar and led to the same conclusion: there was no difference between the control group and paravertebral group in pain at 3 months according to the Brief Pain Inventory.

VAS, visual analogue scale.

patient and compared. The mean AUCs at rest were 34.9 ± 32.2 and 31.7 ± 34.1 VAS score units × hours in the control and paravertebral groups, respectively. There was no significant difference in the mean AUCs between the two groups ($P = 0.388$). The mean AUC during mobilization was 50.4 ± 47.6 VAS score units × hours in the control group and 44.9 ± 44.8 VAS score units × hours in the paravertebral group ($P = 0.288$). However, a comparison of the 2-h postoperative period showed greater acute postoperative pain in the control group at rest (AUC, 4.3 ± 2.8 *vs.* 2.9 ± 2.8 VAS score units × hours, $P < 0.001$; maximum pain score, 3.8 ± 2.1 *vs.* 2.5 ± 2.5 VAS score units, $P < 0.001$) and during mobilization (AUC, 3.7 ± 3.2 *vs.* 2.5 ± 2.5 VAS score units × hours, $P < 0.001$; maximum pain score, 4.0 ± 2.2 *vs.* 2.4 ± 2.5 VAS score units, $P < 0.001$; fig. 5). Fewer patients required morphine in the paravertebral group, 64/165 (38.8%) *versus* 114/163 (69.9%) in the control group (odds ratio, 0.272 [95% CI, 0.171 to 0.429]; $P < 0.001$).

When patients required morphine, the doses were similar in the two groups: 6 ± 3 mg and 6 ± 3 mg in the control and paravertebral groups, respectively (table 1).

There was no difference in the incidence of nausea and vomiting, analgesic consumption over 48 h, or patient satisfaction between the two groups (table 1).

At 3, 6, and 12 months, the Hospital Anxiety Depression Scale and Douleur Neuropathique 4 scores were similar in the two groups (fig. 2 and appendix).

Nine patients presented with Claude Bernard Horner syndrome in the paravertebral group, while 10 and 6 patients in the control and paravertebral groups reported that the injection was painful with a feeling of pressure in the thorax and chest, respectively (table 1).

Discussion

This multicenter, prospective, randomized, double-blind, placebo-controlled study shows that paravertebral block with ropivacaine and systemic multimodal analgesia did not reduce the incidence of chronic pain 3 months after breast surgery (primary endpoint of the study) compared to paravertebral block with saline and systemic multimodal analgesia. These results are similar to some other studies[2,9,10] that did not demonstrate a long-term benefit with paravertebral block analgesia despite a short-term benefit[3,4] but do not agree with the results of other studies.[11,12] Two recent meta-analyses showed no statistically significant reduction in the risk of persistent postoperative pain 3 to 12 months after breast cancer surgery.[3,13] These 2 studies included seven and six trials, respectively, with an overlap of 3 studies; thus, 2 out of 10 studies found paravertebral block to be beneficial.[11,14] In one of the recent abovementioned meta-analyses,[3] the number of treated patients needed for an additional beneficial outcome was 7 (95% CI, 6 to 13), and the evidence was considered low-quality. There were also conflicting results in two other recent studies.[2,12] One

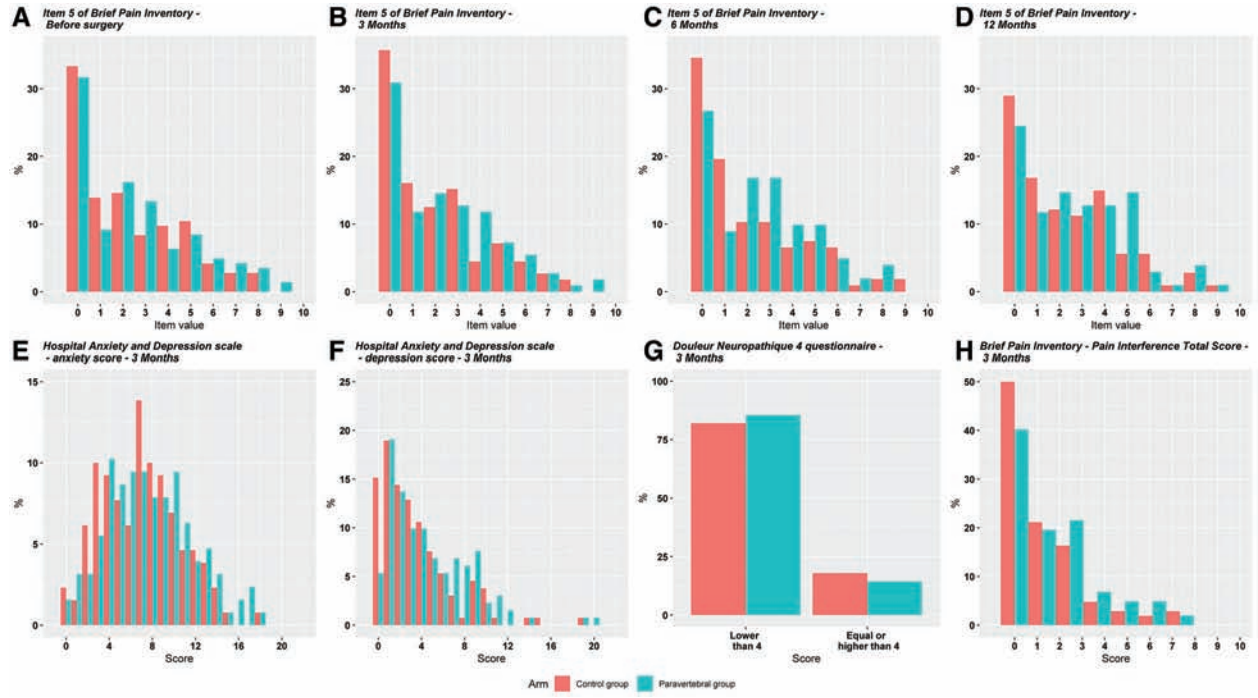

Fig. 2. Brief Pain Inventory before surgery and 3, 6, and 12 months after surgery and Hospital Anxiety and Depression Scale and Douleur Neuropathique 4 questionnaire scores 3 months after surgery. Pain interference at 3 months after surgery was assessed with the Brief Pain Inventory (sleep disturbances, general activity, mood, work, relations with others, walking, and enjoyment of life). The Brief Pain Inventory measures pain severity and interference. Pain severity is measured by four items: worst pain, least pain, average pain in the last 24 h, and pain now. The seven interference items (sleep disturbance, general activity, mood, work, relations with others, walking, and enjoyment of life) are assessed on a 0 to 10 scale, with 0 being "did not interfere" and 10 being "interfered completely." Three subscale scores can be generated: Pain Interference Total Score (the average score of all seven items), physical interference (the average score of work, general activity, and walking), and affective interference (the average score of relations with others, enjoyment of life, and mood). The complete figure with all items is in the appendix. (*A–D*) Brief Pain Inventory, item 5: before surgery and 3, 6, and 12 months after surgery. (*E*) Hospital Anxiety and Depression Scale: anxiety score 3 months after surgery. (*F*) Hospital Anxiety and Depression Scale: depression score 3 months after surgery. (*G*) Douleur Neuropathique 4 questionnaire score equal to or higher than 4 evaluated 3 months after surgery. (*H*) Brief Pain Inventory—Pain Interference Total Score: seven interference items (sleep disturbances, general activity, mood, work, relations with others, walking, and enjoyment of life) 3 months after surgery.

study that reported a lower incidence of chronic pain at 3 and 6 months in the paravertebral group was limited by the absence of pain evaluation during mobilization, and of sensory blockade tests. Moreover, mastectomies were only partial.[12] The second study found that the incidence and severity of persistent postoperative incisional breast pain at 6 and 12 months were unaffected by the analgesia technique. However, pain was not the primary outcome, and the study had several limitations: no reduction in postoperative morphine consumption in the paravertebral group, no sensory blockade tests, and no placebo group for the paravertebral block; thus, the study was not double-blind.[2] The overall incidence of chronic pain at 3 months in our study (53% and 48% in the paravertebral block and control groups, respectively) was similar to that in other published studies (30 to 65%). The wide range of prevalence of chronic pain reported in the literature is probably due to several factors such as the definition and the pain score. Different pain scores might provide different results. A moderate or greater pain score (greater than or equal to 3) is clinically relevant after breast surgery. Less than 3 would be considered mild.

Our study also showed the absence of a statistically significant reduction in the incidence of chronic and neuropathic pain at 3, 6, and 12 months, despite better control of acute pain, which could have been due to the short-term benefit of postoperative pain relief in the paravertebral group. Although we also used numerous tools to identify pain-related functional interference, including the Brief Pain Inventory; Hospital Anxiety Depression Scale; Pain Interference Total Score from the Brief Pain Inventory; the average score of work, general activity, and walking from Brief Pain Inventory; and average score of relations with others, enjoyment of life, and mood from Brief Pain Inventory, no differences in these items were found between the two groups. These scores on patient outcome provide more precise information than pain

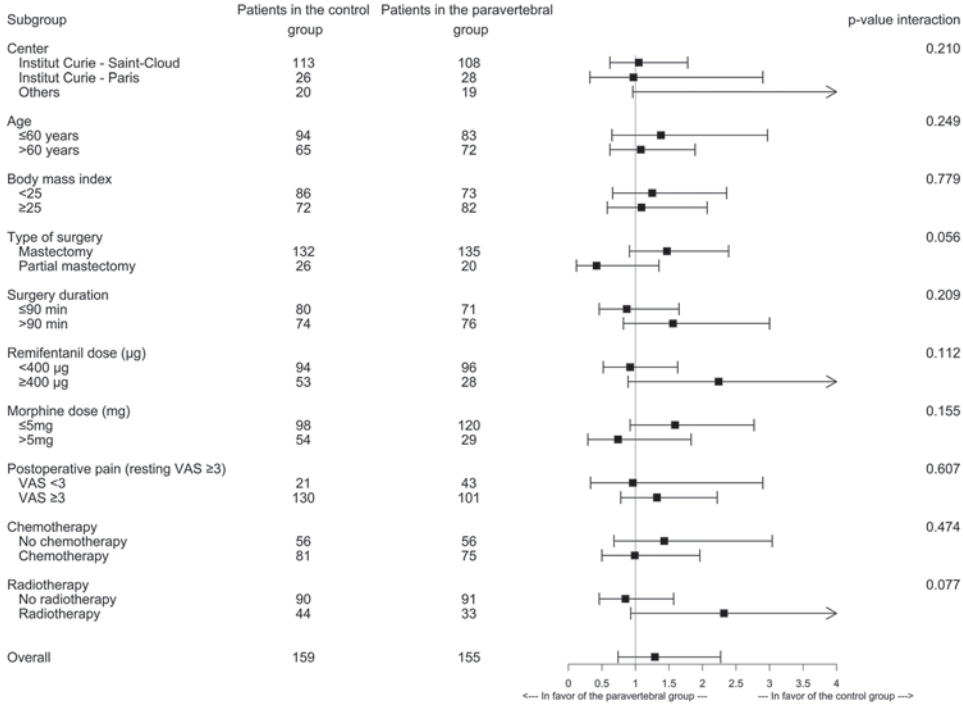

Fig. 3. Forest plot assessing the effects of baseline factors in subgroups groups stratified by treatment (control group or paravertebral group) on chronic postoperative pain 3 months after breast surgery. These results were obtained from the per-protocol population; as for the primary endpoint, the patients with missing Brief Pain Inventory data at 3 months were considered to experience pain. Hazard ratios and interaction *P* values were assessed by logistic regression models. The data in this forest plot appear to show that the type of surgery could be associated with an effect on pain at 3 months depending on the treatment received (interaction *P* value = 0.056). Pain at 3 months tended to be less common in the control group in the case of complete mastectomy, whereas pain tended to be less common in the paravertebral group in the case of partial mastectomy, but the difference is not statistically different. VAS, visual analogue scale.

scores alone and confirmed the absence of a difference in pain and its impact on quality of life.

Acute postoperative pain scores, remifentanil doses during surgery, and morphine consumption in the first 2 postoperative hours were lower in the paravertebral block group than in the control group in our study. One previous study found that a significantly lower pain score in the first 2 h after breast surgery with paravertebral block was associated with a significantly lower consumption of opioids compared to control.[15] In a meta-analysis, there was conclusive evidence that paravertebral block led to a clinically relevant reduction in acute pain (VAS score greater than 1), 24-h morphine consumption, and incidence of nausea and vomiting (greater than or equal to 25% relative reduction). However, the quality of evidence was downgraded to moderate or low due to the lack of adequate blinding and the high degree of heterogeneity across trials, mainly due to differences in baseline analgesia.[4] In our study, this reduction in acute pain and opioid consumption did not persist after the PACU period, and lower opioid consumption did not reduce the incidences of nausea, vomiting, or chronic pain. Therefore, although paravertebral block provided a short-term benefit after breast cancer surgery, unlike in other studies, no long-term benefit was identified with this technique in our study.[2,15]

The risk factors for persistent postoperative pain can be related to the patient and the quality of analgesia, surgery, and cancer treatments.[16,17] Patients at risk of severe postoperative pain (preoperative chronic pain, a reported history of substance abuse or opioid treatment) were not included in our study. Subgroup analyses were performed to detect any subgroups in which a beneficial effect could be observed, but we did not find any significant difference between these subgroups (fig. 3). Although the difference in VAS score for acute pain was significant between the two groups during the first 2 postoperative hours but not associated with a difference in the incidence of chronic pain, the mean VAS scores at rest and during mobilization after the first 2 postoperative hours were less than 2 in both groups. This is considered to be sufficient pain relief after surgery. Notably, low pain scores reduce the likelihood of detecting a significant difference in chronic pain between groups. Our study showed that paravertebral block did not reduce the incidence of chronic pain in patients who underwent partial or complete mastectomy (fig. 3). Although two earlier studies showed that paravertebral block reduces

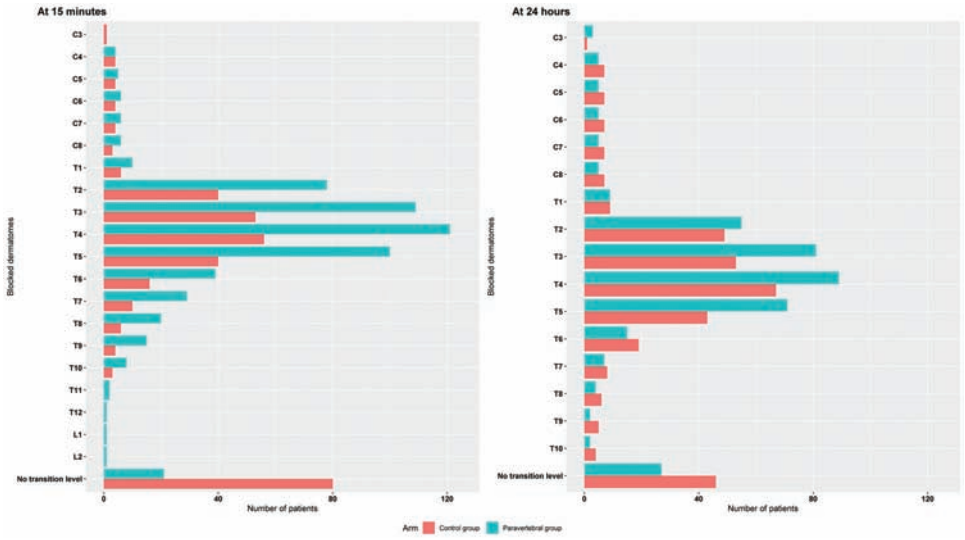

Fig. 4. Blocked dermatomes 15 min and 24 h after an injection of ropivacaine or saline in the paravertebral space in the paravertebral group and control group, respectively. Evaluations of blocked dermatomes were performed through cold ice tests; at 15 min, significantly more patients had at least one dermatome blocked in the paravertebral group than in the control group (84.8% [95% CI, 77.7 to 90.3] *vs.* 43.7% [95% CI, 35.4 to 52.2]; $P < 0.001$). At 24 h, the difference between the two groups concerning blocked dermatomes was still observed, although it was less marked (78.2% [95% CI, 69.9 to 85.1] *vs.* 64.9% [95% CI, 56.1 to 73.0]; $P = 0.019$).

the incidence of chronic pain after partial mastectomy,[11,12] the results regarding complete mastectomy are more conflicting. The breast and chest wall are innervated by a combination of thoracic intercostal (1 to 7), brachial plexus, and superficial cervical plexus nerves. The cephalad part of the breast also receives some innervation from the supraclavicular nerves (superficial cervical plexus). The pectoralis major and minor muscles, as well as their fascia, are supplied by the medial and lateral pectoral nerves. The axilla exhibits complex innervation with a large contribution from the intercostobrachial nerve. While paravertebral block generally results in an ipsilateral blockade of the intercostal and sympathetic nerves, it does not block the supraclavicular nerves, pectoral nerves, or other brachial plexus branches. Therefore, paravertebral block may be insufficient for major breast surgery, especially for deep anatomical structures (pectoralis major and its fascia).[18,19]

The clinical effect of paravertebral block was confirmed by sensory blockade tests. Loss of cold sensation was evaluated 15 min after the block, which corresponded to the onset of ropivacaine. The extent of the loss of cold sensation was similar to that published in a previous study and covered the operative site (thoracic intercostal nerves 1 to 6) after a single injection.[20] Eighty-five percent of the patients in the paravertebral group experienced loss of cold sensation 15 min after the injection in the paravertebral space, and 92% experienced loss of cold sensation either 15 min or 24 h after the injection (fig. 4).

After 24 h, the loss of cold sensation persisted in 78% of the patients in the paravertebral group, with a reduction in the lower dermatome blockade from the sixth thoracic intercostal nerve to the fifth (fig. 4). There are very few studies that have reported unsuccessful sensory blockade, with an incidence of approximately 10%, which is similar to our results.[21,22] It is interesting to note that in the control group, 44% of patients reported that they had loss of cold sensation at 24 h. This result is difficult to evaluate because some nerves may have been injured during surgery. Forty-two percent of the patients in the control group also experienced loss of cold sensation after a paravertebral saline injection. This may be explained by a placebo effect or a false-positive response due to the patients' difficulty in evaluating this loss, even when comparing sensations to a reference cold sensation at the third cervical dermatome. This may also be the effect of the saline solution injection, which was found to be more painful in this group (table 1). The injection of liquid into closed spaces is painful (5 to 10% of patients), and patients can feel pressure in the chest. The incidence of pain is higher when the concentration of the injected ropivacaine is lower, which may explain the difference in pain intensity during the injection between the paravertebral block (ropivacaine 0.75%) and control groups.[23] The injection of saline solution into a closed space and resulting pain may have a transitory effect on nerve sensitivity, explaining the loss of cold sensation. After locoregional analgesia, evaluations of sensory block-extension can be difficult and are probably a limitation in these studies.[20]

Compared to previous studies, the current study includes a large number of patients, making it possible to detect small differences between groups, and different sites allowing

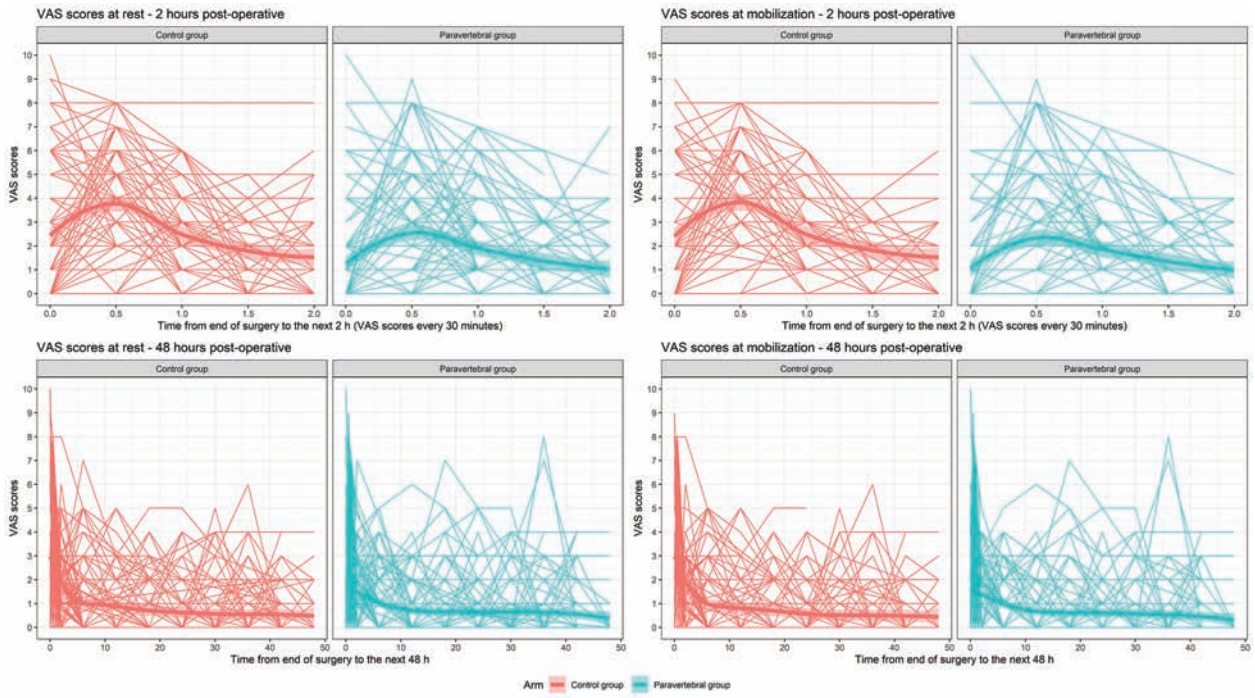

Fig. 5. VAS scores at rest and during mobilization during the first 2 postoperative hours and 48 postoperative hours. In the first 2 postoperative hours, both groups had a maximum pain score approximately 30 min after surgery both at rest and during mobilization. This maximum pain score was higher in the control group than in the paravertebral group. At rest, the mean VAS score at 30 min was 3.8 ± 2.1 in the control group and 2.5 ± 2.5 in the paravertebral group ($P < 0.001$). During mobilization, the mean VAS score at 30 min was 4.0 ± 2.2 in the control group and 2.4 ± 2.5 in the paravertebral group ($P < 0.001$). The AUCs reflects the intensity and duration of mean pain over the first 2 h. A comparison of AUCs between the two groups showed that the pain at rest was greater in the control group (4.3 ± 2.8 VAS score units × hours) than in the paravertebral group (2.9 ± 2.8 VAS score units × hours; $P < 0.001$). For pain during mobilization, the AUCs were 3.7 ± 3.2 in the control group *versus* 2.5 ± 2.5 VAS score units × hours in the paravertebral group ($P < 0.001$). After the first 2 postoperative hours and over the next 46 h, there was no difference in pain between the two groups at rest or during mobilization. AUC, area under the receiver operating characteristics curve; VAS, visual analogue scale.

for generalization of the results. We also provided long-term monitoring of pain with numerous validated tools. Moreover, our study, unlike others, compared the treatment group to a control group that received a saline injection in the paravertebral space, evaluated the results according to type of surgery (complete or partial mastectomy, sentinel or axillary lymph node dissection) and paravertebral block technique (one-level single thoracic puncture under ultrasound guidance), and specifically determined the blocked dermatomes.

Conclusions

Paravertebral block did not reduce the incidence of chronic pain after breast surgery. Paravertebral block did result in less immediate postoperative pain, but there were no other significant differences in postoperative outcomes.

Acknowledgments

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Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available at: isabelle.turbiez@curie.fr. Raw data available at: isabelle.turbiez@curie.fr.

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Appendix

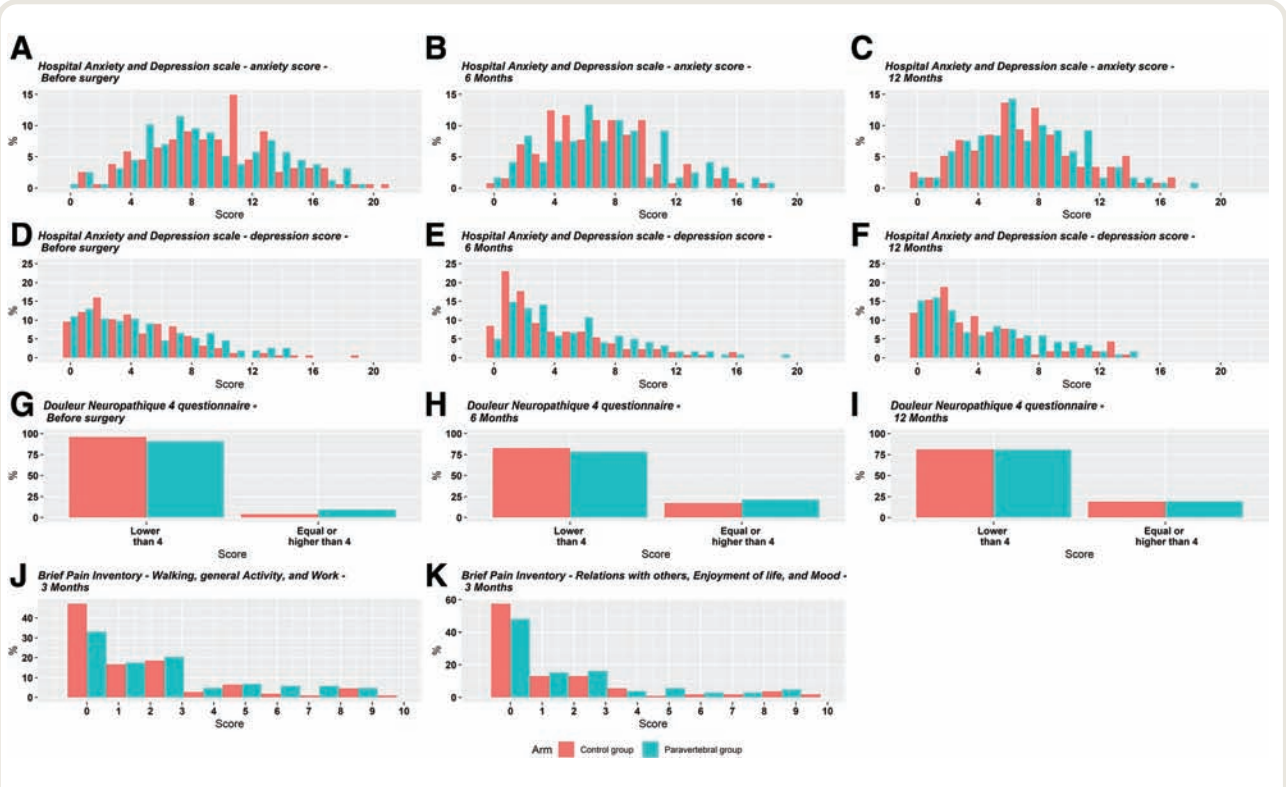

Fig. A1. Secondary endpoints: (*A–C*) Hospital Anxiety Depression Scale-anxiety scores, before surgery and at 6 and 12 months. (*D–F*) Hospital Anxiety Depression Scale-depression scores, before surgery and at 6 and 12 months. (*G–I*) Douleur Neuropathique 4 scores, before surgery and at 6 and 12 months. (*J*) Brief Pain Inventory subscale: Walking, general Activity, and Work scores 3 months after surgery. (*K*) Brief Pain Inventory subscale: Relations with others, Enjoyment of life, and Mood scores 3 months after surgery. Percentages are the percentage of patients for each score.

ANESTHESIOLOGY

Postoperative Pain and Age: A Retrospective Cohort Association Study

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ANESTHESIOLOGY 2021; 135:1104–19

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Worldwide populations are aging, leading to larger numbers of elderly patients receiving surgery
- Reports of associations between age and postoperative pain have been conflicting

What This Article Tells Us That Is New

- Data from the PAIN OUT registry involving more than 11,000 patients undergoing spinal surgery, joint replacement, and laparoscopic cholecystectomy were used in a retrospective cohort analysis
- Pain reported postoperative day 1 declined slightly with age
- Severe postoperative pain was prevalent regardless of age or surgical type

ABSTRACT

Background: As the population ages, the number of elderly people undergoing surgery increases. Literature on the incidence and intensity of postoperative pain in the elderly is conflicting. This study examines associations between age and pain-related patient reported outcomes and perioperative pain management in a dataset of surgical patients undergoing four common surgeries: spinal surgery, hip or knee replacement, or laparoscopic cholecystectomy. Based on the authors' clinical experience, they hypothesize that pain scores are lower in older patients.

Methods: In this retrospective cohort, study data were collected between 2010 and 2018 as part of the international PAIN OUT program. Patients filled out the International Pain Outcomes Questionnaire on postoperative day 1.

Results: A total of 11,510 patients from 26 countries, 59% female, with a mean age of 62 yr, underwent one of the aforementioned types of surgery. Large variation was detected within each age group for worst pain, yet for each surgical procedure, mean scores decreased significantly with age (mean Numeric Rating Scale range, 6.3 to 7.3; $\beta = -0.2$ per decade; $P \leq 0.001$), representing a decrease of 1.3 Numeric Rating Scale points across a lifespan. The interference of pain with activities in bed, sleep, breathing deeply or coughing, nausea, drowsiness, anxiety, helplessness, opioid administration on the ward, and wish for more pain treatment also decreases with age for two or more of the procedures. Across the procedures, patients reported being in severe pain on postoperative day one 26 to 38% of the time, and pain interfered moderately to severely with movement.

Conclusions: The authors' findings indicate that postoperative pain decreases with increasing age. The change is, however, small and of questionable clinical significance. Additionally, there are still too many patients, at any age, undergoing common surgeries who suffer from moderate to severe pain, which interferes with function, supporting the need for tailoring care to the individual patient.

(ANESTHESIOLOGY 2021; 135:1104–19)

In the overall surgical population, 30 to 55% of all patients report moderate or severe pain on the first postoperative day.[1–3] Poorly managed acute pain can lead to complications and prolonged hospital stay, and increases the risk of developing chronic pain.[4,5] Therefore, adequate postoperative pain treatment is important. Within our aging patient population, adequate postoperative pain management is increasingly challenging. The challenge lies in the fact that elderly patients more often have contraindications for analgesic drugs such as nonsteroidal anti-inflammatory drugs and a greater susceptibility to adverse effects of analgesics.

In the literature, the incidence and intensity of postoperative pain in the elderly are conflicting. Some studies suggest that elderly patients report pain to be of a lower intensity than younger patients,[6,7] while other studies do not find differences.[8,9] Studies demonstrate that pain in older patients is underrecognized and undertreated due to lack of pain assessment and concern of increased risks of adverse effects.[10] To be able to improve postoperative pain management in this group, it is important to have more information on the experience of postoperative pain in elderly patients. Since the experience of pain is

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multidimensional and described on several levels—sensory (intensity and character of pain), affective (emotional component), and impact (ability to function)[11]—all these items should be assessed to obtain a comprehensive evaluation of this experience. Additionally, the cultural influence on pain expression should be considered. Using the International Pain Outcome Questionnaire,[12] which assesses these different dimensions of pain, the experience of pain was measured in the unique international PAIN OUT registry.[13] In current study, the objective is to analyze associations between age and a diverse range of pain-related patient reported outcomes and treatments, studying a large sample of patients undergoing spinal surgery, hip replacement, knee replacement, or laparoscopic cholecystectomy. We hypothesize, based on clinical practice, that older patients have lower postoperative pain scores than younger patients.

Materials and Methods

PAIN OUT Registry and Network

The analysis presented here relies on data collected prospectively by the PAIN OUT registry. PAIN OUT (www.pain-out.eu), an international registry and research project, aims at improving postoperative pain management in the clinical routine. PAIN OUT was established with funding from the European Community's Seventh Framework Program. PAIN OUT is registered in ClinicalTrials.gov (NCT02083835). Approval for participation is obtained by each site from its local ethics committee. Informed consent from patients for participation in the survey can be oral or written, depending on requirements of the local ethics committee.

The current analysis is based on data contributed by patients cared for in 268 hospital wards from 26 countries worldwide. Inclusion criteria require that the patient was of consenting age (18 yr or older, in most countries); was on the first postoperative day, back on the ward from the recovery room for at least 6 hours; and agreed to participate in the survey. Patients were approached for participation in the survey by research assistants who could be students, nurses, or medical residents, and they underwent training for approaching patients, collecting data, and entering it into a Web-based password secure portal. As far as possible, research assistants did not have clinical duties on wards from which they collected data.

A standardized postoperative questionnaire, the International Pain Outcomes Questionnaire, which has been validated in English and has been translated using standardized methods into 29 different languages,[12] is used in PAIN OUT. This patient outcome questionnaire is based on the revised American Pain Society Patient Outcome Questionnaire. The construct validity of the International Pain Outcomes Questionnaire is confirmed by the Bartlett test ($P < 0.001$). The factor analysis resulted in a three-factor structure explaining 53.6% of the variance. Chronbach's alpha of the total scale was high (0.86).[12] Patients are asked to evaluate different facets of pain. This includes pain intensity and its duration, pain interference with doing activities in bed, or taking a deep breath or coughing, or sleep, side effects (such as nausea and drowsiness), emotions (anxiety and helplessness), satisfaction with pain treatment, and preoperative presence of chronic pain and its intensity (appendix 1). Patients fill out the International Pain Outcomes Questionnaire in their respective language on the first day after surgery. The International Pain Outcomes Questionnaire uses 11-point Numeric Rating Scale (where 0 = none and 10 = worst imaginable) or binary items (appendix 1). To reduce interviewer bias, patients complete the questionnaire independently with no assistance from family or staff. If a patient requests help, the research assistant can assist. Patient characteristics, sex, age, comorbidities related to pain, use of opioids before admission and clinical data, perioperative analgesics administration, and type of surgery (International Classification of Diseases, Ninth Revision surgical procedure codes) are collected from the medical record by the research assistant. For spinal surgery, International Classification of Diseases, Ninth Revision codes 81.00, 81.04 to 81.08, and 81.62 are used; for hip replacement, 81.51, and partial hip replacement, 81.52; for knee replacement, 81.54; and for laparoscopic cholecystectomy, 51.23 and laparoscopic partial cholecystectomy, 51.24.

Study Design and Variables Used in the Current Study

After approval from the PAIN OUT publication board, an anonymized dataset of patients who underwent spinal surgery, hip replacement, knee replacement, and laparoscopic cholecystectomy between 2010 and 2018 was made available for analysis. The dataset contained records from patients from Europe, Middle East, Asia, and South America. Culture is a complex construct to measure. In this study, we used language as a surrogate measure.

Outcome

The primary outcome was the worst pain on the first postoperative day experienced for each type of surgery. Secondary outcomes were the worst pain in male and female patients, pain interference with physical function and sleep, anxiety, helplessness, side effects (nausea and drowsiness), and opioid consumption before and after surgery in the recovery room and on the ward. Additionally, "wish for more pain treatment" (yes/no) was analyzed in patients speaking different languages subdivided to patients below and above 65 yr old.

Statistical Analysis

A statistical analysis plan was formalized before accessing the data for the primary outcome. Predictors used in the

regression model were *a priori* selected based on literature. No data-driven variable selection models were used. A *post hoc* analysis was performed in the review process, and two possible confounders, "year of data collection" and "anesthesia type," were added to the model. We also performed *post hoc* analyses after initial examination of the data on opioid administration, wish for more treatment, and language.

No statistical power calculation was conducted before the study. The sample size was based on the available data. Datasets were included without setting a minimum number per ward. Datasets were excluded from the analysis when age was missing, or worst pain was lower than least pain. A maximum of 12% of data for a variable was missing (year of data collection, 0%; sex, 0.2%; worst pain score, 3%; presence of chronic pain before surgery, 3%; use of opioids before admission, 6%; presence of comorbidities related to pain, 12%; and anesthesia type, 12% [in imputation sequence]). Using a fully conditional specification multiple imputation technique, 12 imputed datasets were created to be used for the multiple regression models. The pooled results and standard errors are presented in the results section.

Continuous data were expressed as mean ± SD, and categorical data as absolute numbers with percentages for the available data.

Associations between age and worst pain, interference of pain with doing activities in bed, breathing deeply and coughing, sleep, nausea, drowsiness, anxiety, and helplessness for each type of surgery was first assessed using linear regression (on the imputed dataset). We corrected for sex, presence of comorbidities related to pain, presence of chronic pain before surgery, use of opioids before admission, year of data collection, and anesthesia type as they may be confounders.[14] Using a Bonferroni correction, a P value of 0.001 or below was regarded as statistically significant. A logistic regression was performed for the relation between age and wish for more treatment for each type of surgery using the same set of predictors. To avoid effect modification, linear regression analysis was not performed to assess the relationship between age and the interference of pain with activities out of bed because younger patients (less than 65 yr) were out of bed significantly more often than older patients (65 yr or more).

Locally estimated scatterplot smoothing lines were used to fit a smooth curve through the scatterplot with age on the x-axis and a Numeric Rating Scale on the y-axis. It is a nonparametric strategy to find a curve of best fit without assuming the data must fit some distribution shape and enables the reader to visualize the relation between age and Numeric Rating Scale. This approach was also carried out separately for male and female patients, in light of the literature that indicates that there may be differences in pain reports between the sexes.[14]

To further explore the nonlinear patterns of age and worst pain score, we estimated regression models for the four types of surgery separately, adding restricted cubic splines to the model. Using Akaike's Information Criterion, we determined whether cubic splines were a better fit of the data and how many knots would provide the best fit (limited to two, three, or four knots). The knots were placed automatically on the corresponding percentiles of the data. The R package *splines* was used to estimate the models, and *effects* and *ggplot* were used for the visualizations.

Opioids administration and wish for more pain treatment, both dichotomous variables, were expressed as frequencies and calculated for young and older patients (less than 65 yr and 65 yr or more) per surgery category. Wish for more pain treatment of young and older patients was subdivided by language. Differences in means between young and older patients were expressed as effect sizes. This is a quantitative measure of the strength of a phenomenon and is classified as small (d = 0.2 to 0.4), medium (0.5 to 0.7), or large (greater than 0.8).[15] To measure the effect size, we used the Cohen d coefficient with 95% CI. In this study, values were considered clinically relevant when Cohen d was 0.5 or greater. The effect size of the difference in percentages between young and older patients was expressed as risk ratio and is classified as small, 2 to 3; medium, 3 to 4; and large, 4 or more. The cutoff for clinical relevance is 3 or more.[16] Effect sizes are measured with the Practical Effect Size Calculator.[17]

For all analyses, unless indicated otherwise, P values of less than 0.05 were considered statistically significant, and two-sided statistical tests were performed. Statistical analyses were performed using either SPSS Statistical Software, version 20.0 (SPSS Inc, USA), or R version 4.0 (R Studio, USA).

Results

Research assistants approached 15,051 patients for inclusion in the PAIN OUT database. We excluded 3,080 cases who did not undergo one of the four types of surgery. Additionally, 220 cases were excluded due to lack of registered informed consent, 65 because age was missing, and 176 cases because least pain scores were higher than worst pain scores (fig. 1). Of the 11,510 included patients, 3,941 patients received hip replacement, 3,691 knee replacement, 2,894 laparoscopic cholecystectomy, and 984 a spinal fusion.

Patient Characteristics

The mean age of the total cohort was 62 yr, and 59% were female. In table 1, patient characteristics are presented for each type of surgery.

Of patients undergoing hip or knee replacement or spinal fusion, 83 to 90% reported preoperative chronic

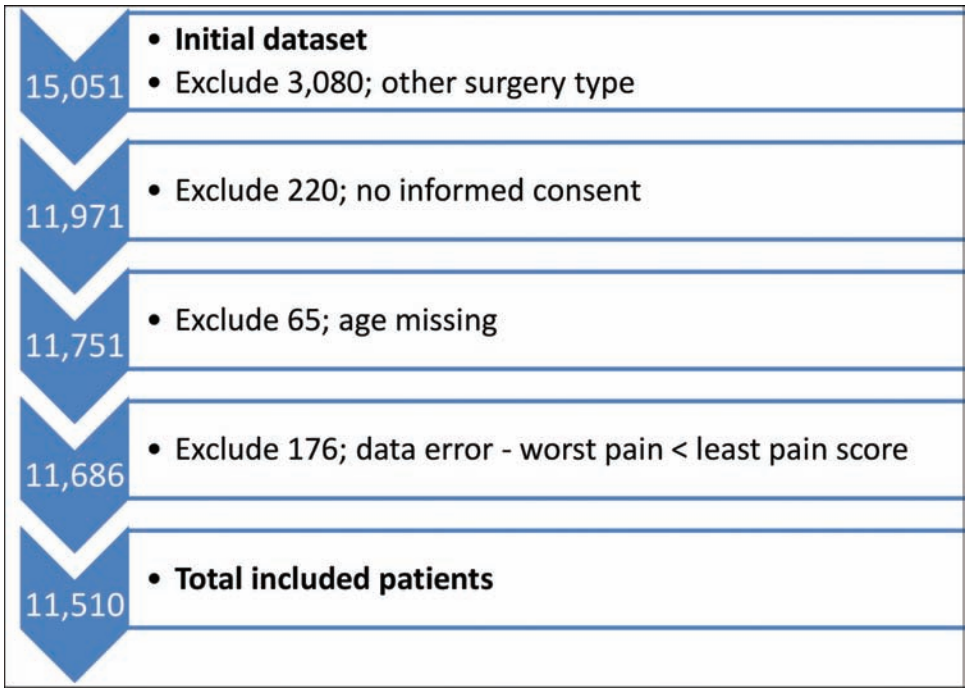

Fig. 1. Study flowchart. Numbers represent patients in the dataset.

Table 1. Patient Characteristics

	Hip Replacement, N = 3,941	Knee Replacement, N = 3,691	Spinal Fusion, N = 984	Laparoscopic Cholecystectomy, N = 2,894
Age, yr, mean ± SD	65 ± 13	67 ± 10	59 ± 13	52 ± 15
≥ 65 yr, No. (%)	2,082 (53)	2,258 (61)	379 (39)	717 (25)
Sex, female, No. (%)	2,140 (54)	2,341 (63)	520 (53)	1,887 (65)
Body mass index, mean ± SD	27.7 ± 5.5	30.8 ± 6.5	28.3 ± 5.6	27.8 ± 5.2
Presence of ≥ 1 comorbidities related to pain, No. (%)*	2,469 (72)	2,621 (80)	672 (73)	1,308 (53)
Presence of preoperative chronic pain, No. (%)*	3,151 (83)	3,215 (90)	785 (83)	1,278 (46)
Intensity of preoperative chronic pain Numeric Rating Scale score, mean ± SD	6.6 ± 2.2	6.7 ± 2.1	7.5 ± 1.8	7.0 ± 2.5
Opioid use before admission, No. (%)*	482 (13)	389 (11)	274 (29)	37 (1)

*Percentages calculated on available data.

pain with average score of 6.6, 6.7, and 7.5, respectively. Opioid use before admission was present in 11 to 29% of cases. Preoperative pain was reported by 46% of patients undergoing laparoscopic cholecystectomy, it was rated with an average of 7.0, and 1% of patients used opioids before admission (table 1).

Age was significantly correlated with presence of comorbidities related to pain, presence of chronic pain before surgery, and use of opioids before admission, with older patients more frequently having comorbidities related to pain, and having chronic pain before surgery and more frequently using opioids before admission.

Postsurgical Pain and Related Symptoms

Patients undergoing spine surgery reported the highest scores for worst pain, interference of pain with moving in bed, sleep, and doing activities out of the bed. Patients after laparoscopic cholecystectomy experienced the highest pain scores with deep breathing or coughing. Most patients

Table 2. Numeric Rating Scale Scores for Worst and Least Pain, Time in Severe Pain, the Interference of Pain, Side Effects, Anxiety, and Helplessness per Type of Surgery

	Hip Replacement, N = 3,941	Knee Replacement, N = 3,691	Spinal Fusion, N = 984	Laparoscopic Cholecystectomy, N = 2,894
Worst pain score	5.7 ± 2.7	6.1 ± 2.8	6.6 ± 2.7	5.0 ± 2.6
Male	5.4 ± 2.6	5.8 ± 2.7	6.3 ± 2.7	4.5 ± 2.5
Female	5.9 ± 2.8‡	6.3 ± 2.8‡	6.9 ± 2.5†	5.3 ± 2.6‡
Least pain score	1.9 ± 1.9	2.2 ± 2.1	2.7 ± 2.1	1.8 ± 1.8
Time in severe pain	29% (25)	33% (27)	38% (28)	26% (23)
Deep breathing/coughing	1.0 ± 1.9	0.8 ± 1.8	3.0 ± 3.1	3.7 ± 3.0
Moving in bed	4.9 ± 3.2	4.6 ± 3.2	6.2 ± 3.0	4.3 ± 2.8
Sleep	3.1 ± 3.1	3.5 ± 3.2	3.9 ± 3.4	2.4 ± 2.7
Out of bed, yes, No. (%)*	1,815 (53)	1,923 (59)	510 (57)	2,186 (89)
Pain out of bed	4.6 ± 3.1	4.7 ± 3.1	4.8 ± 3.0	3.4 ± 2.6
Nausea	2.0 ± 2.9	2.0 ± 3.0	2.3 ± 3.2	2.1 ± 3.0
Drowsiness	2.7 ± 2.9	2.8 ± 3.0	3.1 ± 3.2	3.0 ± 3.0
Itch	0.6 ± 1.7	0.8 ± 1.8	0.8 ± 2.0	0.4 ± 1.3
Dizziness	1.5 ± 2.4	1.6 ± 2.5	2.0 ± 2.7	2.0 ± 2.6
Anxiety	2.3 ± 2.8	2.6 ± 3.0	3.0 ± 3.2	2.1 ± 2.6
Helplessness	2.4 ± 3.1	2.6 ± 3.2	3.3 ± 3.5	1.8 ± 2.6

Results are presented as mean ± SD Numeric Rating Scale score or as otherwise specified. Time in severe pain refers to the percentage of time in severe pain since surgery.
*Percentages calculated on available data. †$P \leq 0.01$. ‡$P \leq 0.001$.

scored below a Numeric Rating Scale of 3 on side effects. Patients after spine fusion scored highest on anxiety and helplessness (table 2).

Age-related Effects on Postsurgical Pain

For all four types of surgery, maximum pain scores decreased significantly with increasing age (table 3). Maximum pain scores were higher when there was use of opioids before admission (β range: 0.9 to 1.0; $P < 0.001$) and in female patients (β range: –0.4 to –0.7; $P \leq 0.008$). When there was presence of chronic pain before surgery, maximum pain scores were higher for knee replacement, spinal fusion, and laparoscopic cholecystectomy (β range: 0.4 to 0.9; $P \leq 0.001$). Locally estimated scatterplot smoothing lines show an age-related decrease of worst pain score for all four surgery types with a stabilization of the worst pain score around the age of 70 yr in patients after laparoscopic cholecystectomy and knee and hip replacement (fig. 2).

Exploring the nonlinear patterns of age and worst pain score for hip replacement, spinal fusion, and laparoscopic cholecystectomy, cubic splines with three knots demonstrated the best fit and also showed an age-related decrease of worst pain. For knee replacement surgery, cubic splines did not improve model fit, and a linear decrease in worst pain scores with advancing age remained to be the best model (appendix 2).

Age-related Effects on Pain Interference with Moving in Bed, Breathing, Coughing, Sleep, and Side Effects

The interference of pain with doing activities in bed decreases significantly with age, as does interference of pain with sleep, with breathing deeply or coughing, nausea, drowsiness, anxiety, and helplessness (table 3). As scores were lower for total hip and knee replacement compared to spinal surgery, the association with age was less robust. When plotting worst pain scores and pain interference with moving in bed, a similar age-related decrease is observed for all types of surgery except for knee replacement (fig. 3). Also, worst pain scores and pain while breathing have a similar age-related decrease for laparoscopic cholecystectomy (fig. 3).

Opioid Treatment in Patients Aged Less than 65 yr or 65 yr and Older

Older patients were less often administered opioids in the recovery room and ward than younger patients for all procedures. Older patients less often had a wish for more pain treatment compared with younger patients for three procedures, not for laparoscopic cholecystectomy. Young patients undergoing hip and knee replacement surgery received opioids more often before surgery compared with older patients (table 4).

Pain and Wish for More Treatment in Patients Speaking Different Languages

Lower maximum pain scores after hip and knee surgery in patients above the age of 65 yr were observed in Spanish-, Dutch-, and German-speaking patients. (table 5). Serbian-, Spanish-, German-, and French-speaking patients above the age of 65 yr less often had a wish for more treatment after hip or knee surgery. In English-speaking patients above the age of 65 yr, the wish for more treatment was higher. In the remaining language groups, no age-related difference was

Table 3. Linear Regression of Relation of Age to Pain, Side Effects, Anxiety, and Helplessness for All Procedures

	Constant*	Age β per Decade (Standard Error)	*P* Value	Numeric Rating Scale Score Difference over a Time Span of 60 yr
Worst pain score				
Spinal fusion	7.2	–0.2 (0.06)	< 0.001	1.3
Hip replacement	6.8	–0.2 (0.04)	< 0.001	1.3
Knee replacement	7.3	–0.2 (0.05)	< 0.001	1.3
Laparoscopic cholecystectomy	6.3	–0.2 (0.04)	< 0.001	1.3
Pain interference with moving in bed				
Spinal fusion	7.5	–0.3 (0.07)	< 0.001	1.9
Hip replacement	4.6	–0.04 (0.04)	0.315	
Knee replacement	3.3	0.1 (0.05)	0.021	
Laparoscopic cholecystectomy	6.2	–0.3 (0.04)	< 0.001	1.9
Pain interference with breathing/coughing				
Spinal fusion	6.8	–0.5 (0.08)	< 0.001	3.2
Hip replacement	1.2	–0.04 (0.03)	0.161	
Knee replacement	0.9	–0.01 (0.03)	0.699	
Laparoscopic cholecystectomy	5.9	–0.4 (0.04)	< 0.001	2.2
Pain interference with sleep				
Spinal fusion	5.9	–0.4 (0.08)	< 0.001	2.6
Hip replacement	3.8	–0.2 (0.04)	< 0.001	1.3
Knee replacement	4.4	–0.2 (0.06)	< 0.001	1.4
Laparoscopic cholecystectomy	4.0	–0.2 (0.04)	< 0.001	1.3
Drowsiness				
Spinal fusion	5.0	–0.4 (0.08)	< 0.001	2.3
Hip replacement	4.1	–0.3 (0.04)	< 0.001	1.6
Knee replacement	5.2	–0.3 (0.05)	< 0.001	2.0
Laparoscopic cholecystectomy	4.5	–0.2 (0.04)	< 0.001	1.4
Nausea				
Spinal fusion	3.8	–0.2 (0.08)	0.019	
Hip replacement	3.7	–0.2 (0.04)	< 0.001	1.1
Knee replacement	2.5	–0.07 (0.05)	0.181	
Laparoscopic cholecystectomy	3.4	–0.2 (0.04)	< 0.001	1.0
Anxiety				
Spinal fusion	5.4	–0.4 (0.08)	< 0.001	2.4
Hip replacement	2.8	–0.2 (0.04)	< 0.001	1.2
Knee replacement	3.3	–0.2 (0.05)	< 0.001	1.3
Laparoscopic cholecystectomy	3.2	–0.2 (0.04)	< 0.001	1.4
Helplessness				
Spinal fusion	6.5	–0.4 (0.08)	< 0.001	2.2
Hip replacement	3.6	–0.2 (0.04)	< 0.001	1.4
Knee replacement	4.4	–0.3 (0.05)	< 0.001	2.0
Laparoscopic cholecystectomy	3.1	–0.2 (0.03)	< 0.001	1.4

Using a Bonferroni correction, we regarded a *P* value ≤ 0.001 as statistically significant.

*The constant is interpreted at the reference level of the covariates; female sex, no presence of comorbidities related to pain, no presence of chronic pain before surgery, no use of opioids before admission, year of data collection starting at 2010 and general anesthesia type.

observed. The effect sizes were small and did not meet the level of clinical significance.

Discussion

The current study assessed the association between age and postoperative pain after hip replacement, knee replacement, laparoscopic cholecystectomy, or spinal fusion using the international PAIN OUT database. The reported maximum pain levels decreased significantly with increasing age. However, this decrease in Numeric Rating Scale (less than 2 Numeric Rating Scale points) over a lifespan is defined as not clinically relevant.[18,19] A decrease in Numeric Rating Scale with increasing age is also observed for interference of pain with doing activities in bed, breathing deeply, coughing, sleep, side effects (nausea and drowsiness), and emotions (anxiety and helplessness). Older patients were less often administered opioids and less often had a wish for more treatment. Our observations correspond with literature showing that younger age is a risk factor for the occurrence of early postoperative severe pain in surgical patients.[14,20,21]

Also important to note is that all patients, independent of surgery type, spent about a third of the first postoperative day in severe pain; a sizeable proportion did not get out of bed; pain during movement indicated moderate to severe levels of pain. Thus, discussing these findings together, we may conclude that although mean worst postoperative pain scores decrease with

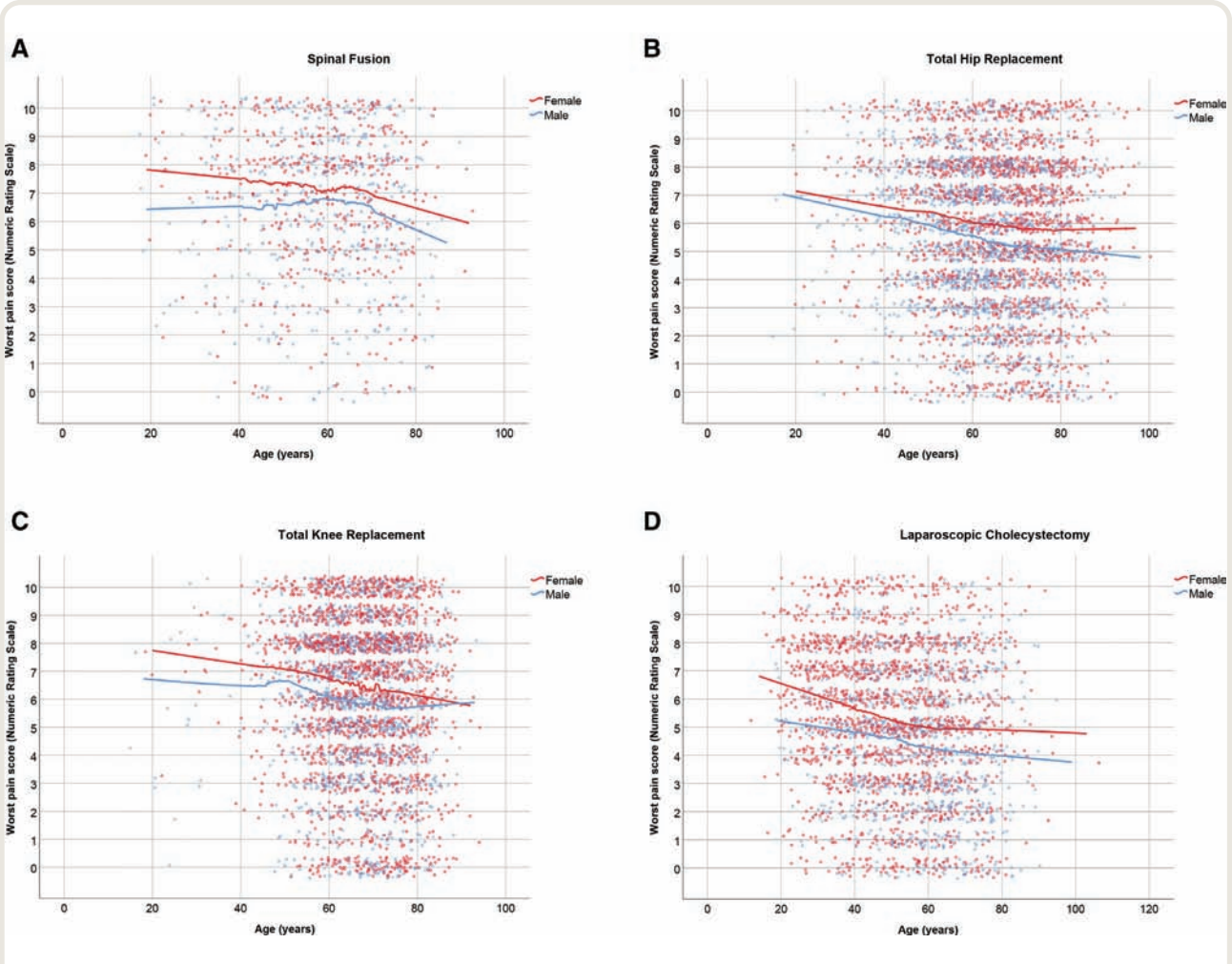

Fig. 2. Association between worst postoperative pain score and age. Numeric Rating Scale for worst pain score (*y-axis*) and age in years (*x-axis*) with locally estimated scatterplot smoothing for female (*red*) and male (*blue*) patients for (*A*) spine surgery, (*B*) hip replacement, (*C*) knee replacement, and (*D*) laparoscopic cholecystectomy. To improve data visualization, a jittering technique was applied.

age, Numeric Rating Scale scores are still in the moderate to severe range for all ages, and do not relieve us clinicians from our obligation to improve postoperative pain management.

There are more observations in this study that are worth mentioning in an effort to improve postoperative pain management. A high percentage of patients receiving regional anesthesia (79%) for a total knee replacement have high pain scores on the ward and receive opioids on the ward in over 80% of cases. This should alert the healthcare providers that it is not enough to provide anesthesia according to guidelines, but management needs to be continued on the ward. Also, female sex, presence of chronic pain before surgery, and use of opioids before admission are related to increased postoperative pain. We argue that current standardized analgesic dosing in adult postsurgical patients is often not sufficient for patients at risk for severe postoperative pain, *e.g.*, a young female patient with preoperative chronic pain on opioids. We therefore encourage clinicians to base their postoperative pain management on the individual patient, taking these risk factors into account, and not solely rely on the current standardized dosing in adult postsurgical patients.

Emphasizing that there is still room for improvement in the postoperative pain management for elderly patients, we also want to discuss the interesting finding that there seems to be an age-related effect on postoperative pain. We hypothesize that there is a multifactorial explanation for the effect of age on postoperative pain. Postoperative pain may be influenced by age-related changes in the structure and function of peripheral sensory pathways, hormonal changes, and/or pharmacokinetic changes, but the assessment of pain and its integration by the elderly patients influenced by psychologic factors (catastrophizing, anxiety, earlier life experiences), cultural, and generational influences may also contribute to this finding. Below we will discuss these factors in more detail.

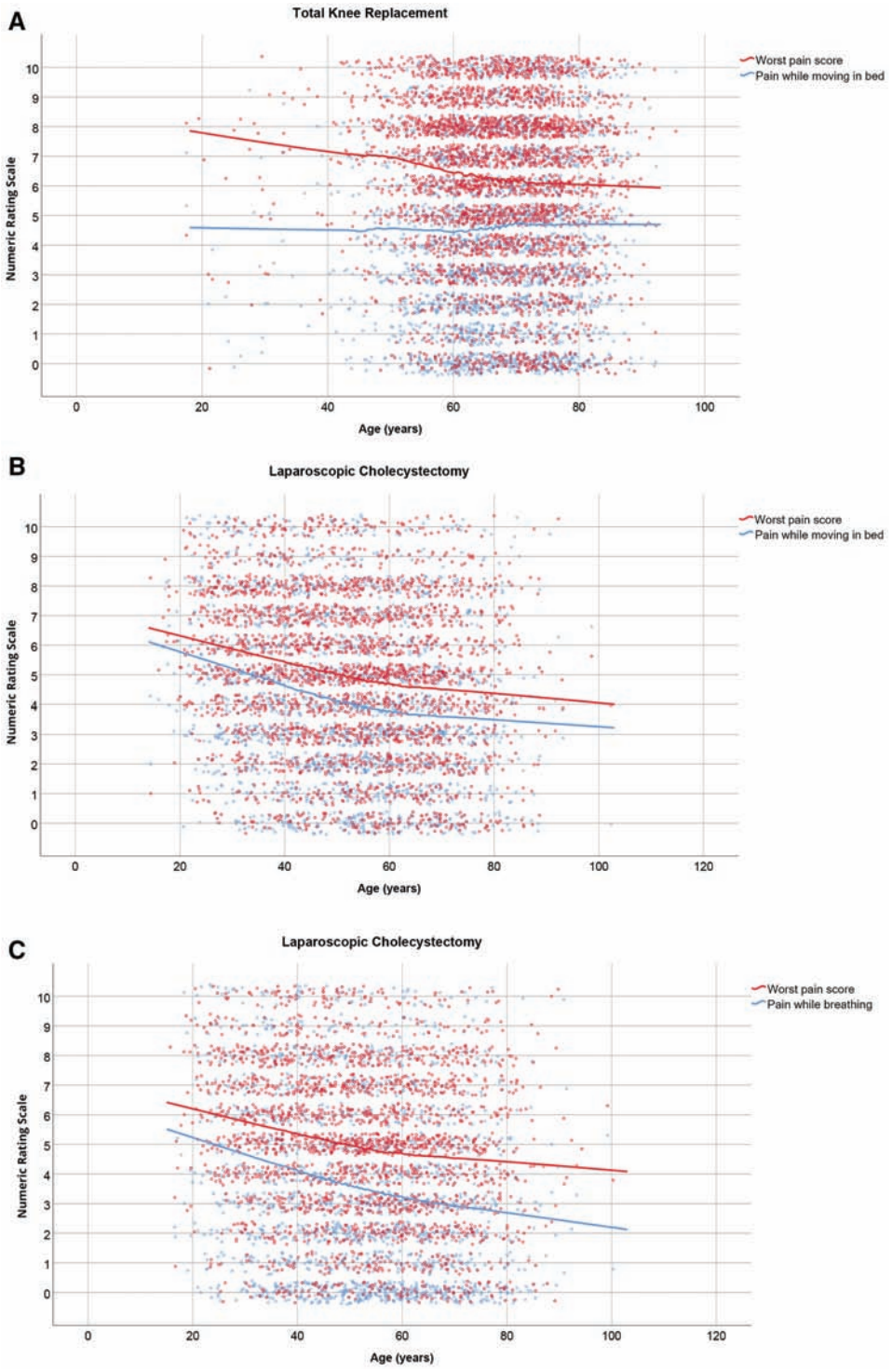

Fig. 3. Association between pain interference and age. (*A* and *B*) Numeric Rating Scale for worst pain score (*red*) and pain while moving in bed (*blue*; *y-axis*) and age in years (*x-axis*) with locally estimated scatterplot smoothing for (*A*) knee replacement and (*B*) laparoscopic cholecystectomy. (*C*) Numeric Rating Scale for worst pain score (*red*) and pain while breathing (*blue*; *y-axis*) and age in years (*x-axis*) with locally estimated scatterplot smoothing for laparoscopic cholecystectomy. To improve data visualization, a jittering technique was applied.

Table 4. Opioid Use and Wish for More Pain Treatment of Young and Elderly Patients per Surgery Type

	< 65 yr, N = 6,074	≥ 65 yr, N = 5436	Effect Size Relative Risk* (CI)
Sex, female, No. (%)	3,566 (59)	3,290 (61)†	0.96 (0.93–1.01)
Spinal fusion, No. (%)	605 (62)	379 (38)	
Opioids before admission	164 (28)	110 (30)	0.93 (0.64–1.36)
Opioids recovery room	452 (76)	257 (69)†	1.10 (0.10–1.21)
Opioids ward	505 (85)	296 (79)†	1.08 (1.00–1.15)
Wish for more treatment	157 (27)	71 (20)‡	1.35 (0.79–2.30)
Hip replacement, No. (%)	1,859 (47)	2,082 (53)	
Regional anesthesia	701 (43)	787 (44)	0.98 (0.87–1.10)
Opioids before admission	252 (15)	230 (12)†	1.25 (0.79–1.97)
Opioids recovery room	1,310 (72)	1,267 (62)§	1.16 (1.10–1.23)
Opioids ward	1,462 (79)	1,508 (74)§	1.07 (1.03–1.11)
Wish for more treatment	362 (20)	278 (14)§	1.43 (1.00–2.04)
Knee replacement, No. (%)	1,433 (39)	2,258 (61)	
Regional anesthesia	1,053 (79)	1,569 (79)	1.00 (0.96–1.04)
Opioids before admission	200 (15)	189 (9)§	1.67 (0.95–2.92)
Opioids recovery room	1,080 (77)	1,518 (69)§	1.12 (1.06–1.17)
Opioids ward	1,254 (88)	1,770 (79)§	1.11 (1.08–1.15)
Wish for more treatment	344 (25)	466 (22)†	1.14 (0.88–1.46)
Laparoscopic cholecystectomy, No. (%)	2,177 (75)	717 (25)	
Opioids before admission	22 (1)	15 (2)†	0.5 (0.001–117.8)
Opioids recovery room	763 (37)	216 (31)‡	1.19 (0.96–1.49)
Opioids ward	899 (42)	280 (40)	1.05 (0.89–1.24)
Wish for more treatment	337 (16)	89 (13)	1.23 (0.68–2.22)

*Risk ratio. †$P \leq 0.05$. ‡$P \leq 0.01$. §$P \leq 0.001$.

Innervation of soft tissue (*e.g.*, skin) and bone tissue changes with advancing age both in animals[22,23] and in humans.[24,25] Age-related changes in nerve conduction, studied in caudal and digital nerves, are represented by a parabolic curve with highest conduction speed during adolescence, decreasing again with advanced age.[22,23,26] Increased thermal and mechanical thresholds measured on the skin using quantitative sensory testing have been observed in the elderly.[27,28] A contradicting finding is that there is also increased temporal summation of pain and reduced pain inhibitory function in older adults, increasing the risk for chronic pain.[29] We hypothesize, taking these preclinical and clinical studies into account, that the net effect of age-related changes in the function and structure of the peripheral sensory pathways may contribute to a decreased pain sensation after surgery.

Hormonal changes and their effect on postoperative pain is a challenging relation to study as menopause coincides with the age that pain is reported most often and with highest pain scores. In studies on chronic pain syndromes and menopause, there is no consensus that menopause itself is related to higher pain scores.[30,31] In current study, we did not observe a peak in reported pain intensity in women aged between 40 and 60 yr after surgery. Men and women showed a comparable age-related decrease in maximum pain score, with slightly higher scores in women compared to men. Female sex is a known risk factor for moderate to severe postoperative pain.[14]

Opioid consumption was lower in older patients in current study. The elderly also less often had a wish for more pain treatment compared to younger patients. This observation corresponds with previous studies.[21,32] There are several explanations for this finding. First, older patients may receive less opioids because of increased risk of adverse events and contraindications for opioid drug treatment due to comorbidities. Second, opioid clearance may be reduced with advancing age.[33] In current study, however, older patients experienced less nausea and drowsiness compared with younger patients.

Catastrophizing, anxiety, and depression are well-known risk factors for development of chronic pain.[34] Also, for acute pain, anxiety has been related to postoperative pain intensity.[21] In current study, older patients had lower anxiety and helplessness scores compared with younger patients, which could very well contribute to the lower postoperative pain scores reported by elderly patients. Many elderly patients believe that pain is a normal part of aging and that pain is something they must live with or endure in silence.[35] Older adults are more often stoic, believing that they should tolerate unnecessary pain, and should not ask for or self-administer analgesia until pain is more severe.[36,37] Resilience, a psychologic construct that allows adults to improve the ability to adapt positively when faced with adversity, is demonstrated to be higher in women than in men, and in older women more so than in younger women. Higher resilience might also be a potential contributor to lower pain scores in older patients.[38,39] Finally, older patients may report less pain because previous painful experiences may cause them to interpret any noxious stimulus in an age-dependent context that decreases perception of severity.[40]

Table 5. Wish for More Pain Treatment and Worst Pain Score in Patients after Hip or Knee Replacement Speaking Different Languages, Subdivided for Patients below and above 65 yr

	N = 7,632		Wish for More Pain Treatment, %				Maximum Pain Score Mean		
Language		No. (%) of Patients ≥ 65 yr	All Patients, No. (%)	< 65 yr, No. (%)	≥ 65 yr, No. (%)	Effect Size (CI) Relative Risk*	< 65 yr	≥ 65 yr	Effect Size (CI) Cohen's d
Spanish—Mexican	373	194 (52)	78 (40)	69 (39)	80 (41)	1.05 (0.71 to 1.56)	4.9	5.6	–0.21 (–0.41 to –0.01)
Hebrew	153	104 (68)	52 (34)	22 (42)	30 (30)	1.40 (0.67 to 2.92)	7.8	7.5	0.11 (–0.21 to 0.44)
Serbian	566	326 (58)	163 (29)	84 (35)	79 (24)‡	1.46 (0.89 to 2.38)	5.5	5.6	–0.04 (–0.20 to 0.13)
Chinese	147	62 (42)	40 (27)	22 (26)	18 (29)	0.90 (0.33 to 2.46)	4.4	4.3	0.04 (–0.28 to 0.36)
English	1,055	306 (29)	236 (22)	152 (20)	84 (28)‡	0.71 (0.45 to 1.14)	6.5	6.6	–0.08 (–0.21 to 0.05)
Spanish	983	727 (74)	204 (21)	80 (31)	124 (17)§	1.82 (1.10 to 3.03)	6.1	5.3§	0.26 (0.12 to 0.40)
Swedish	274	139 (51)	49 (18)	22 (16)	27 (19)	0.84 (0.25 to 2.84)	5.9	5.3	0.20 (–0.03 to 0.44)
Dutch	497	356 (72)	82 (17)	29 (21)	53 (15)	1.40 (0.54 to 3.63)	6.5	5.7‡	0.32 (0.12 to 0.51)
German	1440	825 (57)	203 (14)	100 (16)	103 (13)†	1.23 (0.63 to 2.41)	6.2	5.6§	0.23 (0.13 to 0.34)
Italian	188	133 (71)	30 (16)	10 (17)	20 (16)	1.06 (0.19 to 5.80)	4.8	5.1	–0.10 (–0.41 to 0.20)
French	1,348	820 (61)	162 (12)	75 (14)	87 (11)†	1.27 (0.56 to 2.89)	6.0	5.7	0.12 (0.01 to 0.23)
Other language or missing	608								

*Risk ratio. †$P \le 0.05$. ‡$P \le 0.01$. §$P \le 0.001$.

In the current study, we observed differences in worst pain scores and in the wish for more pain treatment in the different language groups. Cultural differences have been described for pain beliefs/appraisals, coping, and catastrophizing.[41] A recent study on pain in American elderly shows that today's midlife Americans have had more pain throughout adulthood than today's elderly.[42] They find that for those with less education, each successive birth cohort has a higher prevalence of pain at each age. They state that this phenomenon is not observed in other rich countries. Finally, cultural differences may also be present in the way healthcare providers manage pain.[43,44]

The current study is unique due to its large study population, the multinational data collection in a highly standardized manner, and combining patient reports on pain and related symptoms with perioperative data. We focused on four frequently performed surgical procedures, both soft tissue (laparoscopic cholecystectomy) and bone surgery (hip and knee replacements and spinal surgery). Since the mean age differed between the procedures with the youngest patients in the laparoscopic cholecystectomy group and the oldest in the total knee replacement group, and there was variation in the presence of comorbidities, presurgical chronic pain, and opioid use, this selection of procedures, all showing a similar age-related decrease in maximum pain reports, strengthens our conclusion.

There are, however, also limitations. Although the dataset included data from different countries, data from northern America, Africa, and Australia/New Zeeland are missing. Potentially larger cultural differences may hinder the generalizability of the study. Second, within the timeframe of this study (2010 to 2018), changes in pain management have been implemented (*e.g.*, enhanced recovery protocols). We have corrected for "year of data collection," and as changes were implemented for all ages at the same time, we are of the opinion that the primary outcome is not influenced by changes in pain management over the years. Third, we have chosen to relate the worst pain score after surgery to aging, but one may argue that this is not always the best representative of pain suffering. However, our hypothesis still holds for patients after spinal fusion, hip replacement, and laparoscopic cholecystectomy when time in severe pain is used as composite endpoint (*post hoc* analysis, appendix 3). Finally, we only show an association between age and pain on the first operative day and cannot extrapolate these findings to pain developing in the trajectory after surgery.

Conclusions

This study assesses the association between age and postoperative pain after hip replacement, knee replacement, laparoscopic cholecystectomy, or spinal surgery. When looking on a population level, postoperative pain decreases with increasing age. Older patients experience less interference of pain with doing activities in bed, breathing deeply, coughing, sleep, side effects (nausea and drowsiness), and emotions (anxiety and helplessness), and were less often administered opioids and less often had a wish for more treatment. However, we want to stress that on an individual patient level, at any age, there are still too many patients undergoing common surgeries who suffer from moderate to severe pain, which interferes with function. We therefore encourage clinicians to base their postoperative pain management on the individual patient, taking risk factors such as age, being female, presence of chronic pain before surgery, and use of opioids before admission into account

and not solely rely on the current standardized dosing in adult postsurgical patients.

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Competing Interests

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Appendix 1: Questions in the International Pain Outcomes Questionnaire and Answer Options

Questions	Numeric Rating Scale	Percentage	Binary
The worst pain since surgery	X		
The least pain since surgery	X		
How often in severe pain since surgery		x	
Pain interference with doing activities in bed	X		
Pain interference with breathing deeply or coughing		x	
Pain interference with sleeping		x	
Out of bed since surgery			x
Pain interference with doing activities out of bed	X		
Nausea since surgery	X		
Drowsiness since surgery	X		
Itching since surgery	X		
Dizziness since surgery	X		
Feelings of anxiety because of the pain	X		
Feelings of helplessness because of the pain	X		
Wish for more pain treatment			x
Persistent painful condition for 3 months before surgery			x
Pain score of chronic pain	X		
Comorbidities (pain-related)			x

Appendix 2: Nonlinear Relation between Age and Worst Pain Score

Models	β	Standard Error	*P* Value
Spinal fusion			
(Intercept)	6.95	0.53	< 0.001
Knots:			
Age 1	0.16	0.39	0.673
Age 2	–1.72	1.27	0.174
Age 3	–2.04	0.67	0.002
Total hip replacement			
(Intercept)	6.11	0.42	< 0.001
Knots:			
Age 1	–1.06	0.24	< 0.001
Age 2	–0.40	0.95	0.673
Age 3	–0.27	0.39	0.496
Total knee replacement			
(Intercept)	7.56	0.31	< 0.001
Age	–0.02	0.005	< 0.001
Laparoscopic cholecystectomy			
(Intercept)	6.27	0.33	< 0.001
Knots:			
Age 1	–1.87	0.24	< 0.001
Age 2	–2.22	0.84	0.008
Age 3	–0.69	0.59	0.241

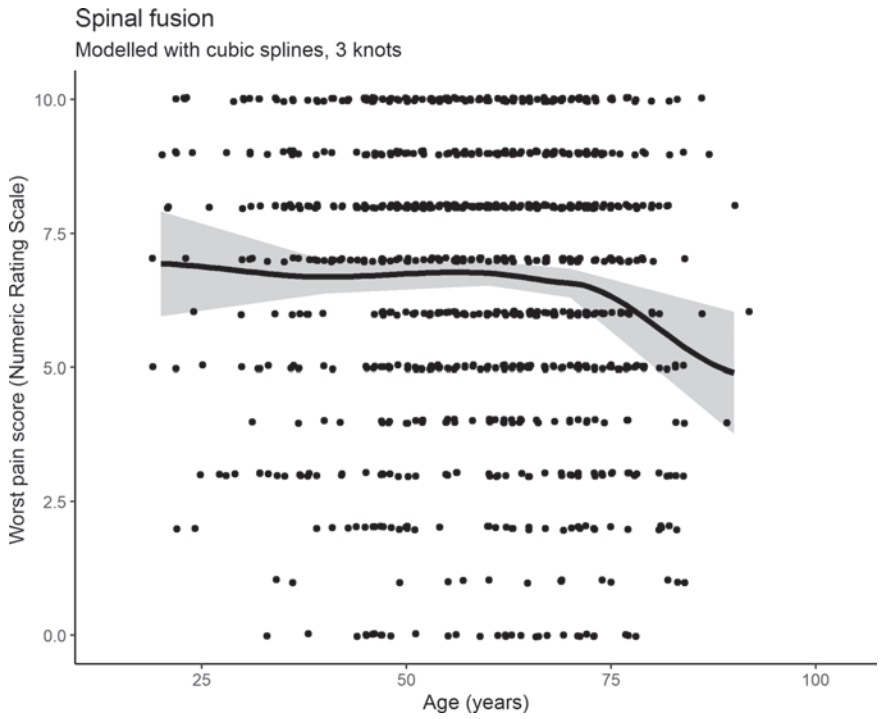


Fig. A2.1. Spinal fusion. Modeled with cubic splines, three knots. *Shaded area* indicates 95% confidence intervals.

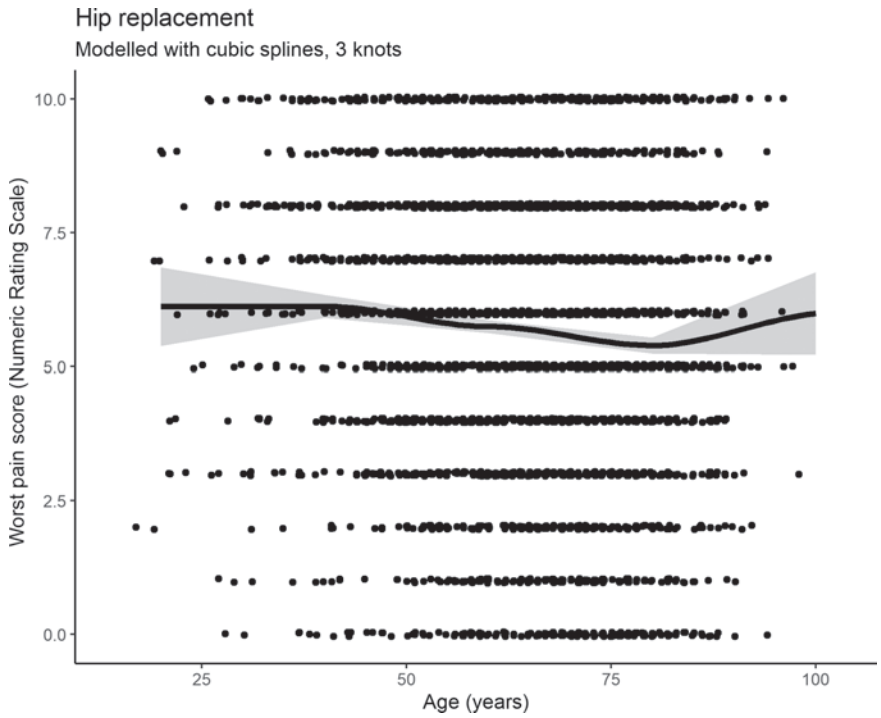


Fig. A2.2. Hip replacement. Modeled with cubic splines, three knots. *Shaded area* indicates 95% confidence intervals.

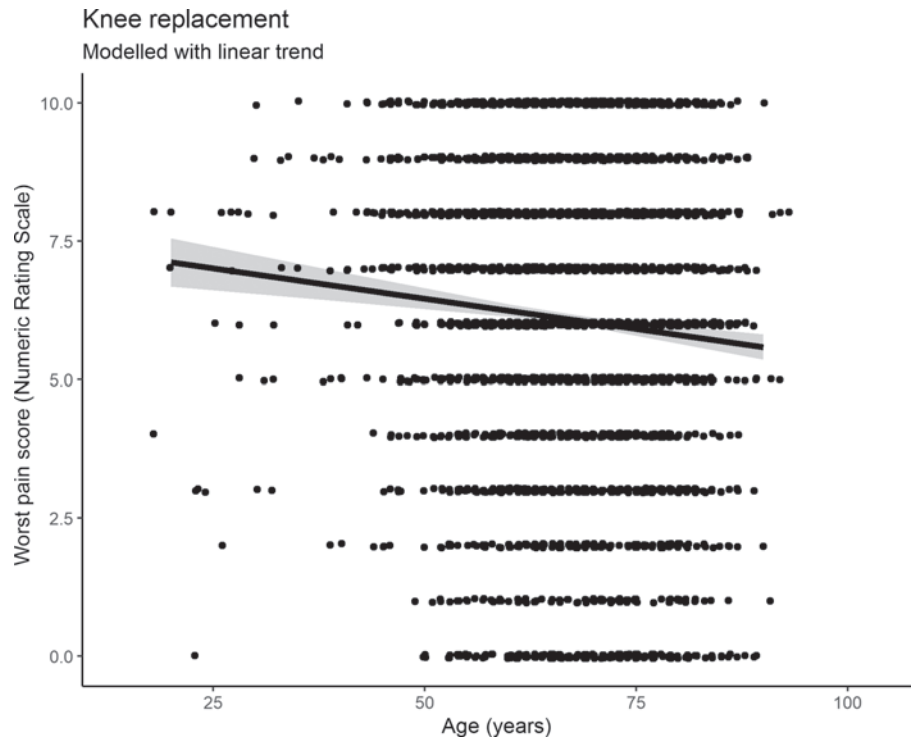


Fig. A2.3. Knee replacement. Modeled with linear trend. *Shaded area* indicates 95% confidence intervals.

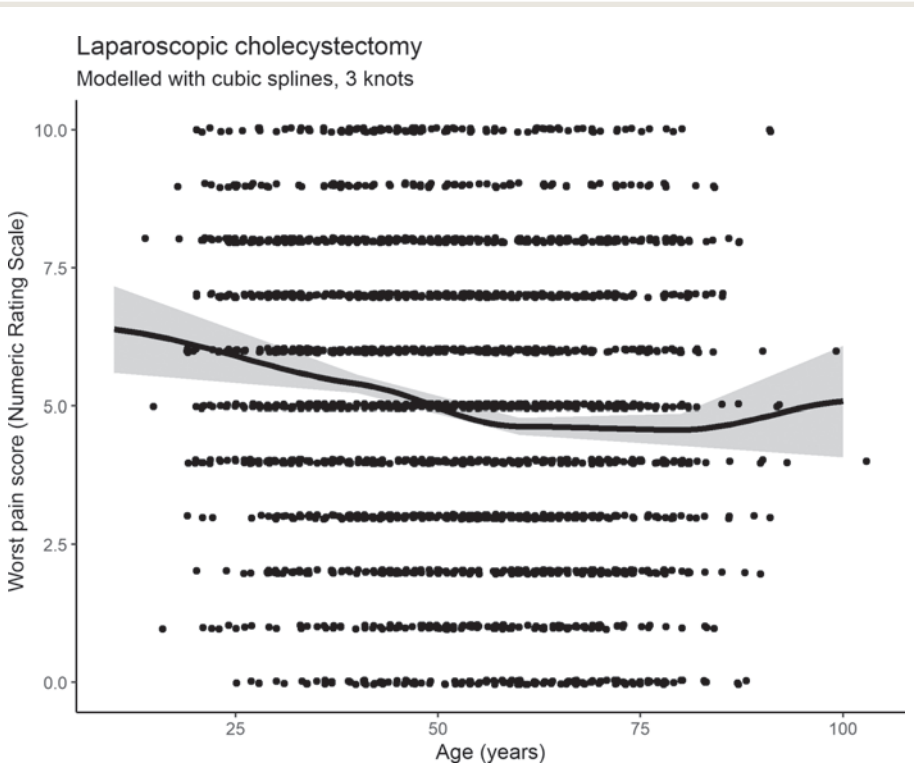


Fig. A2.4. Laparoscopic cholecystectomy. Modeled with cubic splines, three knots. *Shaded area* indicates 95% confidence intervals.

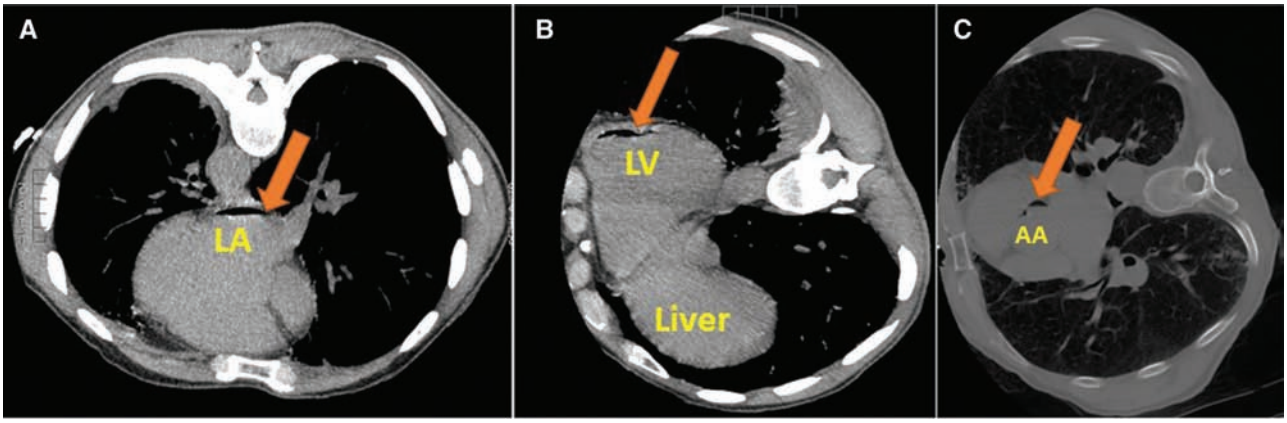
Appendix 3: *Post hoc* Analysis with Composite Endpoint: Time in Severe Pain

Regression Models	Constant	Age β per Decade (CI)	*P* Value
Primary endpoint: worst pain score			
Spinal fusion	7.2	–0.22 (–0.36 to –0.11)	< 0.001
Hip replacement	6.8	–0.22 (–0.30 to –0.15)	< 0.001
Knee replacement	7.3	–0.21 (–0.26 to –0.07)	< 0.001
Laparoscopic cholecystectomy	6.3	–0.22 (–0.28 to –0.13)	< 0.001
Composite endpoint: worst pain score * time in most severe pain			
Spinal fusion	4.2	–0.19 (–0.36 to –0.08)	0.002
Hip replacement	2.2	–0.13 (–0.21 to –0.07)	< 0.001
Knee replacement	1.6	0.02 (–0.08 to 0.13)	0.662
Laparoscopic cholecystectomy	2.2	–0.13 (–0.22 to –0.10)	< 0.001

We performed an additional *post hoc* analysis to verify our hypothesis that postoperative pain scores decrease with age. In our primary analysis, our endpoint is worst pain score. In the *post hoc* analysis, we created a composite endpoint by adding the factor "time in most severe pain" to the primary outcome, resulting in "worst pain score *time in most severe pain." The association between age and worst pain score *time in most severe pain shows a less robust but still significant decrease of pain with advancing age for spinal fusion, hip replacement, and laparoscopic cholecystectomy.

Systemic Air Embolism during Percutaneous Transthoracic Lung Biopsy

Vivek Arora, M.D., Geoff Burks, M.D.



Systemic air embolism is a rare but potentially catastrophic complication of percutaneous transthoracic needle lung biopsy.[1] Systemic air embolism can occur as a result of placement of the biopsy needle tip into a pulmonary vein, thus entraining atmospheric air, or by the formation of bronchial-venous or alveolar-venous fistulous tracks. When pressure in the air containing spaces exceeds venous pressure (*e.g.*, during coughing or positive pressure ventilation), embolization and entry of air into the left heart chambers can occur.[2] Coronary and cerebral embolization can lead to cardiac and neurologic ischemia. A computed tomography scan in a 58-yr-old male who underwent a transthoracic needle lung biopsy in the prone position revealed air in the left atrium (*arrow*, panel *A*). Imaging in the right lateral decubitus position demonstrated air in the left ventricle and ascending aorta (*arrow*, panels *B* and *C*, respectively). Acute neurologic deterioration, bradycardia, and diffuse ST changes ensued.

Risk factors for systemic air embolism include biopsy of a central lung or cavitary lesions and coughing or positive pressure ventilation and use of hollow needles. Treatment of systemic air embolism includes supplying 100% oxygen and maintaining the patient in a right lateral decubitus and Trendelenburg position. In the right lateral decubitus position buoyant forces are hypothesized to keep air bubbles in a nondependent position away from the left ventricle outflow tract.[3] Although controversy exists about the ability of buoyancy to counteract forward flow, appropriate positioning should be maintained until definitive treatment in the form of hyperbaric oxygen can be instituted. Despite aggressive resuscitative efforts, the abovementioned patient died.

Competing Interests

The authors declare no competing interests.

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Tracheal Varicose Veins Associated with Klippel–Trenaunay Syndrome

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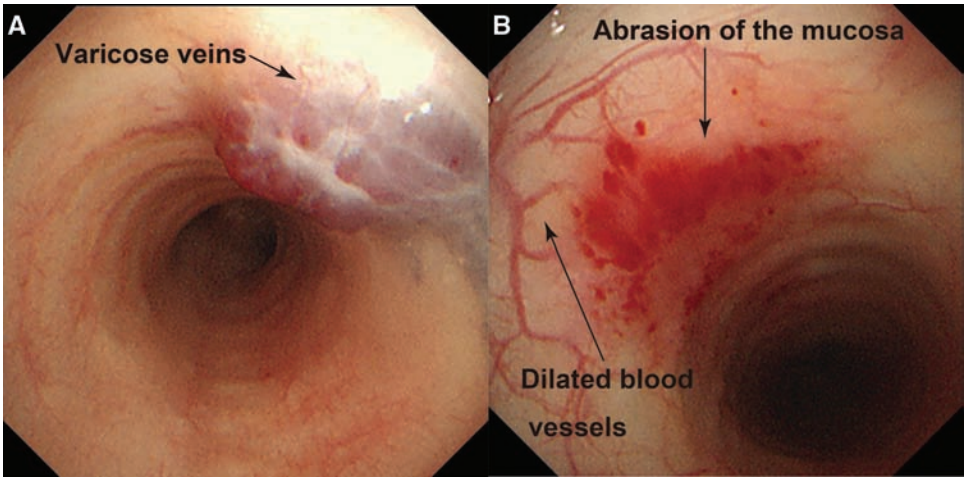

Klippel-Trenaunay syndrome is a rare congenital syndrome involving blood vessels and bony or soft tissue hypertrophy. Vascular malformations may present in any organ or tissue. General anesthesia is generally preferred for surgery, owing to the risks of vascular malformation and coexisting coagulopathy.[1] A 26-yr-old parturient with Klippel-Trenaunay syndrome was scheduled for Cesarean delivery. She had no history of hemoptysis. We performed awake preoperative bronchoscopic evaluation of the airway, because massive bleeding in the trachea was reported in a patient with Klippel-Trenaunay syndrome.[2] Varicose veins on anterior wall of the upper trachea, dilated blood vessels, and abrasion of the mucosa were observed (panels *A* and *B*). Cesarean delivery was performed under spinal anesthesia; however, general anesthesia was performed owing to postoperative hemorrhage. Flexible fiberoptic intubation was performed, and the cuff was carefully placed distal to the varicose vein because of limited space between the glottis and the varices. To minimize coughing and bleeding, the endotracheal tube was removed over a bronchoscope with sedation and muscle paralysis then bridged with a supraglottic airway device, which was removed after confirming spontaneous ventilation. Opioids, dexmedetomidine, or lidocaine may be administered for preventing cough. Endotracheal intubation may cause massive hemoptysis in patients with tracheal varices.[1] If intubation is necessary, flexible fiberoptic intubation should be used. In case of massive hemoptysis, a rigid bronchoscope, a balloon-tipped vascular catheter, and a double-lumen endotracheal tube should be prepared.[3] A thoracic surgeon, pulmonologist, or interventional radiologist should be on stand-by or immediately available if there is high risk of airway bleeding.

Competing Interests

The authors declare no competing interests.

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Prevention of Healthcare-associated Infections in Intensive Care Unit Patients

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Healthcare-associated infections are common in hospitalized patients, impacting 7 to 10% of patients globally.[1] In lower- and middle-income countries, the risk is 15%, with surgical site infection being most common.[2] In higher-income countries, healthcare-associated infections affect up to 30% of intensive care unit (ICU) patients who are vulnerable because of underlying comorbidities and immunosuppression and the presence of invasive catheters and devices.[1] In this review, we summarize current evidence-based strategies for healthcare-associated infection prevention in ICU patients. Healthcare-associated infection risk factors, treatment, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) prevention are not discussed in this review.

Epidemiology

The 2019 Centers for Disease Control and Prevention Healthcare-associated infection progress report, which includes data from many but not all acute care hospitals in the United States, reported 29,669 central line–associated bloodstream infections, 26,376 catheter-associated urinary tract infections, and 4,423 ventilator-associated events in patients from more than 3,600 hospitals.[3] These statistics underestimate the total healthcare-associated infection burden in the United States because not all healthcare-associated infections are required to be reported.

Mortality, Costs, and Reporting

Healthcare-associated infections impact morbidity, mortality, and healthcare cost. According to the World Health Organization (Geneva, Switzerland), healthcare-associated infections cause 37,000 deaths per year in Europe and 99,000 deaths per year in the United States.[1] Healthcare-associated infections with multidrug-resistant organisms increase in-hospital mortality 2-fold.[4] Enterobacterales species (*e.g.*, *Klebsiella pneumoniae*, *Escherichia coli*) are the most common causative organisms in multidrug-resistant infections.[5] Surgical site infection, central line–associated bloodstream infection, and ventilator-associated events are strongly associated with mortality, whereas catheter-associated urinary tract infection is not consistently associated with mortality.[5–7]

Healthcare-associated infections increase healthcare costs in Europe by €7 billion per year and in the United States by $6.5 billion per year.[1] Surgical site infections, particularly deep surgical site infections, are associated with up to a $20,000 increase in cost per patient admission.[8] Increased healthcare costs from healthcare-associated infections are borne by the government, insurance companies, patients, and hospitals. In the United States, central line–associated bloodstream infection, catheter-associated urinary tract infection, *Clostridioides difficile* infection, and some surgical site infections are reported by acute care hospitals to the Centers for Disease Control and Prevention (Atlanta, Georgia) *via* the National Healthcare Safety Network. Hospitals with high healthcare-associated infection rates have reduced global reimbursement or additional financial penalties under the Centers for Medicare and Medicaid Services (Baltimore, Maryland) pay for performance value-based purchasing program. Conversely, hospitals with low healthcare-associated infection rates may receive financial rewards. Individual hospital healthcare-associated infection rates are publicly reported in a format that allows for comparison between hospitals.

Appropriate Perioperative Antibiotic Prophylaxis

Appropriate perioperative antibiotic prophylaxis is an important component of surgical site infection prevention. The Surgical Care Improvement Program, run by the Centers for Medicare and Medicaid Services and Centers for Disease Control and Prevention between 2005 and 2015, included three measures related to perioperative antibiotic prophylaxis, timing, drug appropriateness, and drug discontinuation after surgery. In an observational study of almost 80,000 patients, continuation of prophylactic antibiotics for more than 24 h after surgery was independently associated with increased risk of acute kidney injury and *C. difficile* infection.[9] A meta-analysis, which included 52 randomized controlled trials, found no benefit of continuing antibiotics for more than 24 h postoperatively.[10] In ICU patients with open abdominal or sternal wounds, there is no evidence to support extended antibiotic prophylaxis, despite the fact that bacterial colonization increases in the

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wound over time.[11–13] Taken together, these data suggest that routine antibiotic prophylaxis should not be continued for more than 24 h, unless a specific infection is suspected.

Hand Hygiene and Transmission-based Precautions

The Centers for Disease Control and Prevention core infection prevention and control practices for safe healthcare delivery in all settings recommendations provide guidance for healthcare workers on practices to prevent healthcare-associated infections (www.cdc.gov/hipac/pdf/core-practices.pdf [accessed August 1, 2021]; table 1).[14] These practices include hand hygiene, environmental disinfection, injection and medication safety, use of personal protective equipment, minimization of potential exposures, appropriate reprocessing of reusable medical equipment, transmission-based precautions, removal of temporary medical devices when feasible, and occupational measures that include vaccination and sick leave for healthcare workers.

The Centers for Disease Control and Prevention categorizes microbial transmission into three categories: contact transmission (direct and indirect), droplet transmission, and airborne transmission.[15] Contact transmission is the most common route by which healthcare-associated infections are spread in the ICU. Practices that limit contact transmission of infectious agents include hand hygiene, use of single-patient rooms, correct use of personal protective equipment (proper donning/doffing of gowns and gloves), use of disposable medical equipment, and proper disinfection of rooms between patient use.

Hands are the most common fomite for spreading healthcare-associated infections in ICU patients, and multiple medical devices can serve as fomites, including soap/sanitizer dispensers, humidifiers, nebulizers, pressure transducers, stethoscopes, suction catheters, thermometers, and ultrasound probes.[16] For hand hygiene, the Centers for Disease Control and Prevention recommends alcohol-based hand sanitizer, unless one's hands are visibly soiled or the patient is infected with *C. difficile*. In these cases, the Centers for Disease Control and Prevention recommends hand washing with soap and water. Alcohol-based hand sanitizers increase hand hygiene compliance because of convenience and time efficiency compared with traditional hand washing.[17] Hand hygiene should be performed (1) before touching a patient, (2) before performing an aseptic task, (3) before moving from a soiled body part to a clean body part, (4) after touching the patient or their immediate environment, and (5) immediately after glove removal.[14]

When soap and water are used, it is recommended that the provider's hands are wet, soap is applied, hands are rubbed together for at least 15 s, hands are rinsed with clean water, and the faucet is turned off with a disposable towel. The Centers for Disease Control and Prevention does not recommend use of anti-bacterial soap. For alcohol-based hand sanitizers, the appropriate dose depends on the manufacturer's instructions. The World Health Organization recommends applying a "coin sized" amount of hand sanitizer during each application. Appropriate hand hygiene is associated with a reduction in healthcare-associated infection incidence of up to 50%, including a 50% reduction in methicillin-resistant *Staphylococcus aureus* infection.[18]

For respiratory pathogens, droplet transmission occurs when infectious agents are carried in small water droplets (typically larger than 5 μm) that are exhaled from the respiratory tract. The maximum distance that infectious droplets can travel is not known and depends on particle size, velocity, and environmental temperature and humidity. The Centers for Disease Control and Prevention acknowledges that some infectious respiratory droplets travel up to 6 feet from their source.[15] Examples of pathogens that are spread by droplet transmission include influenza, adenoviruses, and *Mycoplasma pneumoniae*. Airborne transmission occurs by spread of droplet nuclei (desiccated droplets) which are less than 5 μm or other small infectious particles. *Mycobacterium tuberculosis* and *Varicella zoster* are classic pathogens spread by airborne transmission. The dichotomy between droplet and airborne transmission based on particle size is a somewhat artificial construct, with the amount of pathogen spread affected by multiple factors (*e.g.*, humidity, air temperature, total number of infectious particles, and ventilation conditions), and hence droplet or airborne transmission should be considered as general guidance on how a pathogen is spread. The recent coronavirus disease 2019 pandemic has highlighted the need for further research into the numerous factors that affect respiratory pathogen spread.

Staffing

Hospital infection prevention departments with dedicated personnel to perform healthcare-associated infection surveillance and implement control measures are an important aspect of healthcare-associated infection reduction. In the 1980s, these measures were found to be cost-effective and substantially reduced healthcare-associated infections.[19] Ensuring adequate nurse staffing is similarly critical, because nurse shortages with increased patient to nurse ratios are associated with increased healthcare-associated infection incidence.[20,21]

Catheter-associated Urinary Tract Infection

Catheter-associated urinary tract infection is the most common healthcare-associated infection in hospitalized patients. More than 30 million urinary catheters are placed in the United States annually, and the risk for bacteriuria increases by 3 to 7% for every day with an indwelling catheter.[22] Although the unadjusted mortality for catheter-associated urinary tract infection is high in retrospective cohort studies, catheter-associated urinary tract infection is not consistently associated with mortality after risk adjustment, and bacteremia is rare.[6,23] Nevertheless, catheter-associated

Table 1. Centers for Disease Control and Prevention Recommended Strategies for Preventing Device-related and Surgical Site Infections

Healthcare-associated Infection	Recommended Prevention Strategies
Central line–associated bloodstream infection	Site selection 1. Avoid using the femoral vein when possible (Category IA) 2. Use the subclavian vein rather than the femoral vein or internal jugular vein when possible (Category IB) 3. Use a catheter with the minimum number of necessary ports (Category IB) Placement 1. Wear sterile gloves during catheter placement (Category IA) 2. Perform hand hygiene with soap and water or alcohol-based sanitizer before catheter placement (Category IB) 3. Use maximal sterile precautions (Category IB) 4. Clean the patient's skin with > 0.5% chlorhexidine with alcohol, iodine, or 70% alcohol in patients with a chlorhexidine allergy before catheter placement (Category IB) 5. Allow antiseptics to dry according to the manufacturer's instructions (Category IB) Dressing and securing 1. Use a sterile, semipermeable, transparent dressing to cover the catheter insertion site (Category IA) 2. Replace the dressing if damp, loose, or soiled (Category IB) 3. Replace transparent dressings every 7 days (Category IB) 4. Use a sutureless securing device (Category II) Replacement 1. Do not routinely replace catheters (Category IB) 2. Do not perform guidewire exchanges to prevent infection (Category IB) 3. Remove a catheter within 48 h if it was placed without aseptic technique (Category IB) 4. Do not remove catheters based on fever alone (Category II) Removal 1. Promptly remove a catheter that is no longer needed (Category IA)
Catheter-associated urinary tract infection	Appropriate use 1. Minimize catheter days, particularly in high-risk patients such as the elderly, women, and those who are immunosuppressed (Category IB) 2. Remove catheters as soon as possible after surgery, ideally within 24 h (Category IB) 3. Use external urinary collection devices in cooperative patients who do not have urinary retention or obstruction (Category II) 4. Use intermittent catheterization rather than an indwelling catheter in patients with bladder emptying dysfunction (Category II) Insertion technique 1. Perform appropriate hand hygiene before insertion or manipulation of a catheter (Category IB) 2. Insert catheters using aseptic technique and sterile equipment (Category IB) 3. Use sterile gloves, drape, and aseptic solution to clean the periurethral space before catheter insertion (Category IB) 4. Secure indwelling catheters to prevent movement and urethral traction (Category IB) 5. Perform intermittent catheterization at regular intervals in patients with urinary retention (Category IB) 6. Use ultrasound to assess bladder volume and help guide the timing of intermittent catheterization (Category II) 7. Use the smallest catheter possible to prevent urethral and bladder trauma (Category II) Maintenance 1. Maintain a closed drainage and collection system (Category IB) 2. Replace the catheter and collection system if there are any breaks that compromise sterility (Category IB) 3. Maintain unobstructed urine flow by avoiding kinks and maintaining the drainage bag below the bladder (Category IB) 4. Do not give prophylactic antibiotics to prevent catheter-associated urinary tract infection (Category IB) 5. Do not routinely clean the periurethral area with antiseptics (Category IB) 6. If urine is needed for culture, sample it from a needleless port with a sterile syringe after cleaning the area (Category IB) 7. Do not irrigate the bladder, catheter, and collection system with antibiotics (Category II) 8. Do not change urinary catheters or collection bags at regular, fixed intervals (Category II) Quality improvement 1. Implement quality improvement programs to reduce inappropriate catheter use and ensure proper hand hygiene (Category IB) Infrastructure 1. Provide guidelines on catheter insertion, maintenance, and removal (Category IB) 2. Provide periodic in-service training to medical personnel (Category IB) 3. Dedicate personnel and resources to surveillance of catheter-associated urinary tract infections (Category IB) 4. Perform documentation of the indication for catheterization, date of insertion, person who inserted the catheter, and date of removal (Category II) Surveillance 1. Use standardized methods for surveillance such as the number of infections per 1,000 catheter days or catheter utilization ratio (Category IB) 2. Do not perform routine surveillance for asymptomatic bacteriuria (Category II)

(*Continued*)

Table 1. (Continued)

Healthcare-associated Infection	Recommended Prevention Strategies
Surgical site infection	Antibiotics 1. Do not administer additional antibiotics in clean and clean-contaminated cases after the surgical incision is closed in the operating room (Category IA) 2. Administer intravenous antibiotics so that a therapeutic drug concentration is obtained at the time of skin incision (Category IB)* 3. Do not apply topical antibiotics such as ointments, powders, or solutions to the surgical incision to prevent infection (Category IB) Glycemic control 1. Target a blood glucose concentration less than 200 mg/dl during the perioperative period (Category 1A) Temperature management 1. Maintain normothermia (36 to 38°C) during the perioperative period (Category IA) Oxygenation 1. In patients receiving general anesthesia with endotracheal intubation, administer a high FIO_2 during surgery and in the immediate postoperative period (Category IA)† Antiseptic practices 1. Bathe patients with soap or antiseptic the night before surgery (Category IB) 2. Prepare patients with an alcohol-based antiseptic before skin incision in the operating room (Category IA) Blood transfusion 1. Do not withhold blood transfusion to prevent surgical site infection if indicated (Category IB)

Further information on healthcare-associated infection prevention can be found at https://www.cdc.gov/infectioncontrol/guidelines/index.html. The most recent Centers for Disease Control and Prevention (Atlanta, Georgia) guidelines are from 2011 for central line–associated bloodstream infection, 2009 for catheter-associated urinary tract infection, and 2017 for surgical site infection. The categories of recommendations used by the Centers for Disease Control and Prevention are as follows: Category IA, strong recommendation supported by high- to moderate-quality evidence; Category IB, strong recommendation supported by low-quality evidence; and Category II, weak recommendation supported by any quality of evidence.

*No specific timing of administration is currently recommended by the Centers for Disease Control and Prevention, but published studies suggest that intravenous antibiotics should be administered within 120 min and ideally within 60 min of skin incision so that therapeutic levels can be reached in tissues. †More recent studies (after 2017) have suggested that a high inspired oxygen concentration may not be effective in reducing surgical site infection, and the World Health Organization (Geneva, Switzerland) guideline development committee for surgical site infection prevention changed their recommendation from strong to conditional for using a high inspired oxygen concentration during the perioperative period to prevent surgical site infection.

FIO_2, fractional inspired oxygen tension; ICU, intensive care unit.

urinary tract infection is a well established risk factor for increased ICU and hospital length of stay. In 2008, the Centers for Medicare and Medicaid Services designated catheter-associated urinary tract infection as a hospital-acquired complication, which would not be reimbursed.[24]

In the United States, catheter-associated urinary tract infection is diagnosed if a patient fulfills symptomatic urinary tract infection criteria and has an appropriate duration of catheterization.[25] Catheter-associated urinary tract infection is defined by three criteria: (1) the presence of a urinary catheter for more than 2 consecutive days in an inpatient location on the day of the event (includes catheters present for any portion of the calendar day on the day of the event or if removed the day before the event); (2) at least one of the following: suprapubic tenderness, costovertebral angle pain, urinary urgency, urinary frequency, or dysuria; and (3) a urine culture with no more than two species of pathogenic organisms, at least one of which is quantified as at least $\geq 10^5$ colony-forming units/ml.[25] Catheter-associated urinary tract infection does not occur secondary to other sites of infection, and *Candida*, parasites, mold, and dimorphic fungi are excluded.[25]

In ICU patients, urinary catheters are not universally required, and policies that promote early removal reduce catheter-associated urinary tract infection.[26–28] Catheters may be indicated in ICU patients when strict input/output recording is required during the first 48 h of shock, during active titration of vasopressors or inotropes, during diuresis for acute cardiac or pulmonary failure (when hourly monitoring is required to assess therapy), for active monitoring of acute or impending renal failure, or for frequent assessment of intravascular volume in patients with neurologic conditions that disrupt normal fluid balance (*e.g.*, diabetes insipidus).[22,27,28]

The U.S. Agency for Healthcare Research and Quality (Rockville, Maryland) lists numerous tools for implementing policies, procedures, and practices for reducing catheter-associated urinary tract infection with a comprehensive unit-based safety program (https://www.ahrq.gov/hai/tools/cauti-hospitals/toolkit-impl.html [accessed August 1, 2021]). The effect of the comprehensive unit-based safety program on a national level was assessed by Saint *et al.*,[29] showing a reduction in catheter-associated urinary tract infection in non-ICUs, but no change in ICUs. Although the quality of evidence for most individual interventions is low, sustained reductions in catheter-associated urinary tract infection have been achieved when multiple evidence-based interventions are "bundled."[30]

Ventilator-associated Events and Ventilator-associated Pneumonia

Ventilator-associated pneumonia is the most common healthcare-associated infection in the ICU, occurring

in approximately 10% of patients on mechanical ventilation.[31] Two systematic reviews by Melsen *et al.*[32,33] reported a pooled relative mortality risk of 1.27 (95% CI, 1.15 to 1.39) and a 13% attributable mortality with ventilator-associated pneumonia. Some studies have questioned ventilator-associated pneumonia's attributable mortality because of confounding, heterogeneity, and inappropriate accounting of the time-dependent nature of events leading to ventilator-associated pneumonia.[34]

In 2013, the Centers for Disease Control and Prevention proposed an algorithmic approach for ventilator-associated event *surveillance*.[35] The three definition tiers are (1) ventilator-associated condition; (2) infection-related ventilator-associated complication; and (3) possible ventilator-associated pneumonia. To be eligible for a ventilator-associated event, a patient must be mechanically ventilated for at least 4 days with the day of intubation counted as day 1. A ventilator-associated condition is defined by worsening oxygenation for at least 2 calendar days (increased positive end expiratory pressure or F_{IO_2}), whereas infection-related ventilator-associated complication is defined by worsening oxygenation with other features suggestive of infection (*e.g.*, fever or hypothermia, leukocytosis, or initiation of antibiotics for at least 4 days). Possible ventilator-associated pneumonia occurs when one or more of the following criteria are met after a patient develops indicators of worsening oxygenation 3 calendar days after beginning mechanical ventilation: (1) a positive culture from an endotracheal aspirate (more than 10^5 colony-forming units/ml), bronchoalveolar lavage (at least 10^4 colony-forming units/ml), lung tissue (at least 10^4 colony-forming units/ml), or protected specimen brush (at least 10^3 colony-forming units/ml); (2) purulent secretions, defined as lung, bronchial, or tracheal that contain at least 25 neutrophils and at most 10 squamous epithelial cells per low power field *plus* an organism identified by a respiratory specimen obtained as described in criterion 1; and/or (3) a positive diagnostic test identifying an organism in pleural fluid, lung histopathology, *Legionella* species, or a respiratory virus.

Ventilator-associated pneumonia can be clinically diagnosed in any patient who is mechanically ventilated for 48 h or more and develops a new or progressive infiltrate on chest radiography with associated signs and symptoms of infection (*e.g.*, purulent sputum, new fever or hypothermia, leukocytosis, worsening oxygenation, altered respiratory mechanics) and a positive respiratory specimen.[34,36] Different strategies have been proposed for obtaining diagnostic samples for ventilator-associated pneumonia. In a large multicenter randomized trial, endotracheal aspirates with nonquantitative cultures were not associated with different clinical outcomes or antibiotic use when compared to patients who had quantitative cultures performed by bronchoalveolar lavage.[37] In a subsequent systematic review that included 5,064 patients, including 1,367 patients from five randomized controlled trials, similar clinical outcomes were observed when invasive *versus* noninvasive diagnostic strategies were compared.[38] Additional research in this area is required, as there is no "gold standard" for the diagnosis of ventilator-associated pneumonia. Recent work with multiplex polymerase chain reaction–based assays has demonstrated shorter time to identification of pathogens and resistance patterns, as well as an association with faster discontinuation of antibiotics and earlier identification of patients with secondary infections.[39–41]

The strongest evidence for ventilator-associated pneumonia prevention relates to minimizing sedation and mechanical ventilation, improving physical conditioning, minimizing pooled secretions above the endotracheal tube cuff, and elevating the head of the bed 30 to 45 degrees. Recent evidence has brought into question other previously recommended interventions. For example, closed endotracheal suctioning does not consistently reduce ventilator-associated pneumonia.[42] Oral care with chlorhexidine is most effective in cardiac surgical patients but is of questionable efficacy in other ICU patients.[43] Selective digestive decontamination is not effective in ICUs with high rates of antibiotic resistance and is not recommended by the Infectious Disease Society of America or the Centers for Disease Control and Prevention.[42,44] The risks of selective digestive decontamination are also not fully understood. Subglottic suction drainage may prevent ventilator-associated pneumonia but does not shorten mechanical ventilation time or ICU length of stay.[34] Stress ulcer prophylaxis may increase ventilator-associated pneumonia but often cannot be avoided because of strong indications.[42]

Interventions that are *not* currently recommended for ventilator-associated pneumonia prevention include regular monitoring of gastric residual volumes, closed endotracheal suctioning, early parenteral nutrition, routine prone positioning, and kinetic beds.[34,42] Early *versus* late tracheostomy is controversial. Previous systematic reviews concluded that early tracheostomy did not reduce ventilator-associated pneumonia[45]; however, a more contemporary systematic review and meta-analysis that included 3,145 patients found that early tracheostomy (at less than 7 days after initiation of mechanical ventilation) was associated with reduced ventilator-associated pneumonia (odds ratio, 0.59 [95% CI, 0.35 to 0.99]) and more ventilator-free days.[46] In their most recent guidelines, the Infectious Disease Society of America (Arlington, Virginia) does not endorse early tracheostomy to reduce ventilator-associated pneumonia.[36]

Central Line–associated Bloodstream Infection

Central line–associated bloodstream infection is associated with significant morbidity and mortality. ICU patients with multiple central lines are particularly vulnerable. The findings from the 2003 Michigan Keystone ICU study were pivotal, resulting in widespread practice change. Implementation of

a simple evidence-based bundle (hand hygiene, full-barrier precautions during insertion, chlorhexidine to clean the insertion site, avoiding the femoral veins when possible, and removing unnecessary central lines) at over 100 ICUs resulted in a significant, sustained infection reduction; 7.7 central line–associated bloodstream infections per 1,000 catheter days at baseline to 1.4 at 16 to 18 months post intervention.[47] This study highlighted that large-scale healthcare-associated infection reduction requires practice and behavior change and synergy of technical (*e.g.*, central line insertion checklists, ensuring chlorhexidine availability) and adaptive (*e.g.*, forming a safety culture, engaging front line leaders, gaining hospital executive support) prevention strategies.

Chlorhexidine is used as an adjunct for central line–associated bloodstream infection prevention beyond central line insertion. Chlorhexidine-impregnated dressings have been shown to reduce central line–associated bloodstream infection rates (from 1.3 to 0.4 per 1,000 catheter days) when studied in a seven-ICU randomized controlled trial.[48] A systematic review and meta-analysis that included 17 trials found that daily chlorhexidine bathing was associated with a 56% relative risk reduction for central line–associated bloodstream infection. Chlorhexidine bathing was also associated with decreased methicillin-resistant *S. aureus* colonization.[49]

C. difficile Infection

C. difficile infection occurs in the setting of a disrupted normal gut microbiome when *C. difficile* proliferates beyond host immune control and produces toxins A and B, which disrupt the normal cytoskeletal structure of colonic epithelial cells causing diarrhea, paralytic ileus, and in rare cases colonic perforation. Broad-spectrum antibiotics are a common instigator for *C. difficile* infection because they alter the normal gut microbiome allowing *C. difficile,* if present in the colon, to proliferate.

The main prevention strategies for *C. difficile* infection are eliminating transmission of the organism from patient to patient or from an infected patient to the ICU environment. *C. difficile* can exist in a hardy spore form, which has the ability to persist on surfaces, spreading to patients' and healthcare workers' hands. *C. difficile* typically requires a bleach-based product for disinfection, but select non-bleach–based products are also sufficient. A list of appropriate disinfectants can be found on the U.S. Environmental Protection Agency (Washington, D.C.) website (https://www.epa.gov/sites/default/files/2021-02/documents/02-22-2021_list-k.pdf [accessed August 1, 2021]). "No-touch" technologies such as ultraviolet light may be a useful adjunct in limiting *C. difficile* infection. One randomized controlled trial in nine hospitals demonstrated a significant reduction in *C. difficile* infection when disinfecting ultraviolet light was added to standard terminal room cleaning procedures.[50] Further studies are needed to confirm the efficacy of disinfecting ultraviolet light.

Patients with *C. difficile* colonization or infection should be placed in a private room, and healthcare workers should don gowns and gloves upon room entry. Hand hygiene with soap and water, as opposed to alcohol-based hand sanitizer, is important after glove removal, to ensure adequate spore removal. Gastric acid suppression facilitates *C. difficile* reaching the colon, because normal stomach pH is altered. Hence, judicious use of proton pump inhibitors and other gastric acid suppressants is an important aspect of *C. difficile* infection prevention.[51]

Finally, *C. difficile* proliferation and toxin production can be prevented by maintaining a normal gut microbiome. Antibiotics and chemotherapy are the most common disrupters of the normal colonic microbiome. Antimicrobial stewardship is key in *C. difficile* infection prevention. Approximately 30% of antibiotics prescribed in U.S. acute care hospitals are unnecessary or suboptimal.[52] Ensuring that antibiotics are given only when necessary, are as narrow-spectrum as possible, and are given for the shortest effective duration is the cornerstone of *C. difficile* infection prevention. Fecal transplant, to restore the normal gastrointestinal microbiome, is a successful strategy to prevent recurrent *C. difficile* infection.[53]

Appropriate Diagnostic Testing

Inappropriate diagnostic testing for healthcare-associated infections increases healthcare cost, and testing should be performed only when clinically indicated. Figure 1 shows one potential algorithm for appropriate diagnostic testing in ICU patients with suspected infection. Targeted cultures should be obtained in (1) patients who have fever or are hypothermic *and* who have a significant change in their clinical condition or (2) patients who have fever or are hypothermic, have no significant change in their clinical condition, and have not had surgery within 24 h but have a high suspicion for a specific infection based on other clinical or laboratory findings.

Conclusions

Healthcare-associated infections continue to burden ICU patients with excess morbidity, mortality, and cost. Given these issues and the fact that healthcare-associated infections lead to financial penalties for hospitals, it is critical for ICU providers to understand evidence-based prevention strategies. Healthcare-associated infection prevention also offers an opportunity for anesthesiologists to lead important research, quality improvement, and policy development efforts within acute care hospitals. More widespread adoption of best practices will lead to improvements in patient outcomes and cost reductions in U.S. healthcare.

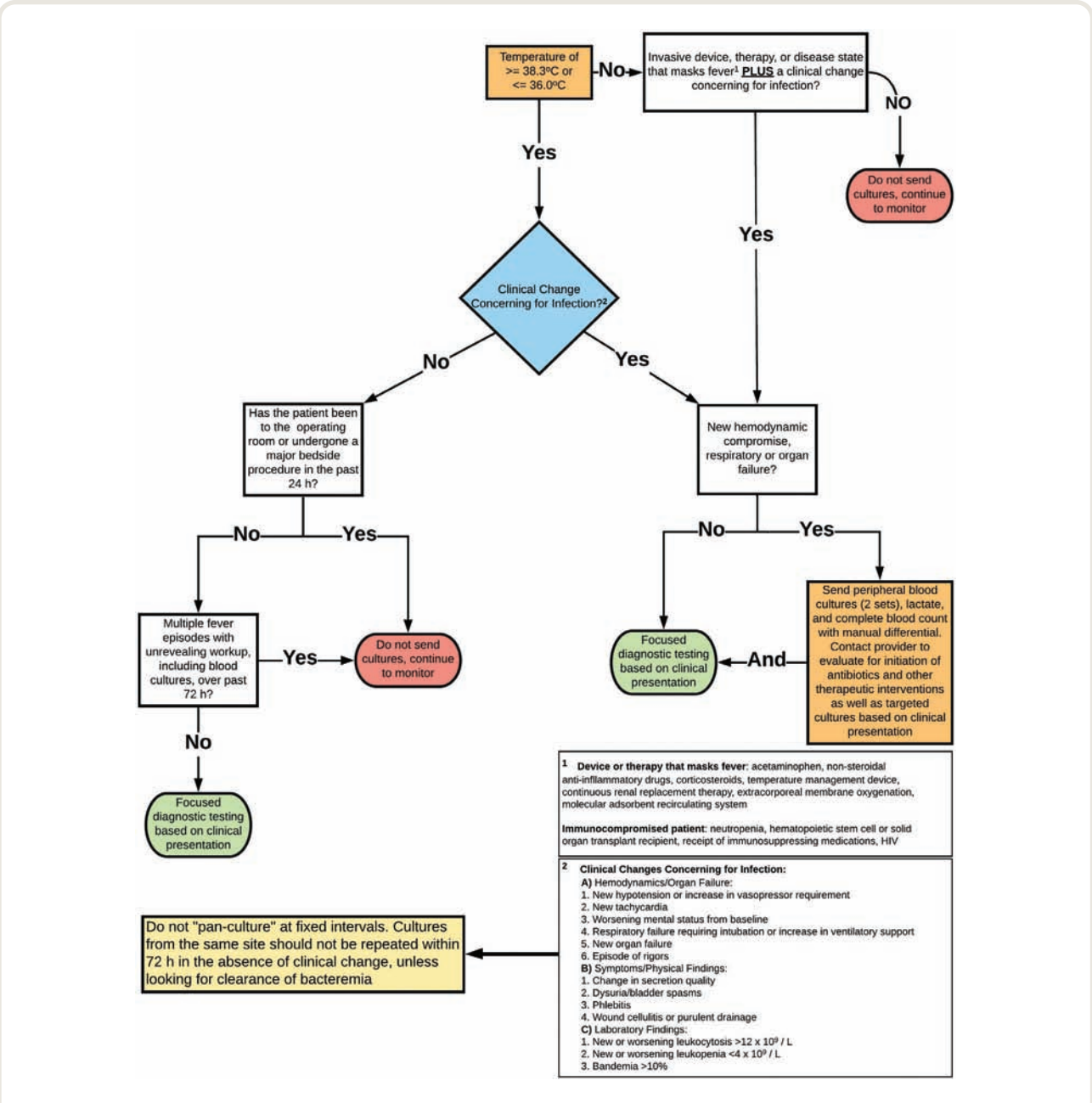

Fig. 1. A potential algorithm for obtaining appropriate cultures in an intensive care unit patient with a suspected healthcare-associated infection. Focused diagnostic testing is based on clinical presentation. HIV, human immunodeficiency virus.

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Competing Interests

Dr. Mazzeffi has active research grant funding from the Society of Cardiovascular Anesthesiologists (Chicago, Illinois) and has previously received compensation for consulting from HemoSonics Corporation (Charlottesville, Virginia). Dr. Galvagno has active research grant funding from the U.S. Department of Defense (Wright-Patterson Air Force Base, Ohio, and Fort Detrick, Frederick, Maryland). He has also previously received honoraria from Up to Date (Waltham, Massachusetts), the American Board of Anesthesiology (Raleigh, North Carolina), and the American Board of

Psychiatry and Neurology (Deerfield, Illinois). He reports receiving speaking fees for Northwest Anesthesia Seminars (Pasco, Washington) and compensation for medical-legal expert reviews. Dr. Rock has active research grant funding from the Centers for Disease Control and Prevention (Atlanta, Georgia; Epicenter grant). She is also the founder and owner of Infection Prevention Strategy Consulting LLC (Baltimore, Maryland).

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ANESTHESIOLOGY

Sleep, Pain, and Cognition: Modifiable Targets for Optimal Perioperative Brain Health

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ABSTRACT

The prevention of perioperative neurocognitive disorders is a priority for patients, families, clinicians, and researchers. Given the multiple risk factors present throughout the perioperative period, a multicomponent preventative approach may be most effective. The objectives of this narrative review are to highlight the importance of sleep, pain, and cognition on the risk of perioperative neurocognitive disorders and to discuss the evidence behind interventions targeting these modifiable risk factors. Sleep disruption is associated with postoperative delirium, but the benefit of sleep-related interventions is uncertain. Pain is a risk factor for postoperative delirium, but its impact on other postoperative neurocognitive disorders is unknown. Multimodal analgesia and opioid avoidance are emerging as best practices, but data supporting their efficacy to prevent delirium are limited. Poor preoperative cognitive function is a strong predictor of postoperative neurocognitive disorder, and work is ongoing to determine whether it can be modified to prevent perioperative neurocognitive disorders.

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As older persons increasingly rely on surgical treatment, preventing perioperative neurocognitive disorders including postoperative delirium, delayed neurocognitive recovery, and postoperative neurocognitive disorder has become a priority for patients, for families, and for perioperative research.[1,2] Defined by an acute, fluctuating disturbance in attention and awareness, postoperative delirium occurs in up to 50% of older patients and is associated with excess hospital costs, higher risk of long-term cognitive impairment, and poor functional outcomes.[3,4] Characterized by cognitive deficits in memory and executive function, delayed neurocognitive recovery (diagnosed within 30 postoperative days) and postoperative neurocognitive disorder (diagnosed within 3 to 12 months) were once considered mainly as research outcomes with questionable clinical impact. However, they are now recognized as key barriers to optimal functional recovery after surgery.[5,6] For decades, strategies to prevent perioperative neurocognitive disorders by targeting isolated perioperative interventions have produced negative or inconclusive results.[7–10] Given that there are numerous potential inciting factors for perioperative neurocognitive disorders, it is likely that multicomponent interventions may be more effective. For example, one of the most successful evidence-based multicomponent prevention strategies is the Hospitalized Elder Life Program (HELP), which has been shown in meta-analysis to consistently prevent delirium in hospitalized older persons.[11] There are 14 core interventions in HELP, highlighting the complex and myriad precipitating factors that can contribute to delirium and the challenges faced by clinicians seeking to employ a comprehensive program. The objective of this narrative review is to highlight and expand upon three key intervenable targets to consider in any multicomponent intervention designed to optimize perioperative brain health: sleep, pain, and cognition (fig. 1).

Sleep

Sleep, Circadian Rhythms, and Brain Health

Sleep is a complex, naturally occurring physiologic state that is critical to survival and health in animals and humans. A fundamental aspect of ensuring optimal physiologic functions, including sleep, is the adherence to ~24-h cycles known as circadian rhythms, which are thought to be ubiquitous to life on earth. If separated from our environmental and lifestyle choices, sleep–wake cycles are governed by our circadian system *via* the sleep-promoter hormone melatonin, which peaks during darkness.[12]

Sleep appears critical to optimal brain health and cognitive function, but only recently has there been increasing attention within the perioperative field.[13,14] What is defined as "normal" sleep varies from individual to individual and with age and comorbid disease. Broadly, the following five dimensions of sleep appear the most relevant to definitions and measurements of sleep health: (1) sleep duration: the total amount of sleep obtained per 24 h, with between 7 and 8 h considered optimal for most; (2) sleep continuity or

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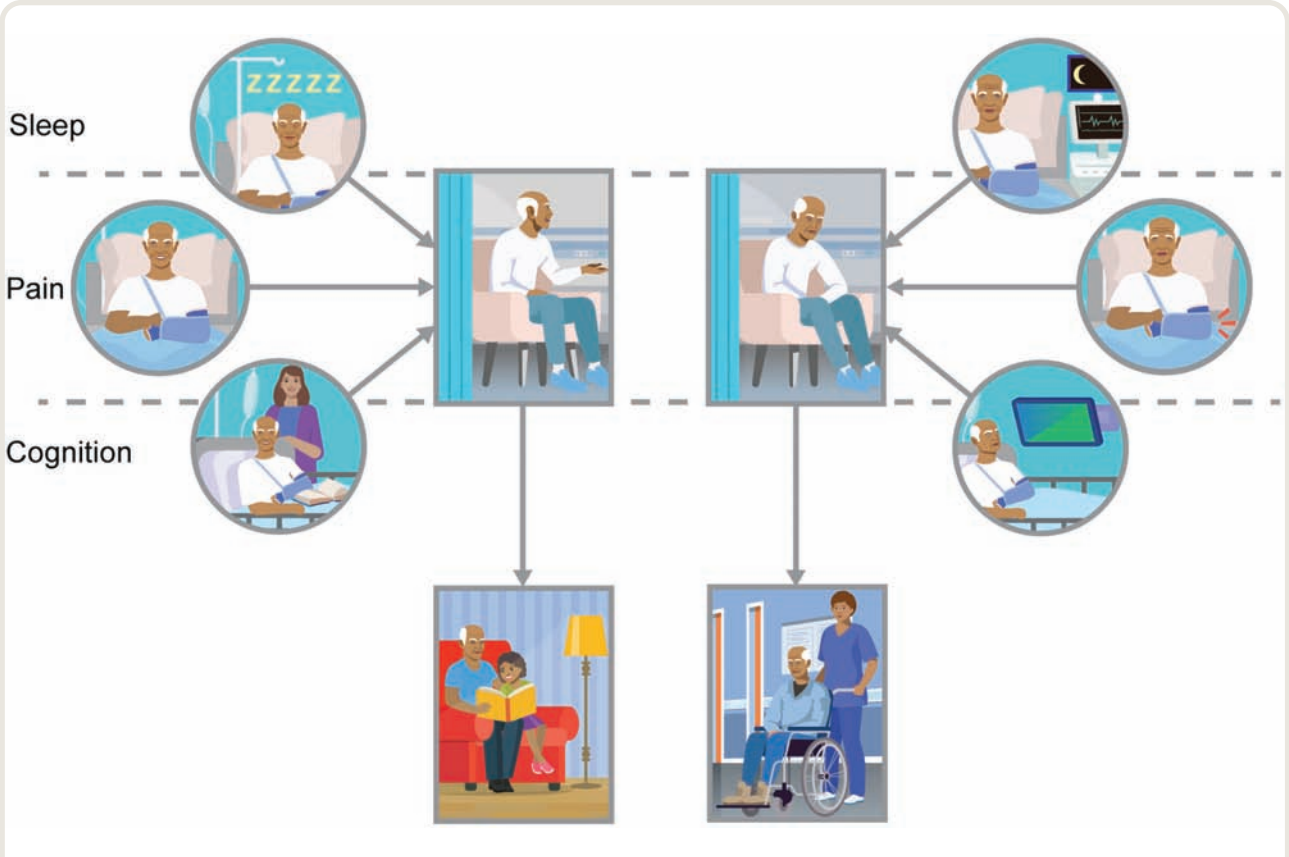

Fig. 1. The impact of sleep, pain, and cognition on perioperative brain health and postoperative recovery. Here depicted is a patient presenting for orthopedic surgery. The scenarios depict how the patient's sleep, pain, and cognition are well managed throughout the postoperative period (*left*). The patient then remains delirium-free in the hospital and returns home at their cognitive and functional baseline (*left center*). Conversely, if sleep, pain, and cognition are poorly managed (*right*), the same patient may experience delirium and/or the inability to return to their cognitive and functional baseline (*right center*).

efficiency: the ease of falling asleep and returning to sleep after awakening; (3) timing of the sleep–wake cycle within the 24-h day; (4) alertness/sleepiness: the ability to maintain attentive wakefulness; and (5) satisfaction/quality: the subjective assessment of "good" or "poor" sleep.[13] All sleep "disorders" or "disturbances" can be understood *via* one or commonly multiple dimensions. For example, insomnia is characterized by difficulty initiating or continuing sleep, but this often leads to lower sleep duration, irregular timings, subjective sleepiness and poor satisfaction/quality.

Unfortunately, as many as one in three people will experience some form of sleep and/or circadian disturbances in their lifetimes; these disturbances often go unaddressed, are increasingly common worldwide, and worsen over time.[15–19] Despite clinicians' familiarity with the diurnal nature of our own sleep and behavioral cycles and the physical and psychologic toll associated with its disruption (*e.g.*, after a busy night on-call), there remains relatively few considerations given to the impact of sleep and circadian disruption in our patients and how it may impact their brain health and overall functional recovery during the perioperative period.

Sleep Disturbance and Delirium

There is now increasing recognition for the potential link between sleep disturbances and perioperative neurocognitive disorders including delirium.[20] Sleep/circadian disturbances are more common in older persons and are more pronounced after critical illness and in neurodegenerative diseases such as Alzheimer disease, the very groups most vulnerable to perioperative neurocognitive disorders.[19,21–23]

Sleep disruption before surgery has been shown to predict postoperative delirium. In an observational study of 50 adults undergoing major noncardiac surgery in which sleep patterns were assessed objectively the night before surgery with a wearable actigraphy device, patients who developed postoperative delirium had significantly higher measures of preoperative sleep fragmentation including both the percentage of time spent wake after sleep onset (mean [SD], 44% [22%] *vs.* 21% [20%]; $P = 0.012$) and frequency of nightly awakenings (mean [SD], 17 [9] *vs.* 9 [6]; $P = 0.047$) compared to those without delirium.[24] This finding has been demonstrated in other studies and in a recent meta-analysis of data from 12 studies and 1,199 patients in which the pooled odds ratio for postoperative

delirium for patients with preoperative sleep disturbances was significantly higher than for those without a preoperative sleep disturbance (odds ratio [95% CI], 5.24 [2.28 to 3.69]; $P < 0.001$; $I^2 = 0\%$).[20] Possible shared pathophysiological pathways between sleep disturbance and delirium include altered melatonin metabolism, neurotransmitter imbalance, and reduced neuroprotection from key deficiencies such as vitamin D.[25–29] Undergoing major surgery with preexisting sleep disruption makes it likely these symptoms will be exacerbated during the postoperative recovery period as pain, nausea, light, noise, and immobility ensue.

However, based on current evidence, one cannot conclude causation. The extent to which sleep disturbances may cause delirium or *vice versa* is not yet fully understood, but these two conditions may share a common neuropathology. There is some evidence that poor sleep behavior traits and circadian disruption predicts incident Alzheimer disease, but few large prospective studies exist for sleep and delirium.[19,30] Sleep disruption and problems with rest–activity cycles are also comorbid with many conditions relevant to brain health and perioperative neurocognitive disorders including heart failure and pain, and therefore these issues could potentially be a manifestation of underlying disease such as preclinical neurodegeneration.[31,32] Whether disordered sleep directly increases the risk of delirium or whether it is indicative of an underlying comorbidity that increases risk may be difficult if not impossible to determine. Testing whether treatment of sleep disorders reduces delirium in controlled studies may be the best way to sort out these direct or indirect effects. How this affects the perioperative physician is also evolving. The role of sleep in the preservation of perioperative cognition is an active area of research, and it may be that sleep disruption comes to be seen as a chronic condition in need of optimization rather than reversal.

Sleep-disordered Breathing, Continuous Positive Airway Pressure, and Delirium

Sleep-disordered breathing is a complex, multisystemic disorder that warrants particular mention. In particular, the obstructive variant of sleep apnea (or OSA) is associated with obesity and increased risk for airway difficulties, adverse cardiac events, postoperative respiratory complications, and perioperative neurocognitive disorders.[33] In the general population, OSA is associated with reductions in cognitive reserve, increased risk for cognitive impairment and worsening executive function, and amyloid deposition in key brain regions.[34–36] Because many of these findings share characteristics of perioperative neurocognitive disorders, a link between OSA and perioperative neurocognitive disorders has also been proposed. Possible mechanisms underlying the association between OSA and delirium include abnormalities in sleep architecture leading to sleep disruption, hypoxia, vascular injury, low-grade systemic inflammation, oxidative stress, and decrease in insulin growth factor-1, as has been seen with neuronal injury and apoptosis.[37]

Using objective polysomnography, preoperative sleep-disordered breathing defined by a high apnea–hypopnea index was associated with more than six-fold increased odds for postoperative delirium (odds ratio [95% CI], 6.4 [2.6 to 15.4], $P < 0.001$), including patients without an existing formal OSA diagnosis.[38] In a small cohort of older patients undergoing elective knee replacement, the incidence of delirium was significantly higher in patients with OSA as compared to those without OSA (8 of 15 [53%] *vs.* 19 of 95 [20%]; $P = 0.0123$).[39] However, a recent retrospective observational cohort study of 7,792 surgical patients did not find a significant association between preoperative OSA and postoperative delirium after adjustment for perioperative confounders.[40] Both OSA and postoperative delirium remain greatly underdetected, and on balance of evidence, their relationship still warrants close attention. For example, the Society of Anesthesia and Sleep Medicine currently recommends using preoperative screening tools such as the STOP-Bang preoperative screening for OSA, given the link with increased perioperative complications.[41]

Although the use of continuous positive airway pressure slows the deterioration of cognition, brain function, and mood in nonsurgical patients with OSA, thus far data from the surgical population is less conclusive.[42–44] When patients who were at risk for sleep apnea were randomized in a continuous positive airway pressure group *versus* standard care, the perioperative use of continuous positive airway pressure did not change the incidence of postoperative delirium (12 of 58 [21%] *vs.* 9 of 56 [16%]; odds ratio [95% CI], 1.36 [0.52 to 3.54]; $P = 0.53$).[45] Whereas both preoperative and postoperative residual OSA severity as defined by apnea-hypopnea index were significantly correlated with delirium severity in this sample, continuous positive airway pressure use was not found to be significantly correlated. Further studies with particular attention on continuous positive airway pressure adherence or the use of other respiratory adjuncts such as high-flow nasal oxygen are ongoing and may yield positive results in the future. It remains unclear whether the best strategy to prevent postoperative delirium is to treat the OSA directly using continuous positive airway pressure or to consider OSA patients at high risk and use more general delirium prevention strategies in this group. Currently, it is unknown whether OSA is a risk factor for delayed neurocognitive recovery or postoperative neurocognitive disorder. In the coming years, prospective clinical trials investigating this area will provide much-needed data.[46,47]

Other Postoperative Sleep-related Interventions and Delirium

In terms of pharmacologic interventions to prevent delirium, dexmedetomidine and melatonin have been extensively studied. For intensive care unit (ICU) patients who are mechanically ventilated, sedation with dexmedetomidine may be less likely to be associated with delirium compared to benzodiazepines or propofol.[48,49] Although there are

inconsistent findings between studies, recent meta-analyses suggest that sedation of critically ill patients with dexmedetomidine may reduce the frequency and duration of delirium.[50,51] Although these findings may primarily reflect the benefit of avoiding deliriogenic sedatives, the exact mechanism remains unclear. However, unlike all other sedatives and the commonly used anesthetics, dexmedetomidine appears most likely to preserve sleep architecture as currently inferred *via* electroencephalogram (EEG). In healthy volunteers, dexmedetomidine induced stage N3 non–rapid eye movement sleep in a dose-dependent fashion with an EEG pattern mimicking natural sleep without impairing next-day psychomotor performance.[52] A low-dose dexmedetomidine infusion prolonged total sleep time and increased sleep efficiency and time spent in stage N2 non–rapid eye movement sleep in 76 older ICU patients.[53] In a randomized, blinded, placebo-controlled trial of 700 older noncardiac surgery patients, a low-dose dexmedetomidine infusion given to both ventilated and extubated patients from the time of ICU admission until 8 AM the morning of postoperative day 1 greatly reduced the risk of delirium as compared to placebo (32 of 350 [9%] *vs.* 79 of 350 [23%]; odds ratio [95% CI], 0.35 [0.22 to 0.54]; $P < 0.0001$).[54] Additionally, patients in the dexmedetomidine group reported significantly better sleep quality (2 [0 to 4] *vs.* 4 [2 to 6]); 0 to 11 scale, where lower scores indicate better sleep; the values are shown as medians [interquartile range]; $P < 0.0001$). Finally, oral dexmedetomidine is now a possibility after successful testing in human subjects; however, optimal dosing has yet to be established, and it is not yet approved by the Food and Drug Administration (Silver Spring, Maryland). Subjects taking oral dexmedetomidine displayed both preserved sleep architecture on EEG and next-day psychomotor vigilance.[55] This may open new possibilities outside of the ICU for investigation as to whether dexmedetomidine can be effective as a sleep-promoting agent.

Melatonin is commonly used in the general population and in the ICU for the promotion of sleep. Given its increasing use, some understanding of its role in sleep and circadian rhythms is warranted. As previously mentioned, the sleep–wake cycle is perhaps the most obvious and important behavior under intrinsic circadian output control. However, sleep–wake cycles are also affected by external cues. Of these cues, light is by far most important; others are food, sound, and exercise, many of which are disrupted in sickness and hospital settings. Melatonin is the major sleep-promoting hormone under circadian control. Taking its external cue from low light, its concentration peaks just before sleep initiation. Melatonin levels are measured from the saliva or serum, often in serial measurements, and are an accepted surrogate marker for our "internal time."[56] Critical care settings often involve exposure to light, noise, pain, nausea, or clinical care at night, which may explain the evidence for suppressed nocturnal melatonin peak secretion in ICU patients.[57]

Recent data suggest that delirious patients may also have reduced serum levels of melatonin.[58] For this reason, melatonin supplementation has been investigated as a potential intervention to prevent delirium. In a prospective before–after trial of 500 cardiac surgery patients where prophylactic melatonin was given the night before surgery, the incidence of postoperative delirium was significantly lower in the intervention group (21 of 250 [8.4%] *vs.* 52 of 250 [20.8%]; $P = 0.001$).[59] Although a randomized trial investigating the prophylactic use of the melatonin receptor agonist ramelteon showed some promise in preventing delirium in older medical patients (1 of 33 [3%] *vs.* 11 of 34 [32%], ramelteon *vs.* placebo; $P = 0.003$), it was not shown to prevent postoperative delirium in elective cardiac surgery patients in another trial (19 of 59 [32%] *vs.* 22 of 58 [38%], ramelteon *vs.* placebo; $P = 0.516$).[60,61] Other clinical trials of melatonin or ramelteon have not demonstrated similar success, and a recent meta-analysis of 16 clinical trials concluded that evidence neither supports nor opposes the use of melatonin in the prevention of delirium of hospitalized patients.[62] Trials with individually targeted timing and dosing in those who are most at risk for suppression and misalignment of melatonin secretion may yield improved results. However, this may require accounting for sleep and circadian rhythm regulation before the perioperative period.

Aside from postoperative delirium, the impact of melatonin levels and melatonin supplementation on other perioperative neurocognitive disorders has been less extensively studied. In 97 patients aged 65 to 90 undergoing major orthopedic or abdominal surgery, patients with more than two-fold fluctuations in 6-sulfatoxymelatonin, a main metabolite of melatonin, had a significantly higher incidence of delayed neurocognitive recovery as determined by a cognitive battery 1 week postoperatively (22 of 39 [56%] *vs.* 9 of 56 [16.7%]; $P < 0.01$).[63] In contrast, a study of 36 abdominal surgery patients with a mean age of 70 found no association between abnormal 6-sulfatoxymelatonin levels and the incidence of delayed neurocognitive recovery.[64] In a placebo-controlled trial of 139 patients older than 65 undergoing hip arthroplasty, patients given melatonin beginning the night before surgery and then for the next 5 nights had significantly higher Mini Mental State Exam scores on days 1, 3, and 5, but scores between groups were similar on day 7.[65] It should be noted that delayed neurocognitive recovery as defined as a predetermined decrease from the baseline Mini Mental Status Exam score was not an outcome in this trial. Significantly worse subjectively rated fatigue and sleep quality were found in the control group. In another placebo-controlled trial of 54 patients undergoing breast surgery, patients administered nightly melatonin for 1 month preoperatively until 3 months after surgery did not have significantly different rates of delayed neurocognitive recovery at 2 weeks or postoperative neurocognitive disorder at 3 months, despite subjective improvements in sleep efficiency and total sleep duration.[66] Because of the small sample size and resulting lack of power, as well as the substantial heterogeneity in outcome definition seen in these studies, there is a clear need for further work on the relationship between melatonin and perioperative neurocognitive disorders other than delirium.

Finally, because of the overall paucity of effective sleep-promoting medications, there have now been increased efforts to trial multifaceted nonpharmacologic sleep interventions to prevent ICU delirium. A before–after quality improvement project in 300 medical ICU patients implemented a bundle of environmental changes including ear plugs, eye masks, and soothing music to decrease nighttime sleep disruption and promote daytime wakefulness. In the intervention group, the incidence of delirium was significantly less than in the preintervention group (odds ratio [95% CI], 0.46 [0.23 to 0.89]; $P = 0.02$).[67] Taken as a whole, bundled sleep interventions may reduce the risk of delirium, but more work is needed to confirm these findings in adequately controlled trials and to pinpoint which aspect(s) of the multicomponent sleep bundles are the most effective.

Summary

Sleep and circadian disturbances are important risk factors for the development of neurodegenerative diseases including Alzheimer disease, which in turn are important predisposing factors for postoperative delirium (fig. 2). To what extent sleep disturbances may cause delirium, which sleep disorders are particularly risky, or at which time point in the perioperative course these factors are important are unclear. Certain chronic sleep patterns may predispose to delirium and may in turn make patients more susceptible to acute perioperative sleep disturbances that may precipitate delirium. Additionally, postoperative delirium may cause acute *de novo* sleep disturbances, adding further complexity. More work is needed to untangle these relationships to derive effective interventions. Although the relationship between sleep and circadian health and delirium is beginning to emerge, further work is also needed to understand the consequences of sleep disturbances and delayed neurocognitive recovery and postoperative neurocognitive disorder. Finally, there is a large degree of overlap between sleep disorders, pain, and cognition. Thus, future trials should aim to incorporate multimodal targets incorporating these components.

Pain

Pain and Perioperative Neurocognitive Disorders

The relationship between pain and perioperative neurocognitive disorders and the modification of that relationship by the treatment of pain are incredibly complex (fig. 3). Inflammation and pain are closely biochemically linked, and many of the mediators of the body's response to injury and inflammation in both the peripheral and central nervous

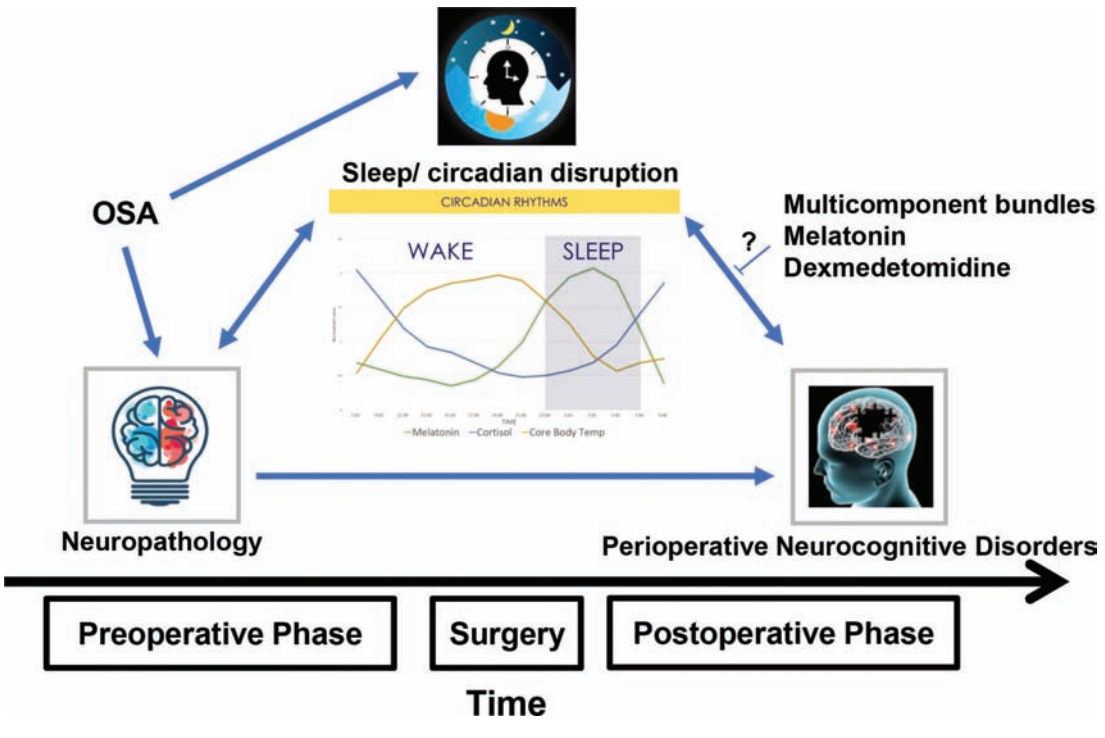

Fig. 2. Sleep and circadian disruption and perioperative neurocognitive disorders. Preexisting sleep disorders and baseline neuropathology may contribute to sleep and circadian rhythm disruption in the perioperative period, which may then be a precipitating factor for perioperative neurocognitive disorders. OSA, obstructive sleep apnea.

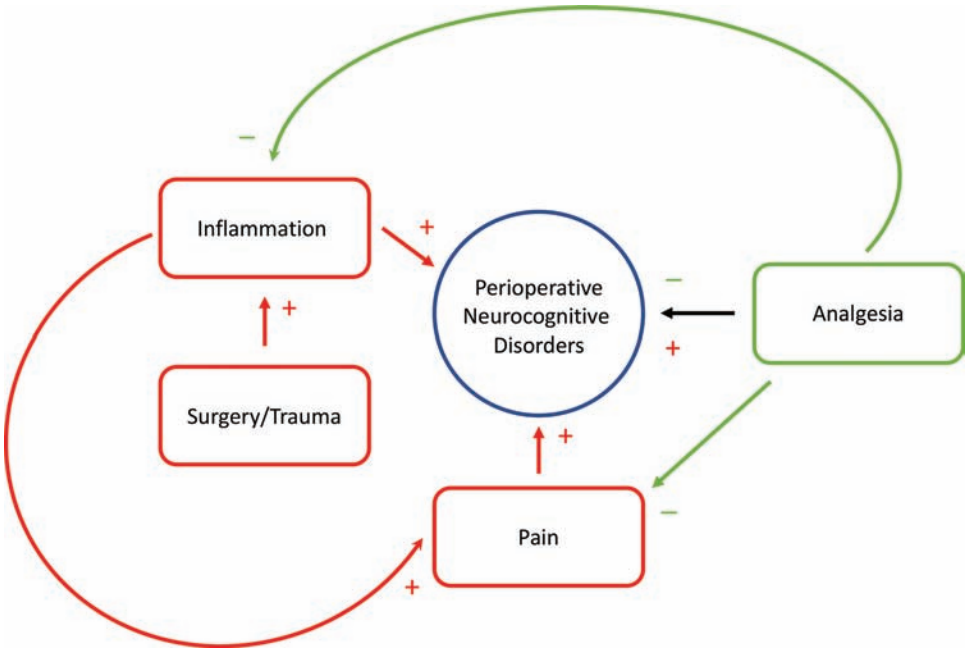

Fig. 3. The relationships between pain, inflammation, and analgesia on the risk for perioperative neurocognitive disorders. *Red lines* and *plus signs* signify processes that may worsen other conditions. *Green arrows* and *minus signs* indicate processes that may ameliorate or improve other conditions.

system including prostaglandins, bradykinins, interleukins, and tumor necrosis factor-α can be elevated in painful conditions.[68,69] This relationship is relevant to perioperative neurocognitive disorders, because one commonly proposed mechanistic framework for both postoperative delirium and delayed neurocognitive recovery is through neuroinflammation.[2,5,6,70,71] In this proposed mechanism, either peripheral or central nervous system injury leads to inflammatory cytokine release, endothelial activation, breakdown of the blood–brain barrier, and activation of microglia, potentially culminating in neuronal injury and subsequent brain dysfunction.[72–74] Another interesting link between pain and cognitive dysfunction comes from the knowledge that cholinergic neurons modulate pain signals, and cholinergic deficiency and anticholinergic medication use have been implicated in both pain hypersensitivity and delirium.[27,75] These biochemical links between inflammation, pain, and neuronal injury or dysfunction are more easily identified in preclinical models than in clinical studies given the difficulties inherent to selecting and sampling the ideal mediators in perioperative patients. Despite this limitation, there are a number of studies supporting an association between pain and subsequent perioperative neurocognitive disorders that are worthy of review.

The majority of clinical studies linking pain to perioperative neurocognitive disorders focus on the potential association between postoperative pain and postoperative delirium. Although this focus is reasonable given their temporal association, the presence of preoperative pain may also play a significant role and should not be overlooked. For example, in a cohort of 333 major noncardiac surgery patients 65 and older, the presence of moderate preoperative pain (odds ratio [95% CI], 2.2 [1.2 to 4.0]; $P < 0.05$) and the presence of severe preoperative pain (3.7 [1.5 to 9.0]; $P < 0.05$) at rest were independently predictive of postoperative delirium.[76] An increase in pain scores from preoperative baseline to postoperative day 1 was also predictive of postoperative delirium (1.1 [1.01 to 1.2]; $P < 0.05$). In 459 older patients undergoing elective orthopedic surgery, the severity of preoperative pain was significantly associated with an increased risk of subsequent delirium (severe pain *vs.* no/mild pain; odds ratio [95% CI], 2.0 [1.4 to 3.0]; $P = 0.013$) for trend between no/mild, moderate, and severe pain).[77] The relationship between pain and delirium may be modified by the presence of underlying depression, because subgroup analysis of patients with depression from this cohort revealed that for every 1-point increase on the postoperative visual analog pain scale, the risk of delirium significantly increased. Interestingly, investigations of alterations in synaptic connectivity in the prefrontal cortex suggest that changes may occur in this region for patients with depression, in chronic pain, and in disorders of executive function, suggesting a potential close neuropathological link between these conditions.[78]

As previously mentioned, the preponderance of clinical evidence associating pain and perioperative neurocognitive disorders involves acute postoperative pain. In a cohort of 541 older patients with hip fracture, cognitively intact patients with any episode of severe postoperative pain at rest (as defined by a score of 4 or greater on a 5-point scale) through postoperative day 3 had a nine-fold increase in the risk of subsequent delirium (risk ratio [95% CI], 9.0 [1.8 to 45.2]; $P = 0.01$).[79] In 361 patients with a mean age of 66 undergoing major noncardiac surgery, postoperative pain at rest was significantly associated with subsequent postoperative delirium (risk ratio, 1.20 [1.04 to 1.37] per 1-point increase on the visual analog scale; $P = 0.015$).[80] In a similar population, patients with high levels of postoperative pain and receiving high doses of opioids had significantly higher rates of delirium, in both patients at low risk for delirium (17 of 34 [50%] *vs.* 35 of 174 [20%]; $P = 0.0004$) and patients at high risk for delirium (23 of 32 [72%] *vs.* 46 of 93 [49%]; $P = 0.031$) compared to patients with lower levels of pain.[81] In contrast, in 89 older patients undergoing major abdominal surgery, uncontrolled pain as defined by a pain score of greater than 5 without adequate medication administration was not found to be significantly associated with delirium (risk ratio [95% CI], 1.0 [0.7 to 1.4]; $P = 0.91$).[82] It should be noted when discussing the evidence linking pain to perioperative neurocognitive disorders that the assessment of pain can be very challenging in patients with impaired cognition, and therefore current guidelines recommend using a multisource, multidimensional approach to the assessment of pain in older persons.[83] Additionally, many of the above-referenced trials do not contain information as to whether chronic pain or opioid use was present preoperatively, limiting the interpretation of these results.

Pain Treatment and Perioperative Neurocognitive Disorders

The adequate diagnosis and management of pain is a core intervention in HELP, as well as multicomponent ICU care guidelines such as the ABCDEF bundle, and is also recommended in consensus guidelines for reducing postoperative delirium from multiple interdisciplinary working groups.[11,84–86] As previously mentioned, data from multiple perioperative studies suggest that the presence of preoperative or postoperative pain or worsening severity of pain in the postoperative period is associated with subsequent delirium. In many of these studies, it is difficult to determine based on their results whether adequate treatment of pain can prevent delirium or conversely whether undertreatment of pain can precipitate delirium. Because low pain scores may indicate either absence of pain or effective treatment of pain, evaluation of the impact of pain treatment on the risk of perioperative neurocognitive disorders requires adjustment for either factor. This relationship is confounded even further when considering the specific medication used to treat pain, because many drugs have been implicated as precipitating factors for delirium, especially opioids.

Opioids

Amid the enhanced awareness of perioperative neurocognitive disorders and the opioid epidemic, avoidance or minimization of opioids has become an essential consideration in perioperative care. On one hand, opioids remain some of the most effective analgesics for acute pain, especially for severe painful conditions such as after trauma or surgery. On the other hand, opioid-related side effects such as sedation or hallucination may precipitate, worsen, or mimic symptoms of delirium such as disorientation or hypoactive motor and cognitive function. Given these considerations, current guidelines for best practices to avoid delirium advocate for avoiding opioids, at least as first line agents.[70,86] However, data suggest that simply administering fewer opioids may not prevent perioperative neurocognitive disorders. For example, in a retrospective matched cohort study of 86 medical–surgical patients with a mean age of 80 admitted with painful conditions and with an opioid ordered, delirious patients received a significantly lower fraction of the allowed dose ordered than nondelirious patients (11 of 43 [26.14%] *vs.* 21 of 43 [48.21%]; $P < 0.001$).[87] In the cohort study of hip fracture patients mentioned previously in which pain at rest was associated with a nine-fold increased risk of delirium, investigators found that patients administered less than 10 mg of morphine equivalents per day were at significantly increased risk of delirium compared to patients receiving more than 10 mg (risk ratio [95% CI], 5.4 [2.4 to 12.3]; $P < 0.001$).[79] In 236 patients older than 65 undergoing hip fracture repair, opioid consumption during the first 3 postoperative days was not different between patients with and without delirium (mean [SD], 0.66 [0.82] *vs.* 0.49 [0.59] mg/kg morphine equivalents; $P = 0.176$), but patients with delirium did have significantly higher pain scores (mean [SD], 2.6 [1.9] *vs.* 1.7 [1.8]; $P = 0.007$).[88] Although the higher risk of delirium with lower opioid doses does not directly imply that those patients' pain was less well treated, data from these cohorts suggest that increased opioid dose is not associated with an increased risk of postoperative delirium, at least in the context of acute pain. Given the clinical and societal importance of limiting opioid use, it is reasonable to employ multimodal efforts to control pain before resorting to opioids.[89] Ideally, effective analgesia can be accomplished while limiting opioids, but in the event that opioid-sparing techniques such as use of anti-inflammatory agents and regional, neuraxial, or local analgesia are not successful, residual untreated pain may have more of an effect on delirium than further limiting opioid use.

In terms of specific opioids, tramadol and meperidine have been linked to an increased risk of delirium, but there are limited data on the differential impact of the agents more typically used in the perioperative period such as fentanyl

or hydromorphone.[90] The mode of opioid administration may be more relevant. In the cohort study of 333 patients undergoing major noncardiac surgery mentioned previously, patients who only received oral opioid analgesics were found to have a significantly reduced risk of postoperative delirium compared to patients treated with intravenous opioids (odds ratio [95% CI], 0.4 [0.2 to 0.7]; $P < 0.05$).[81] Additionally, a prospective cohort study of 225 patients older than 65 yr undergoing noncardiac surgery found that patients who were treated with oral opioids alone had significantly reduced odds of delayed neurocognitive recovery as assessed by a three-test battery as opposed to those treated with intravenous opioids *via* a patient-controlled system (odds ratio [95% CI], 0.22 [0.06 to 0.80]; $P = 0.02$). This finding came after controlling for a number of patient- and surgery-specific confounders including pre- and postoperative pain levels.[91]

Nonopioid Analgesics

The pathophysiological overlap between inflammation, pain, and neuronal injury makes analgesics with anti-inflammatory effects attractive candidates to prevent delirium in patients with acute postoperative pain. In a randomized trial of 620 older patients undergoing elective total joint arthroplasty, scheduled parecoxib (a selective COX2 inhibitor) for 3 days led to a significant reduction in the incidence of postoperative delirium compared to placebo (19 of 310 [6.2%] *vs.* 34 of 310 [11%]; $P = 0.031$).[92] The parecoxib group also had significantly less delayed neurocognitive recovery, defined by a decrease of more than 2 points on the Mini Mental Status Exam from baseline, than placebo controls on postoperative days 1, 3, and 5 (day 5: 28 of 310 [8.7%] *vs.* 53 of 310 [19.4%]; $P < 0.001$). It should be noted that the Mini Mental Status Exam is limited in its utility as a test for detecting cognitive dysfunction and is not recommended for this purpose by the perioperative neurocognitive disorder nomenclature working group.[1] Although acetaminophen is not considered an anti-inflammatory, it shares some characteristics of nonsteroidal anti-inflammatory drugs including action on the cyclooxygenase pathway and putative blockade of central nervous system prostaglandin production.[93] A randomized, placebo-controlled factorial trial in 121 cardiac surgery patients older than 60 yr found that scheduled intravenous acetaminophen for the first 48 h postoperatively significantly lowered the incidence of delirium as compared to placebo (6 of 60 [10%] *vs.* 17 of 60 [28%]; $P = 0.01$).[94] Patients receiving acetaminophen also had significantly reduced delirium duration (median 1 *vs.* 2 days; $P = 0.03$). The rates of delayed neurocognitive recovery at discharge were not different between groups.

In both the parecoxib and acetaminophen trials, there were either clinically insignificant differences or no differences found between groups in opioid equivalents administered and in postoperative pain scores, suggesting that neither opioid sparing nor superior pain control were the main drivers of the results. It is possible that this finding was instead related to the prevention of neuroinflammation; however, this hypothesis will have to be confirmed in subsequent studies because neither trial included biomarker analyses. Additionally, the possibility that the effect of these interventions occurred through reducing neuroinflammation should be taken in context with the negative findings of multiple clinical trials investigating the intraoperative use of different drugs with both anti-inflammatory and analgesic properties including intravenous lidocaine, magnesium, and steroids to prevent perioperative neurocognitive disorders after cardiac surgery.[95–99]

Gabapentin is another nonopioid analgesic that has been investigated as an intervention to minimize perioperative opioid use. In a large double-blind placebo-controlled trial involving 697 patients with a mean age of 72 yr undergoing noncardiac surgery, the administration of 900 mg of gabapentin preoperatively and for the first 3 postoperative days did result in a small but significant reduction in the amount of morphine equivalents on the first postoperative day (median [interquartile range], 6.7 [1.3 to 20.0] *vs.* 6.7 [2.7 to 24.8] mg; $P = 0.04$).[100] However, there were no differences between the gabapentin and placebo groups in the primary outcome of postoperative delirium (84 of 350 [24%] *vs.* 72 of 347 [20.8%]; $P = 0.30$). Commonly, especially in enhanced recovery pathways, multimodal and opioid-sparing analgesia protocols will combine multiple agents. Data for this approach are limited, but one prospective study of a fast track protocol for 220 older patients undergoing major joint replacement found no cases of postoperative delirium employing a multicomponent strategy including standardized anesthetic and postoperative analgesic protocols utilizing various combinations of paracetamol, gabapentin, tramadol, celecoxib, and ibuprofen across four different centers.[101]

Ketamine is another commonly used opioid-sparing analgesic. Like opioids, ketamine has potential psychotropic effects such as hallucinations, nightmares, or psychosis that are undesirable in patients at risk for perioperative neurocognitive disorders.[102] These effects may be dose-dependent; therefore trials evaluating ketamine's effectiveness in reducing opioid consumption and perioperative neurocognitive disorders focus on low-dose interventions. In a three arm randomized active and placebo-controlled trial of 56 adult patients undergoing major open abdominal surgery, the administration of low-dose (0.25 mg/kg bolus and 0.125 mg · kg^{-1} · h^{-1} infusion) and minimal-dose (no bolus, 0.015 mg · kg^{-1} · h^{-1} infusion) ketamine during the anesthetic and the following 48 h resulted in lower postoperative opioid consumption as compared to placebo (mean [SD], 42.7 [13.4] *vs.* 40.2 [13.5] *vs.* 72.7 [15.3] mg piritramide; $P < 0.0001$).[103] However, patients in the low-dose group had significantly higher Intensive Care Delirium Screening Checklist scores than both the minimal-dose and placebo groups (median [interquartile range], 2 [1 to 3] *vs.* 1 [0 to

1] and 0 [0 to 1], respectively; $P = 0.007$). In 58 patients older than 55 yr of age undergoing cardiac surgery with cardiopulmonary bypass, patients randomized to receive an intravenous bolus of 0.5 mg of ketamine had significantly lower rates of postoperative delirium than placebo controls (1 of 29 [3%] *vs.* 9 of 29 [31%]; $P = 0.01$).[104] In a different study in the same population by the same investigators, they found that the same intervention could possibly reduce the incidence of delayed cognitive recovery at 1 week postoperatively, as defined by a 2 SD decrease on assessments of memory and executive functions, as compared to placebo (7 of 26 [27%] *vs.* 21 of 26 [81%]; $P < 0.001$) after adjusting for training effects using assessment data from concurrent nonsurgical controls.[105]

The Prevention of Delirium and Complications Associated with Surgical Treatments (PODCAST) trial sought to more definitively investigate whether the prophylactic intraoperative administration of ketamine could prevent postoperative delirium, also using a three-armed design.[9] In the trial, 672 patients older than 60 yr undergoing major cardiac and noncardiac surgery were randomized to either low-dose (0.5 mg/kg) or high-dose (1.0 mg/kg) ketamine boluses or placebo given in the time between induction and surgical incision. There was no difference in the incidence of postoperative delirium during the first 3 postoperative days between patients who received any dose of ketamine as compared to placebo (88 of 450 [19.45%] *vs.* 44 of 222 [19.82%]; $P = 0.92$). There was also no significant difference found in delirium rates across all three groups (40 of 227 [17.65%] *vs.* 47 of 223[21.3%] *vs.* 44 of 222 [19.82%] in low-dose, high-dose, and placebo groups, respectively; $P = 0.80$). Furthermore, no significant differences among groups were found with respect to time to delirium onset, severity, or duration of delirium. Postoperative opioid consumption was not significantly different between the three groups at any time point. Last, more patients in the ketamine groups reported experiencing hallucinations (45 of 227 [20%] *vs.* 62 of 223 [28%] *vs.* 40 of 222 [18%] in low-dose, high-dose, and placebo groups, respectively; $P = 0.01$) and nightmares (27 of 227 [12%] *vs.* 34 of 223 [15%] *vs.* 18 of 222 [8%]; $P = 0.03$). Therefore, the results of the PODCAST trial should give providers caution when considering intraoperative ketamine as a means to either reduce the risk of delirium or postoperative opioid consumption, because neither high- nor low-dose regimens were effective for these outcomes, and there was evidence of significant harm from ketamine with regards to its psychotropic effects.

Regional or Neuraxial Analgesia

A successful regional nerve block may be very effective for postoperative pain control when placed in an appropriate candidate. If this effective analgesia can be obtained while also sparing the use of opioids, then it is theoretically possible that regional nerve blocks can prevent delirium in multiple ways. The best available data for this approach come from studies in orthopedic surgery patients. In 207 patients at intermediate- or high-risk of delirium undergoing hip fracture surgery who were randomized to undergo a fascia iliaca or sham block administered on admission and repeated every 24 h until delirium occurrence or discharge, the use of the fascia iliaca block resulted in a significantly reduced incidence of delirium (11 of 102 [10.78%] *vs.* 25 of 105 [23.8%]; risk ratio [95% CI], 0.45 [0.23 to 0.87]).[106] Additionally, patients who received fascia iliaca blocks experienced lower delirium severity (mean [SD], 14.34 [3.6] *vs.* 18.61 [3.4) DRSR-98 score; $P < 0.001$) and shorter delirium duration (mean [SD], 5.22 [4.28] *vs.* 10.97 [7.16] days; $P < 0.001$). For patients undergoing total knee arthroplasty, a cohort study of 85 patients demonstrated that analgesia *via* a femoral nerve catheter in addition to patient-controlled analgesia (PCA) was associated with lower rates of postoperative delirium as compared to PCA alone (7 of 28 [25%] *vs.* 31 of 51 [61%]; $P = 0.002$).[107] After controlling for preoperative cognitive function, the odds of postoperative delirium were significantly higher in the PCA group than patients who received a femoral nerve catheter in addition to their PCA (odds ratio [95% CI], 7.02 [2.06 to 23.97]; $P = 0.002$). The use of intraoperative spinal anesthesia as an alternative to general anesthesia has been proposed to reduce anesthetic exposure for patients at risk for postoperative delirium. Interestingly, this may not always be the case, because patients under spinal anesthesia with supplemental monitored anesthesia care may still receive high doses of intravenous sedatives.[108] This makes the interpretation of trials investigating the benefit of neuraxial anesthetics on postoperative delirium challenging. A large randomized controlled trial is currently underway specifically examining whether spinal anesthesia or general anesthesia is superior for older patients undergoing hip fracture surgery, with postoperative delirium as a secondary outcome.[109]

For operations on the thorax or abdomen, analgesia *via* the use of an epidural catheter can be very effective, albeit with the inherent risk of hypotension.[110] In a trial of 70 patients older than 70 yr of age randomized to either combined general and epidural anesthesia followed by epidural PCA with bupivacaine and sufentanil compared to general anesthesia and PCA alone, the use of epidural PCA did not significantly reduce the incidence of delirium (8 of 31 [26%] *vs.* 8 of 33 [24%]; $P > 0.05$).[111] A higher proportion of patients in the PCA group demonstrated poor scores on the Abbreviated Mental Test than the epidural PCA group on postoperative day 4 (number of patients with scores ≤ 8, 9, and 10 was 5, 11, and 17 *vs.* 1, 5, and 25; $P < 0.05$) and postoperative day 5 (5, 13, and 15 *vs.* 1, 7, and 23; $P < 0.05$). In a secondary analysis of the PODCAST trial, the investigators found that patients who received postoperative epidural analgesia did not have a significantly reduced odds of postoperative delirium within the first 3 postoperative days compared to those without an epidural after adjusting

for several confounders including age and type of procedure (adjusted odds ratio [95% CI], 0.65 [0.32 to 1.35]; $P = 0.247$).[112] A *post hoc* analysis was performed in which patients treated with an epidural were less likely to experience any episode of delirium during the study follow-up, after adjustment for the same confounders (adjusted odds ratio [95% CI], 0.36 [0.17 to 0.78]; $P = 0.009$). Because postoperative delirium is often defined by any single episode of delirium, and this analysis was conducted post hoc, it is unclear how impactful this finding is.

Finally, the use of epidural analgesia has been included in studies evaluating the effectiveness of enhanced recovery pathways for colonic surgery. In one trial, 240 open colorectal surgery patients older than 70 yr were randomized to a fast-track protocol (consisting of preoperative dietary, hydration, and bowel preparation interventions, thoracic epidural anesthesia and postoperative epidural PCA with ropivacaine only, and postoperative mobilization and dietary interventions) or traditional care (notably consisting of general anesthesia and postoperative fentanyl).[113] Patients in the fast-track group had a significantly lower incidence of postoperative delirium within the first 5 days (4 of 117 [3.4%] *vs.* 15 of 116 [12.9%]; $P = 0.008$).

Summary

Severe or uncontrolled preoperative or postoperative pain and increased levels of pain from the preoperative to postoperative period are all associated with postoperative delirium. Proper diagnosis and adequate treatment of pain remains a key component of preventative strategies for postoperative delirium. Although multimodal analgesic strategies including nonopioid analgesics and regional or neuraxial analgesia have demonstrated success in effectively controlling pain and potentially reducing opioid requirements, at this time the quality of evidence underlying any one analgesic approach to prevent delirium is low. Evidence is stronger, however, that undertreatment of pain is more of a significant risk factor for postoperative delirium than treatment with potentially deliriogenic medications. There are few data available on the relationship between pain, pain treatment, and delayed neurocognitive recovery or postoperative neurocognitive disorder.

Cognition

A disturbance in cognition, either temporarily or longer term, is a defining feature of postoperative delirium, delayed neurocognitive recovery, and postoperative neurocognitive disorder.[1] An emerging component of perioperative care now consists of perioperative multicomponent strategies to enhance recovery. In this context, preoperative optimization and the goal of the best possible functional recovery for surgical patients increasingly includes measures taken to protect perioperative cognitive function.[114] Thus, the detection of perioperative neurocognitive disorders and evaluation of strategies employed to prevent them relies on a thorough understanding of the cognitive areas affected in the perioperative period, the development of validated instruments to measure perioperative cognition, and the current state of evidence for strategies to improve postoperative cognitive function.

Baseline Cognitive Performance and Perioperative Neurocognitive Disorders

The degree of preexisting organ dysfunction is an important risk factor for many types of postoperative complications.[115–117] The same can be said for brain function, because poor baseline cognition is a strong predictor of future cognitive dysfunction. Although there is continuing debate as to which cognitive test or battery of tests is best suited for the perioperative period, there is strong evidence that patient performance on a preoperative cognitive test can predict perioperative neurocognitive disorders. Screening tests such as the Mini-Cog and Mini Mental Status Exam, which were originally designed to detect mild cognitive impairment or dementia, have been used to evaluate perioperative cognitive function. In two longitudinal cohort studies of surgical patients older than 65 yr, investigators found that a preoperative Mini-Cog score indicative of moderate cognitive dysfunction (3 or lower or 2 or lower) was associated with a significantly higher risk of postoperative delirium (odds ratio [95% CI], 2.4 [1.2 to 4.9]; $P = 0.015$; and 4.5 [1.3 to 15.7]; $P = 0.017$, respectively) and more days with postoperative delirium (mean [SD], 4 [6] *vs.* 1 [2] days; $P = 0.012$).[118,119] In 425 older hip fracture surgery patients, those with a Mini Mental Status Exam score of less than 24 had a significantly increased incidence of postoperative delirium (76 of 141 [54%] *vs.* 73 of 284 [26%]; $P \leq 0.001$).[120] In a similar population, a higher preoperative Mini Mental Status Exam score was associated with a lower incidence of postoperative delirium (odds ratio [95% CI], 0.67 [0.52 to 0.86]; $P = 0.002$).[121]

In addition to tests of global cognitive function, poor performance on targeted tests of executive function can also predict postoperative delirium in older patients undergoing major noncardiac surgery (odds ratio [95% CI], 1.23 [1.06 to 1.43]; $P < 0.01$ for a three-test composite and log mean ratio [95% CI], 1.27 [1.11 to 1.46]; $P < 0.01$ for color trial 2).[122,123] Preoperative test performance is also associated with persistent cognitive deficits, because older hip arthroplasty patients who performed less than 2 standard deviations on at least two of seven neuropsychological tests had higher incidences of both delayed neurocognitive recovery at 7 days (23 of 91 [25.3%] *vs.* 26 of 195 [13.3%]; $P = 0.012$) and of postoperative neurocognitive disorder at 3 months (13 of 87 [14.9%] *vs.* 14 of 197 [7.1%];, $P = 0.039$) and 12 months (5 of 83 [9.4%] *vs.* 2 of 188 [1.1%]; $P < 0.001$).[124] In a cohort of 566 older surgical patients, lower preoperative scores on an 11-test cognitive battery was identified as the dominant risk factor for postoperative delirium

after adjustment for other established predictors (risk ratio [95% CI], 2.0 [1.5 to 2.5] for each 0.5 SD decrease; $P < 0.05$).[125] Last, preoperative test performance may also help identify patients at risk for long-term cognitive decline, because a higher preoperative Mini Mental Status Exam score was associated with a lower risk of dementia 5 yr after cardiac surgery (odds ratio [95% CI], 0.68 [0.54 to 0.84]; $P < 0.001$).[126] Based in part on the findings of these studies, the Perioperative Neurotoxicity Working Group recommends evaluating baseline cognition using a screening test in patients older than 65 or who are at otherwise high risk for perioperative neurocognitive disorders.[127] They do not recommend one screening test in particular, however, because more work is needed to assess the predictive power and clinical utility of these screening tests in perioperative patients.

Cognitive Reserve

Cognitive reserve can be described as resiliency of an individual's cognitive processes in the face of injury. In contrast to cognitive performance assessed at one point in time, cognitive reserve is characterized by the accumulation or loss of cognitive abilities over the lifespan. Differences in cognitive reserve have been theorized to explain observed differences between patients in phenotypes or degrees of impairment seen after similar pathologic findings of neurologic injury such as stroke or Alzheimer disease, and the concept can be applied to perioperative neurocognitive disorders (fig. 4).[128] Cognitive reserve is typically described in terms of years of education attained, occupational complexity, and cognitive lifestyle behaviors. There is some evidence to suggest that differences in cognitive reserve may predict perioperative neurocognitive disorders. In two cohort studies of hospitalized older patients, each year of education obtained was associated with a significantly decreased risk of delirium (odds ratio [95% CI], 0.91 [0.87 to 0.95]; $P < 0.01$; and 0.76 [0.62 to 0.95]; $P = 0.016$, respectively).[129,130] Low educational attainment was also found to be a strong predictor of postoperative delirium in older patients after hip fracture surgery or hip replacement (odds ratio [95% CI], 3.59 [1.14 to 11.25]; $P < 0.05$).[131] However, a large cohort study of similar patients did not find an association between years of education or multiple other markers of cognitive reserve and postoperative delirium.[132] It should be noted that this cohort exhibited a

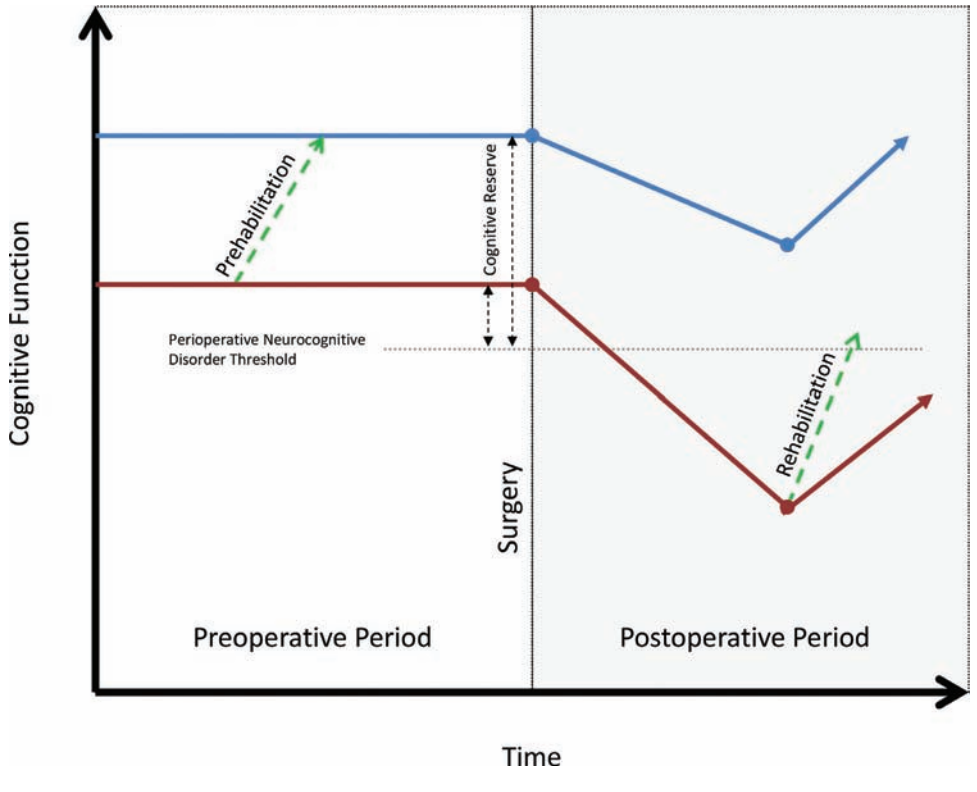

Fig. 4. Cognitive trajectories and perioperative neurocognitive disorders. Depicted are theoretical cognitive trajectories of a patient with high baseline cognitive reserve (*blue line*) and a patient with low baseline cognitive reserve (*red line*). Both patients experience an event in the perioperative period leading to a decrease in cognitive function, but only the patient with low baseline reserve may manifest symptoms. The *green dashed lines* represent the theoretical mechanism through which cognitive interventions in the pre- and postoperative phases may influence cognitive reserve and either prevent or aid recovery from perioperative neurocognitive disorders. Adapted from Stern.[128]

high median years of education (15 yr), suggesting that this effect may not be as evident in highly educated populations.

Educational attainment may also predict long-term postoperative cognitive function. In a large longitudinal cohort of older patients undergoing major noncardiac surgery, educational achievement of high school or higher was associated with a significantly lower risk of delayed neurocognitive recovery at 1 week (odds ratio [95% CI], 0.6 [0.4 to 0.9]; $P = 0.002$), but not for postoperative neurocognitive disorder at 3 months.[133] In another large prospective cohort of major noncardiac surgery patients of which 355 were older than 60, patients with postoperative neurocognitive disorder at 3 months had slightly fewer mean years of education (mean [SD], 13.2 [2.4] or 13.7 [2.8] years; $P = 0.013$).[134] Less well characterized than educational level is the relationship between baseline cognitive lifestyle behaviors and perioperative neurocognitive disorders. In a cohort of 141 patients with a mean age of 71 yr, greater participation in preoperative cognitive lifestyle behaviors including reading books, using email, or playing computer games was found to be protective against delirium after elective orthopedic surgery (increase of one activity per week; odds ratio [95% CI], 0.92 [0.86 to 0.98]; $P = 0.006$).[121]

Prehabilitation to Prevent Perioperative Neurocognitive Disorders

Prehabilitation refers to the attempt to optimize preoperative modifiable risk factors to improve functional outcomes after surgery, often focusing on preoperative physical, nutritional, and psychologic health. Of these three domains, physical prehabilitation has been the most studied. Although there are inconsistent results among trials and uncertainty with regards to whether physical prehabilitation can reduce postoperative complications, multiple clinical trials in abdominal and orthopedic surgery have demonstrated improved postoperative physical capacity in patients who participated in home-based exercise regimens as compared to usual care.[135] Nutritional prehabilitation, consisting mainly of nutritional supplements and dietary counseling, may potentially accelerate the return to preoperative functional capacity in colorectal surgery when added to a physical prehabilitation program.[136] Both physical deconditioning and poor nutritional status are elements of frailty, which has been shown in retrospective studies to be strongly associated with postoperative delirium and possibly postoperative neurocognitive disorder.[137,138] Such elements may be modifiable. In a six-armed randomized trial of 246 older prefrail or frail adults, physical, cognitive, nutritional, or combined intervention training were all shown to reduce future frailty scores to a significantly larger degree than a usual care control.[139] If physical and nutritional prehabilitation can improve postoperative functional outcomes and reverse frailty in older persons, it is then possible that these interventions may prevent perioperative neurocognitive disorders. Data from clinical trials evaluating this potential effect are limited, however. In a single center before and after unblinded study of 627 patients undergoing major abdominal surgery, the incidence of postoperative delirium was found to be significantly lower in patients who underwent a multicomponent intervention to improve physical and nutritional health and reduce frailty factors as compared to patients who did not receive this intervention (22 of 267 [8.2%] *vs.* 42 of 360 [11.7%]; adjusted odds ratio [95% CI], 0.56 [0.32 to 0.98]; $P = 0.043$).[140]

Bolstered by the theory that increasing cognitive reserve can protect against neurologic injury and experimental data suggesting that neurogenesis and neuroplasticity still occur in later life, numerous investigators have evaluated whether cognitive exercise can improve cognitive performance in older persons.[141–144] Perhaps the most notable example is the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial, which demonstrated that 10 h of computerized cognitive training led to sustained improvements in processing speed over the following 10 yr.[145] In perioperative research, attempts have been made to apply this technique to prevent perioperative neurocognitive disorders. In a randomized trial of 141 abdominal surgery patients older than 60, 3 h of supervised memory exercises 1 to 4 weeks before surgery significantly reduced the incidence of delayed neurocognitive recovery at 1 week compared to usual care (11 of 69 [15.9%] *vs.* 26 of 72 [36.1%]; $P = 0.007$).[146] In contrast to its success in older adults in the general population, computerized cognitive training appears to be less feasible in older surgical patients.[147] Although a small feasibility trial of 45 older cardiac surgery patients noted high degrees of patient interest and enjoyment with a computerized cognitive prehabilitation program, there were low rates of adherence (39% during the preoperative period), and no effect on the incidence of postoperative delirium or delayed cognitive recovery was found.[148] In a recent randomized trial of 251 patients older than 60 undergoing major noncardiac nonneurologic surgery, preoperative computerized cognitive exercise did not significantly reduce the risk of postoperative delirium as compared to usual care in the primary analysis. However, a *post hoc* per-protocol analysis excluding patients who never used the cognitive exercise program revealed a significantly reduced incidence of postoperative delirium favoring the cognitive exercise group (16 of 121 [13.2%] *vs.* 29 of 126 [23%]; $P = 0.04$).[149] It should be noted that for this trial and the feasibility trial that used the same cognitive exercise platform, the median length of time spent training was ~4.5 h, which falls short of "recommended dose" of 10 h of cognitive exercise in the ACTIVE trial. Further investigation is necessary to determine whether adherence to cognitive prehabilitation can be improved and whether cognitive prehabilitation can reduce delirium and/or other perioperative neurocognitive disorders in an adequately powered trial.

Postoperative Cognitive Training

Postoperative cognitive training may also prevent perioperative neurocognitive disorders. A randomized trial of 47

lung transplant patients with a mean age of 65 yr demonstrated greater score improvements at 12 weeks on the Forward Digit Span (mean [SD], 0.93 [1.09] *vs.* 0.04 [0.52]; $P = 0.004$) and Verbal Fluency tests (mean [SD], 1.32 [1.82] *vs.* 0.1[1.53]; $P = 0.033$) with the use of a computerized program for 8 weeks after surgery.[150] Among 46 lung transplant recipients with a mean age of 66 yr, the use of 8 weeks of computerized cognitive training started 4 weeks after surgery resulted in significantly higher scores on the digit span forward test (mean [SD], 0.93 [1.09] *vs.* 0.04 [0.52]; $P = 0.0044$) and verbal fluency (mean [SD], 1.32 [1.82] *vs.* 0.10 [1.53]; $P = 0.0331$).[150] It should be noted, however, that these mean differences are less than the SD for the group, which is a common benchmark used in previous studies to define perioperative neurocognitive disorders. The best known multicomponential intervention to prevent hospital delirium, HELP, includes the provision of cognitively stimulating activities at least three times daily as a core intervention.[151] In a before–after study of 179 consecutive abdominal surgery patients older than 65 in which a modified version of HELP was implemented that focused only on nutrition, mobilization, and cognitively stimulating activities including discussing current events or word games, the delirium rate was significantly reduced in the intervention group (0 of 102 [0%] *vs.* 13 of 77 [16.7%]; $P < 0.001$).[152] A similar approach employing daily cognitively stimulating conversation and word games was employed in a randomized pilot trial in 50 older hip or knee arthroplasty patients. The investigators found that patients in the intervention group had a significantly lower incidence of delayed neurocognitive recovery as defined by a decrease of 2 points or more from the baseline Mini Mental Status Exam score as compared to usual care controls (3 of 25 [12%] *vs.* 11 of 25 [44%]; $P = 0.012$).[153]

Summary

Poor baseline cognition, defined by either poor preoperative performance on screening tests of cognitive function or decreased markers of cognitive reserve, is strongly associated with perioperative neurocognitive disorders. As such, the routine use of a validated screening test in the preoperative period has been recommended to help identify at-risk patients. Although physical and nutritional prehabilitation may improve postoperative functional capacity and reverse frailty in nonoperative patients, more investigation is necessary to determine whether these interventions can prevent perioperative neurocognitive disorders. Cognitive prehabilitation has been shown to reduce delirium incidence in one clinical trial, but further studies are needed to replicate this finding, to determine the optimal training regimen, to improve adherence, and to investigate whether the technique can prevent delayed cognitive recovery and/or postoperative neurocognitive disorder. Postoperative cognitive exercise may improve postoperative cognition and prevent postoperative delirium, but high-quality evidence from adequately powered clinical trials is needed to better determine these effects.

Conclusions

The increasing awareness of the long-term negative consequences of perioperative neurocognitive disorders on functional outcomes after surgery has led to the development of multicomponent interventions to optimize postoperative brain health. Decades of perioperative research targeting isolated intraoperative interventions focusing on altering the exposure to anesthesia or surgery have not yet been able to identify a singular intervention to successfully prevent perioperative neurocognitive disorders. Given the

Table 1. Summary of Evidence and Future Directions

Summary	Questions for Future Research
Sleep	
Chronic sleep disorders including obstructive sleep apnea are associated with future delirium.	Can improving preoperative sleep quality reduce delirium risk?
	Can increasing perioperative adherence to continuous positive airway pressure prevent delirium?
Perioperative sleep disruption is a precipitating factor for delirium.	Can restoring circadian rhythm, either naturally or with the use of melatonin, prevent delirium?
	Can preferential use of dexmedetomidine prevent postoperative delirium in patients requiring postoperative sedation?
Pain	
Preoperative pain is a risk factor for postoperative delirium.	Can optimization of preoperative pain lower the risk of postoperative delirium?
Poorly treated postoperative pain can precipitate postoperative delirium.	Do multisource tools for pain assessment identify patients at risk for delirium?
	Does the use of multimodal analgesia prevent postoperative delirium?
Little evidence exists describing the association between postoperative pain and longer term perioperative neurocognitive disorders.	Is poorly controlled pain associated with delayed neurocognitive recovery?
	Does chronic postoperative pain increase the risk of postoperative neurocognitive disorder?
Cognition	
Poor preoperative cognitive function is one of the strongest predictors of perioperative neurocognitive disorders.	Which cognitive screening test(s) best predict perioperative neurocognitive disorders?
	Does preoperative cognitive trajectory predict perioperative neurocognitive disorders?
Perioperative cognitive exercise may prevent postoperative delirium.	Can cognitive prehabilitation prevent perioperative neurocognitive disorders?
	Which type of cognitive exercise is best suited to prevent perioperative neurocognitive disorders? What is the most effective dose?

multiple predisposing and precipitating risk factors for postoperative delirium and the incomplete overlap with risk factors for delayed neurocognitive recovery and postoperative neurocognitive disorder, it is likely that a multicomponent approach encompassing all phases of the perioperative period (preoperative, intraoperative, and postoperative) may be more effective. Going forward, critically needed perioperative research into three targets for optimal perioperative brain health: sleep, pain and cognition, will enable providers to better identify high-risk patients and confidently employ interventions into well defined care plans (table 1). When this can be achieved, perioperative medicine may reach its goal of an ideal recovery for both the bodies and minds of surgical patients.

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Competing Interests

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MIND TO MIND

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

Stephen T. Harvey, M.D., Editor

Counterintuitive Gerunds

Kathryn Elizabeth McGoldrick, M.D., F.C.A.I.(Hon)

When I think of lessons learned during decades of living,
my reflections coalesce around dualities and complementarities:
yin and yang, obverse and reverse, warp and woof.
As I navigated the ebb and flow of life,
I wondered why
there is a time to lead and a time to follow,
a time to speak up and a time to be silent.
Perhaps the tension is resolved by realizing
To live is to embrace contradiction,
to transcend logic-locked polarities.
Teaching is learning
from the questions of those "taught."
Believing is doubting
that this is all there is.
Laughing is weeping
at the absurdity of life.
Forgiving is remembering

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our own imperfections.

Failing is succeeding

at recognizing new opportunities.

Hoping is stumbling with every tentative step,

yet trusting steadfastly in the next.

Nurturing is letting go,

encouraging independence.

Accepting is rejecting

intolerance that crushes understanding.

Loving is appreciating

that distance and mystery are inevitable.

Mourning is celebrating

a life well-lived.

Dying is living on

In the hearts of those whose lives we touched.

MIND TO MIND

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

Stephen T. Harvey, M.D., Editor

Anesthesia Reunion in Hospice

Ellen Roark Basile, D.O.

In December, all eight of us were together for the first and last time since graduating from our anesthesia residency program in Philadelphia. Before going our separate ways after graduation, we had made plans for a 10-year reunion. Years later, we never imagined our celebration would be held at hospice.

Eight months before our reunion, Tom, one of our co-residents, told us he had been diagnosed with stage IV cancer. He was told there was no cure. Two months later, Tom was being prepped for emergency surgery. One of our classmates was Tom's anesthesiologist for the surgery! Neither of them had any idea their paths would cross on that day. When the pre-op curtain was pulled back, our classmate was totally surprised to find Tom on the stretcher. Thankfully, the surgery went well. Tom arrived safely in the PACU, wondering when the procedure would start.

Anesthesia is amazing, but, sadly, it does not cure cancer. Tom failed multiple rounds of chemo, and all options for treatment were exhausted.

Out of necessity, we moved the reunion up because 10 years was no longer an option. The week of the reunion, Tom was moved to in-patient hospice.

We gathered at his bedside.
His breathing was slow and shallow; we knew it would not be long.
We held hands.
There were tears.

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We shared a prayer that was not exactly a prayer: "If we never see each other again, it doesn't matter, because you are in our hearts already, and that's forever."

Nothing can prepare you for medical training. Regardless of the specialty, it is a sacrifice. We were fortunate; our residency class was unusually close during our training years. We often ran to help each other in the OR. Outside the OR, we shared monthly themed parties, weekend study groups, dinners out, and spring break trips. Just like siblings, we had disagreements, but if there was a trauma in OR 9, everyone showed up. I am so thankful for those years. I wish, somehow, we could go back to the day before he was diagnosed.

Tom's wife called 3 hours after we had left hospice to let me know Tom had died. We exchanged the usual sentiments you say when someone dies, which is to say, almost nothing at all. But as we hung up she sweetly added, Tom wouldn't have missed our reunion for the world!

Burnout in Anesthesiologists: Comment

To the Editor:

I read with great interest Afonso *et al.*'s[1] article on burnout rates and risk factors among anesthesiologists. I am very concerned that the entry of private equity firms and the resultant need to compete with these firms have increased the focus on profit (= revenue – costs).[2]

Private equity firms are not organized for long-term consistent growth but are, by definition, looking for short-term growth. These short-term goals may allow for leadership to tolerate staffing shortages, resulting in longer work hours and high productivity pressures as well as failing to support the local anesthesiologist in the clinical setting. All these are high-risk factors identified by Afonso *et al.*[1] for burnout and burnout syndrome. But from a short-term perspective, clinician burnout is a long-term issue!

Unfortunately, this issue for anesthesiologists is not new but has been accelerated by the entry of private equity firms as well as national anesthesiology staffing companies. Many hospital administrators are also under short-term financial incentives and are looking to reduce costs in any possible way. The willingness of some national staffing companies to provide anesthesia care in less costly ways has led to similar situations of staffing shortages and productivity pressures.

As one may have noted, none of these short-term goals has included maintaining, let alone improving, quality of care. It is impossible to study quality of care and patient safety in rigorous scientific methods when short-term plans lead to a change in clinician composition, removal of physician-led care,[3] a lack of local support, and staff attrition; therefore, we are left with anecdotal evidence.

But a lack of scientific evidence[4] is not a reason to ignore the impact of short-term financial goals on our patients and our clinicians.

Competing Interests

The author declares no competing interests.

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Burnout in Anesthesiologists: Reply

In Reply:

We appreciate Dr. Abouleish's[1] interest in our study[2] of burnout in U.S. anesthesiologists; this response highlights the need to address well-being from a systems and policy standpoint. We recognize the need for physicians, and all clinicians, to be in an environment that allows them to provide the high level of quality care that they have trained for. Unfortunately, intervening factors can impede their ability to do so. Organizational decisions are often made without the input of those delivering the care and ask of them to provide care in a manner inconsistent with the values of the clinical teams on the front lines.

We are encouraged by anesthesiologists like Dr. Abouleish who bring an informed healthcare economic perspective to the table to challenge solutions. Staffing shortages are an independent risk factor for both being at high risk for burnout and full burnout syndrome in U.S. attending anesthesiologists,[2] and there is ample evidence that investing in

clinician well-being can yield strong return on investment.[3] Additionally, as the COVID-19 pandemic has tested the resilience of the anesthesiology workforce and challenged both organization and clinician financial solvency, we need to take steps forward to identify those at high risk and prevent the serious ramifications of clinician burnout.

Fiscal solvency and clinician well-being are not mutually exclusive. But to attain both, practicing clinicians need a louder voice at the table.

Competing Interests

The authors declare no competing interests.

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Availability of Inpatient Pediatric Surgery: Comment

To the Editor:

On behalf of the American College of Surgeons (Chicago, Illinois) Children's Surgery Verification program, we wish to clarify some of the statements in the article by McManus and França[1] entitled "Availability of Inpatient Pediatric Surgery in the United States," and the accompanying editorial by Ambardekar and Schwartz.[2] Though we completely agree that there has been consolidation of pediatric surgery toward high-capability pediatric centers, we disagree with the statement that "the American College of Surgeons launched its Children's Surgery Verification Quality Improvement program to promote regionalization." Regionalization is defined as the "integrated organization of a healthcare system, wherein regional structures are responsible for providing and administrating health services in a specific region."[3] This was never the intent of the American College of Surgeons Children's Surgery Verification program. In contrast, the program strives to provide care in appropriate settings without the need for consolidation by developing standards not only for Level 1 but also for Level 2 and 3 centers and defining optimal pediatric surgical care within the scope of practice of the institution and providers. The clearly articulated vision of the American College of Surgeons Children's Surgery Verification is that "every child in need of surgical care in North America today will receive this care in an environment with resources optimal for his/her individual need." While there is some intrinsic correlation between patient volume and available resources, the American College of Surgeons Children's Surgery Verification program has focused on defining optimal resources and assuring that the right resources are available at the bedside at the time of a child's need. One of the lessons learned from the early years of the program has been that even premiere dedicated children's institutions have required change in order to meet the 24/7/365 expectation of having the right resources for infants and children at all times.

An essential component of a Level 1 American College of Surgeons Children's Surgery Verification–verified center is the engagement with all acute care facilities, designated centers, and nonspecialty hospitals within the referral area in the performance improvement process.[4] As part of the verification process, Level 1 centers must show that they provide leadership in education, research, and system planning and the provision of technical assistance and education to regional hospitals and providers for the purpose of improving system performance. As a part of this, investigators have recently begun the process of defining low-risk pediatric surgical procedures to determine when surgery can be safely provided closer to home or by adult practitioners. This is illustrated by a recent study from Lawrence *et al.* demonstrating better outcomes after pediatric laparoscopic cholecystectomy with higher hospital or surgeon laparoscopic cholecystectomy volume rather than surgeon pediatric subspecialization.[5]

We agree with the concern that "overconsolidation of services could produce access barriers and other unintended consequences," especially in rural areas of the country. We contend that the best way to optimize children's surgical care is to provide a team approach that emphasizes system building by forging alliances with other surgical specialties (including anesthesiology), pediatrician and family practice colleagues, and administrative entities that can provide the essential infrastructure in rural hospitals that care for children.[6] System building is a relatively new concept, different from regionalization, that has the potential to optimize pediatric surgical care even in the face of uncontrolled consolidation.

Competing Interests

Dr. Oldham is the Chair and Drs. Houck, Barnhart, Deshpande, and Fallat are members of the American College of Surgeons Children's Surgery Verification Committee, Chicago, Illinois.

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The corresponding author of the original article referenced above has read the letter and does not have anything to add in a published reply.

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Obesity and Positive End-expiratory Pressure: Comment

To the Editor:

We read with great interest the recent article by Simon *et al*.[1] In this study, the authors have shown that individualized positive end-expiratory pressure (PEEP) exerts lower driving pressure.[1] This in turn proved the redistribution of ventilation toward dependent lung areas, as measured by electrical impedance tomography. These sound results imply great notions regarding intraoperative respiratory management. However, we highlight four concerns regarding the methodology used.

First, the study combined data from a multicenter[2] and a single-center trial. This was likely to cause selection bias. The inclusion periods were separated at 4-yr intervals. The authors divided the combined cohort into three treatment groups: individualized PEEP, fixed low PEEP, and fixed PEEP of 12 cm H_2O. The differences in the patient characteristics were unclear. The Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) score greater than 44 was noted in one patient (4%) in the individual PEEP group, which is less in comparison with the other two groups. We would like to know whether preoperative pulmonary function (forced expiratory volume in 1 s/forced vital capacity), oxygenation, and partial pressure of carbon dioxide differed among the groups. We question this because capnoperitoneum time and duration of an operation are basic information for considering postoperative pulmonary complications. To us, it seems that these might have influenced the results.

Second, the results clearly demonstrated that the individualized PEEP group needed larger amounts of fluid infusion and doses of vasoactive medication than the other two groups. There was no doubt as to whether these discrepancies were related to pulmonary management

strategy. We question how intraoperative infusion management strategies differed between the period of the single-center study (2012 to 2013) and the multicenter study (2016 to 2018). Additionally, preoperative oral intake or dose of hypertensive drugs may have differed in the 4-yr interval.

Third, the complications related to individualized PEEP cannot be studied in totality. Hemodynamic depression attributable to excessive PEEP may be a risk factor for patients with cardiovascular diseases. In this study, the transpulmonary pressure was not measured, which could have been used as an alternative parameter for lung injury. It is known that intracranial pressure or perfusion in the brain is largely influenced by PEEP.[3]

Finally, the definition of postoperative pulmonary complications described by the authors was not relevant to the process of early recovery after surgery. The postoperative complications earlier included acute respiratory distress syndrome, bronchospasm, new pulmonary infiltrates, and so on[2]. In our opinion, setting a clinically relevant outcome could be as simple as the need for oxygen therapy, including a low-flow nasal cannula. This approach would resemble ventilator-associated event surveillance for intubated mechanically ventilated patients and in turn support studies for ventilator-associated pneumonia.[4] We wish to know how the length of oxygen therapy differed among the groups after surgery. Additionally, we would like to have information on new relevant criteria that matches the early recovery after surgery concept.

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Competing Interests

The authors declare no competing interests.

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Obesity and Positive End-expiratory Pressure: Reply

In Reply:

We thank Suzuki *et al.*[1] for their interest in our recent work[2] and would like to address their concerns. The challenge of combining patients of different study protocols spanning several years is a potential bias we noted ourselves.[2] However, the single-center setting means that investigators and surgeons remained the same and the highly elective patients for bariatric surgery only were treated according to clinical standards which remained unchanged during the time. It seems unlikely that positive end-expiratory pressure (PEEP)–dependent physiologic effects were influenced by any minor change over time. Moreover, randomization guarantees that differences within each study are the result of chance alone, and the difference in ARISCAT (Assess Respiratory rIsk in Surgical patients in CATalonia) scores between the groups are both clearly presented and not in the least indicative of a meaningful imbalance in our opinion. In line with our clinical pathway for bariatric surgery and current anesthesia guidelines, lung function measurements were not performed before surgery.[3] Patients with pulmonary disease, cardiac insufficiency, or increased intracranial pressure were not included in either study.

Indeed, duration of anesthesia and the operation differed significantly between groups. However, the individualized

PEEP group was the one with the greatest duration but also the group with the best intraoperative lung mechanics and the highest oxygenation. Thus, even if the time of mechanical ventilation and capnoperitoneum time influenced our results, this emphasizes even more the necessity of an individual ventilation strategy.

As correctly noted by Suzuki *et al.*,[1] the intraoperative amount of fluid applied was higher in the individualized PEEP group. This arises from a coloading performed by the attending anesthesiologist during the recruitment maneuvers to intercept a drop in blood pressure and from PEEP titration, which increased the duration of anesthesia and thus the time during which the patient was administered fluids. Despite the measured differences in the groups, in all groups it is intraoperative restrictive fluid management.[4] Applying more restrictive fluid infusion targets might further increase vasopressor requirements in obese patients, especially when using high PEEP, and this potential risk must be balanced with potential benefits of minimizing intraoperative atelectasis with higher PEEP.[5] However, only patients scheduled for bariatric surgery were included in the studies in our center, where perioperative procedures (including preoperative oral intake) are highly standardized following the early recovery after surgery concept for bariatric surgery.[3] The protocol was not changed during the study period without any systematic change in preoperative hydration or in dose of hypertensive drugs in the 4-yr interval in question.

Higher PEEP values may lead to cardiovascular instability as a result of impaired venous return, which was reflected in our study by the highest cumulative noradrenaline doses in the individualized PEEP group. However, mean arterial blood pressure did not differ between groups and overall norepinephrine doses were low, so we do not consider this to be a relevant issue in most patients. Excessive PEEP values should, however, be avoided in patients with significant right heart failure, and such patients were excluded in our study. Predefined rescue protocols were available if a PEEP level was not tolerated,[5,6] but none of our patients needed such a rescue protocol. Concerning the influence of PEEP on brain perfusion and intracranial pressure (ICP), an increase in thoracic pressure is partially transmitted to central venous pressure (CVP) and may thus increase venous downstream pressure of the brain. According to the vascular waterfall model of compressible tubes, cerebral venous outflow is only impaired if CVP is greater than ICP. Clinical data have shown that for patients with decreased chest wall compliance, as with our obese patients, higher PEEP had no effect on cerebral hemodynamics.[7]

Transpulmonary pressure was not included in the endpoints of the two original studies because its use as a correlate of lung stress has known limitations.[8] Although electrical impedance tomography enables detection of regional information on overdistension and collapse, regional variations in lung expansion may not be adequately reflected by local pressure measurements in the esophagus. As noted in our article, in the context of predefined low tidal volume, information on regional heterogeneity might be more relevant to identify regions of increased stress as a substrate for postoperative pulmonary complications.

Suzuki and colleagues correctly note that postoperative outcomes differed from those of the original PROBESE (Effect of High PEEP *vs.* Low PEEP on Postoperative Pulmonary Complications in Obese Patients) study. In contrast to the PROBESE-study, our subanalysis was neither intended nor adequately powered to investigate postoperative pulmonary outcomes associated with an individualized ventilation strategy. The early recovery after surgery guidelines discussed the use of adequate PEEP with recruitment maneuvers to reduce postoperative pulmonary complications.[3] Atelectasis plays a significant role in obese patients and should be avoided with regard to ventilator associated complications,[9] The aim of the subanalysis was to investigate the effects of individualized PEEP on ventilation distribution and atlectasis formation with implications for lung function. Because there were no clear instructions when to stop oxygen therapy in the postanesthesia care unit in the single-center study, the duration of oxygen therapy would not be an adequate endpoint. Furthermore, to be able to better classify the results, the endpoints were based on previously published studies on individual ventilation, including one of the two studies included here.[5,10]

We highly appreciate the interest in our work and agree with Suzuki *et al.* that further research is necessary to determine whether the benefits of an individualized ventilation strategy lead to a lower incidence of postoperative pulmonary complications.

Competing Interests

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Evidence Supporting Anesthesiology Guidelines: Comment

To the Editor:

We have read with great interest the article by Laserna *et al.*,[1] "Levels of Evidence Supporting the North American and European Perioperative Care Guidelines for Anesthesiologists between 2010 and 2020: A Systematic Review," in the most recent issue of Anesthesiology. Without a doubt, this is an issue of great importance, and it is imperative to take actions against this problem. On the other hand, it is worth mentioning that this is not a new problem. In 1994 Altman[2] mentioned the existence of low-quality medical research in his article "The Scandal of Poor Medical Research," and a more recent article by Van Calster *et al.*,[3] "Methodology over Metrics: Current Scientific Standards Are a Disservice to Patients and Society," also takes up this issue, arguing that the main problem is a paradox: "The methodology, the backbone of science, is still too trivialized by the scientific community that finances, undertakes, and informs (pre) clinical research." Although the methodologic approach is important for the resolution of this problem, we do not believe that it is the only one.

In our opinion, a training approach should be emphasized with three points that should be considered:

1. Stop training "doctors" and focus on training "scientists": One of the most basic characteristics of science is

that scientists assume that the universe we live in follows predictable rules. Scientists theorize using a variety of different reasoning to make new discoveries:

a) Inductive: observe a series of events and try to discover a rule that governs the event to extrapolate it and formulate theories of observed and yet to be observed phenomena.
b) Abductive: when seeking to propose explanations for events such as unexpected findings.
c) Deductive: processes that correspond to the conditions in which a hypothesis can lead to a conclusion or is deductible to it (deductive logic).[4]

2. Introduce students to basic science areas: Basic science helps researchers understand systems processes of life. Today more than ever, clinicians need the skills to assess the quality and relevance of the content they are adding to their expanding database of medical knowledge. Therefore, the emphasis of medical education should be on acquiring, interpreting, and applying new knowledge in real scenarios rather than memorizing old (and rapidly obsolete) knowledge; yet, despite the explosion of scientific knowledge in these areas, time spent on teaching basic sciences has been shrinking rather than expanding. Maybe it is time to seriously consider sending students to basic science laboratories. We must recognize that the process of acquiring knowledge is as important, if not more, as the actual knowledge acquired.[5]
3. Statistics is also important: Statistical hypothesis testing, although considered a cornerstone in many research areas, has great limitations (such tests are asymmetric—they cannot produce evidence in favor of the null hypothesis, only evidence against it). Further, there are detractors with compelling arguments, such as: "statistical hypothesis testing is widely used but logically indefensible"[6] or "all age findings of statistical significance are wrong and should be redone."[7] Statistical hypothesis testing has survived and has grown in the face of criticism because it meets an important need, yet even if some standard is necessary, it is reasonable to ask whether these tests provide the best standard for medical research. Several alternatives to this problem have been proposed, but two are particularly popular, both of which are "penalized probability criteria": Akaike's information criterion and Bayesian information criterion.[8]

Conclusion

Although the methodology approach is important in solving this problem, it is not the only one, and it requires a multidisciplinary effort—methodology, statistics, teaching, and basic sciences—with the sole objective of changing the way in which the next generations perceive scientific research in medical areas, thus improving the quality of knowledge creation.

Competing Interests

The authors declare no competing interests.

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The corresponding author of the original article referenced above has read the letter and does not have anything to add in a published reply.

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Extra Life: A Short History of Living Longer

By Stephen Johnson. New York, Riverhead Books, 2021. Pages: 320. Price: $20.49 (Hardcover), $14.99 (Digital).

Ever wonder how long you will live? We all query this at some point in our lives. Stephen Johnson (1968–present; "author of … books on the intersection of science, technology, and personal experience"[1]) asked and answered this question in *Extra Life: A Short History of Living Longer*.[2] Recognizing that life expectancy has dramatically increased over the past century, Johnson notes that humankind has accrued "twenty thousand extra days of life on average."[2] *Extra Life* considers what accounts for this extension to our existence.

Johnson catalogues factors that have increased longevity, including anesthesia, on his list of innovations that have saved millions of lives. He offers an intriguing narrative of how medical and nonmedical people took step-by-step actions that connected the dots of information to enable breakthroughs in science, human health and welfare. He describes a lesson: multidisciplinary networking has great benefit in scientific inquiry.

Julius Comroe, M.D. (1911 to 1984; physician researcher) taught this lesson in *Exploring the Heart*.[3] Scientific breakthroughs, he noted, are not brought about by one individual taking one giant leap from ground level to the mountain top; rather, small treks up the mountainside by a multitude are necessary to ultimately reach the pinnacle.

Johnson subscribes to this notion (*i.e.*, a process of connecting the scientific dots to achieve medical breakthroughs). *Extra Life* provides a list of innovations that have increased life expectancy and saved lives: hundreds of millions saved by antibiotics and pasteurization of milk; billions by toilets, sewers, and vaccines. Like Comroe, Johnson notes: "developments represent the culmination of decades, if not centuries of work, conducted by hundreds of persons, complete with false starts, wild claims, and bitter rivalries. The breakthrough is really the latest in a series of small incremental advances, perhaps the one that has finally reached clinical relevance."[2] This sounds very compatible with our Journal's mission: "Anesthesiology endeavors to be the vanguard of trusted evidence that moves the field forward, informs new discoveries, and improves practice."[4]

Johnson tells stories of connecting the dots. Individuals asked questions, gathered data, and linked their facts to the work of others, resulting in major medical practice breakthroughs. Each chapter has lessons for clinical and research anesthesiologists.

The chapter on infant mortality describes Lady Mary Montagu (1689 to 1762; English aristocrat) and Edward Jenner, M.D. (1749 to 1823; physician and immunologist), recognizing the value of vaccination to eradicate smallpox, a major factor in infant mortality.

In the chapter focused on the value of clean water, Johnson points out the importance of: (1) data collection and epidemiology employed by John Snow (1813 to 1858; physician anesthesiologist and medical epidemiologist) that resulted in the removal of the handle of the London water pump implicated in a cholera outbreak; (2) recognition of the negative impact of industrialization on life expectancy by William Farr, M.D. (1807 to 1883; British epidemiologist and medical statistician), whose work contributed to the founding of the Centers for Disease Control and Prevention; and (3) analysis of racial disparities in human health by W. E. B. DuBois (1868 to 1963; sociologist and civil rights activist).

A chapter considers pasteurization and chlorination, explaining how Frank Leslie (1821 to 1880; pen name of Henry Carter, a journalist, author of an exposé on milk as a "liquid poison") and Louis Pasteur (1822 to 1895; a microbiologist and chemist) guided us to eliminate the transmission of the tuberculosis to human beings by processing and refrigerating milk.

The chapter on regulation of medications, ultimately through the creation of the U.S. Food and Drug Administration in 1953, explains how the persistent inquiry about the safety of thalidomide by Frances Oldham Kelsey (1914 to 2015; pharmacologist, physician, and Food and Drug Administration reviewer) was an essential ingredient in the development of our modern-day evidence-based study technique, the randomized, controlled, double-blind trial.

A chapter recounts the story of the discovery of penicillin that presaged development of our vast array of antibiotics, when Alexander Fleming (1881 to 1955; physician microbiologist) observed "the mold that changed the world."[2]

The chapter on automobile and industrial safety focuses on accidental death by machines. It was Nils Bohlin (1920 to 2002; Swedish mechanical engineer) who designed the seat belt for Volvo. The company released the design to the world as an open patent that enabled effective sharing of the discovery that has saved countless lives.

The final chapter describes the multiple settings in which reversing the world's pockets of famine has extended longevity.

Extra Life is a fascinating read about things we don't know and endeavor to understand. As was so aptly stated

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by Donald Rumsfeld (1932 to 2021; U.S. Secretary of Defense, 1975 to 1977 and 2001 to 2006), "there are known knowns … there are known unknowns … there are also unknown unknowns—the ones we don't know we don't know … it is the latter category that tends to be the difficult ones."[5] Physicians (*i.e.*, anesthesiologists), be they clinicians or researchers, strive to understand all of the unknowns to provide the most effective and safe care of patients. *Extra Life* is a fascinating narrative about many individuals who pondered and solved known and unknown unknowns and how their successes have extended life expectancy. Anesthesiologists will benefit from reading *Extra Life* to appreciate how one can connect the scientific dots discovered by others and contribute to the breakthroughs that benefit humankind.

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Empire of Pain: The Secret History of the Sackler Dynasty

By Patrick Radden Keefe. New York, Doubleday, 2021. Pages: 560. Price: $19.50 (Paperback), $28.63 (Hardcover), $15.99 (E-book).

John Bonica (1917–1994) was not the first person to think that anesthetic techniques and drugs could be used to help people with chronic pain. But he was a larger-than-life character with a larger-than-life vision, and because of where his vision led us, he is considered to be the founding father of pain medicine. His belief, shared by many pioneers of the field of pain medicine, was that the combined forces of researchers and clinicians from a wide range of disciplines could make significant headway in reducing people's pain. The immediate effect was a growth in multidisciplinary pain clinics, a recognition of the value of psychologists in the management of chronic pain, an international consolidation of pain research, and the inception of pain-focused professional groups and societies. Yet, chronic pain and its treatment are larger problems today than they were in Bonica's time, and an opioid crisis in the United States has been blamed in part on the overreach of pain specialists. Bonica worked with the World Health Organization to encourage global availability of opioids for the treatment of cancer pain, which in his time tended to be a rapidly fatal disease that caused a huge amount of suffering at the end of life. But he and other pioneers never considered opioids to be suitable treatment for chronic pain. In fact, in Bonica's own multidisciplinary pain program at the University of Washington in Seattle, patients were weaned from opioids in recognition that it was difficult to make headway with chronic pain if people were taking opioids. What changed all that was greed.

In his book *Empire of Pain*, Patrick Radden Keefe exposes the incredible greed and hubris of a single family—the Sacklers. Their name is known all over the world because of their philanthropic support of the arts. There were Sackler galleries in London, Paris, New York, Washington, D.C., and Boston, but many institutions now are rejecting the name. But the Sackler family was always careful to shield itself from public recognition of the source of its billions—Purdue Pharma and its drug OxyContin. Unlike many other philanthropists who delight in having the name of their company preserved in perpetuity on the portals of buildings, the Sacklers shielded themselves from the name Purdue Pharma. It was as if, despite their protestations, they knew that there was something shameful about their business. And there was. Turning to what has become a huge resource of exposed secret documents from the multitude of lawsuits against Purdue Pharma, Keefe has woven new evidence of Sackler deceit into a rip-roaring and highly readable tale of how one family managed to turn the heads of a whole medical community. It all started with the older brother, Arthur, who became a pioneer of pharmaceutical advertising. Arthur saw medical advertising as a seduction of both physicians and patients, and so successful were his methods that they were at once considered a triumph for the industry and a scourge for society. OxyContin was not launched until after Arthur's death, but he had taught his two younger brothers, Mortimer and Raymond, the art of persuasion. It was their methods, probably above all else, that made OxyContin such a successful drug. They pervaded doctors' offices, regulatory bodies, the U.S. Food and Drug Administration, pain professional societies, The Joint Commission (health facility quality assurance in the United States), postgraduate education, national and international pain meetings, and patient groups. They broke down the restraint in opioid prescribing that had existed for decades because of previous opioid epidemics. The Sacklers presented themselves as owners in name only, but it turns out that their involvement was distinctly hands-on. They and the company's executives were given early evidence that their drug was leaking into the community and causing problems, information they concealed and failed to act upon, while continuing to insist that it was bad people who were the problem, and not their drug, which would "rarely cause addiction if used to treat pain." Years went by, and the societal problem caused by their drug grew into a problem that is now very difficult to reverse. To make matters worse, other companies were so taken with the success of OxyContin, that they followed suit with their own opioid products and promoted them using Purdue Pharma's playbook.

The Sacklers were not the only people who profited from pain. People are willing to pay a great deal of money for the hope of pain relief. Countless profitable ventures have grown out of Bonica's idea that medicine had the means to reduce pain, many of which deceive in their own right. But none has done as much harm to the ideals of Bonica and the early pioneers of pain medicine as the opioid debacle. The pioneers' efforts were not about profiting from pain. They did not promote opioid treatment of chronic pain. They recognized that complex chronic pain could not be successfully treated with a single modality, and that a multidisciplinary approach with psychologists at the helm was the only approach that could help the most refractory cases. How that ideal became corrupted is the story of Keefe's book. For

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anyone, including the present authors, who have watched while our chosen field became tarnished by money, it should be obligatory reading. And whether as an exercise in self-reflection, a revelation of what was hidden behind the world we have labored within, or a thoroughly good read, it is a page-turner that you will be glad to have picked up.

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Prediction Score for Postoperative Neurologic Complications after Brain Tumor Craniotomy: A Multicenter Observational Study: Erratum

In the article beginning on page 1111 in the December 2018 issue, readers are directed in Supplemental Digital Content 5 (http://links.lww.com/ALN/B779) to see the CranioScore formula and examples of the CranioScore value calculation for two simulated patients. However, both the formula and the examples table contained errors.

The original formula was incorrect and incomplete. It has been corrected to specify the if/else criteria for each dichotomous variable and the units for each parameter and to include the formula for converting the CranioScore model result into the CranioScore value. The complete, corrected formula appears below.

> CranioScore model (CS) = -4.8094 + (1.5149 * [1 if Pre-operative Glasgow Coma Score ≤ 14, else 0]) + (1.0534 * [1 if History of brain tumour neurosurgery YES, else 0]) + (0.00878 * Greatest size of tumour, in mm) + (0.5114 * [1 if Mid-line shift ≥ 3mm, else 0) + (0.5164 * [1 if Transfusion of packed red blood cells and/or plasma and/or platelets YES, else 0]) + (0.0118 * Maximum operative Systolic Arterial Pressure, in mmHg) – (0.0130 * Minimum operative Systolic Arterial Pressure, in mmHg) + (0.2981 * Duration of surgery, in hours)

$$\textit{Cranio Score value}\,(\%) = \frac{e^{CS}}{1+e^{CS}} \times 100$$

In the simulated patients table, the first parameter has been corrected to read "Preoperative Glasgow Coma Score ≤ 14" rather than "Preoperative Glasgow Coma Score =15," and the value for Simulated Patient No. 1 has been changed from "Yes" to "No" accordingly. Additionally, units have been added parenthetically for the four nondichotomous parameters. The "Duration of surgery" parameter was originally given in minutes but has been corrected to be given in hours; consequently, the value for Simulated Patient No. 1 has been corrected from 110 to 1.8, and that for Simulated Patient No. 2 from 118 to 2.0. Last, the final CranioScore value (%) for Simulated Patient No. 2 has been corrected from 8.9 to 31.0%. The corrected table appears below.

Table 1. Example of the CranioScore Value with Two Simulated Patients

	Simulated Patient No. 1	Simulated Patient No. 2
Preoperative Glasgow Coma Score ≤ 14	No	Yes
History of brain tumour surgery	No	Yes
Greater size of brain tumour at imaging (mm)	23	30
Mid-line shift in cerebral imaging ≥ 3mm	No	No
Transfusion of blood product during surgery (red blood cell/platelet/plasma)	No	No
Maximum of Systolic Arterial Pressure during surgery (mmHg)	123	146
Minimum of Systolic Arterial Pressure during surgery (mmHg)	75	87
Duration of surgery (hours)	1.8	2.0
Value of the CranioScore (%)	2.7%	31.0%
	Low risk patient	High risk patient

The authors regret these errors. The online version of the Supplemental Digital Content has been corrected and replaced.

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Reference

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