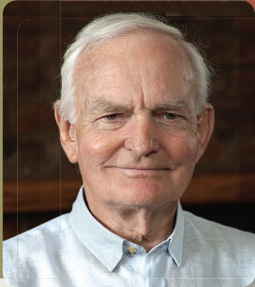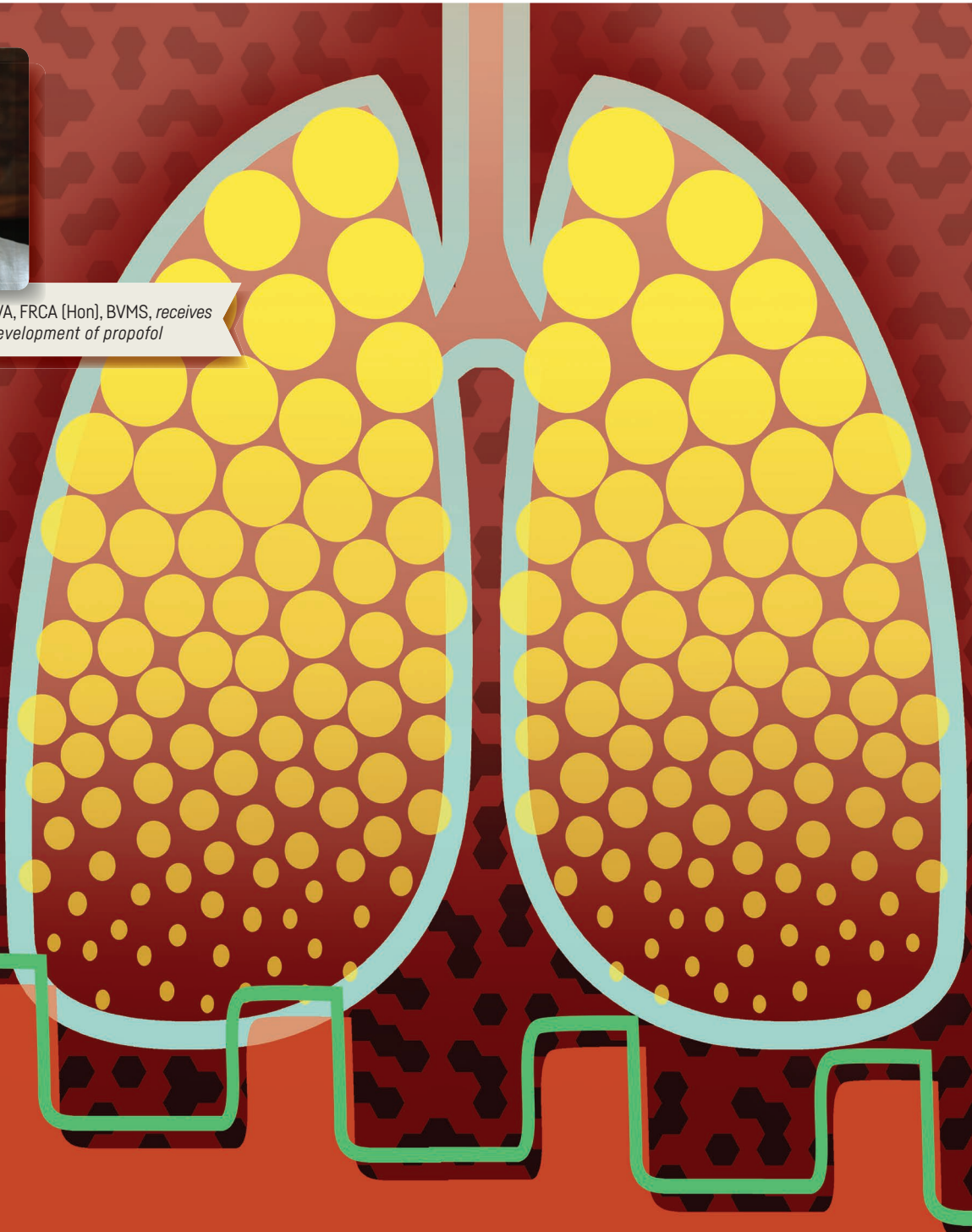# ANESTHESIOLOGY

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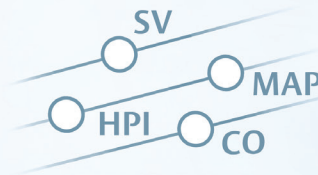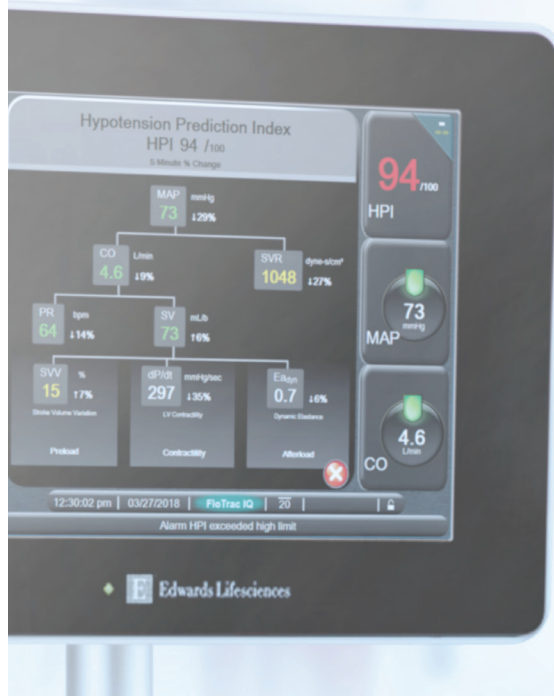**The Journal of the American Society of Anesthesiologists, Inc. • anesthesiology.org**

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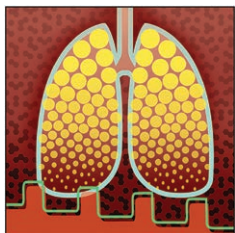
1070 Individual Positive End-expiratory Pressure Settings Optimize Intraoperative Mechanical Ventilation and Reduce Postoperative Atelectasis

While the protective role of more physiological tidal volume has been strongly suggested, there is no agreement on the value of optimal positive end-expiratory pressure. One fixed value of positive end-expiratory pressure is unlikely to fit all patients. The hypothesis that the optimized positive end-expiratory pressure guided by electrical impedance tomography would vary among different patients and that it would reduce postoperative atelectasis was tested in a randomized controlled trial of 40 patients undergoing elective abdominal surgery. Patients were randomized to have positive end-expiratory pressure titrated by electrical impedance tomography or a fixed positive end-expiratory pressure of 4 cm H_2O. The individually adjusted positive end-expiratory pressure, providing the optimum compromise between lung collapse and hyperdistention, ranged from 6 to 16 cm H_2O. Optimal positive end-expiratory pressure not only reduced driving pressure and improved compliance intraoperatively compared to a fixed positive end-expiratory pressure of 4 cm H_2O, but also reduced atelectasis in the postoperative period. *See the accompanying Editorial View on **page 1057.** (Summary: M. J. Avram. Illustration: A. Johnson, Vivo Visuals.)*

1132 Ultrasound Is Superior to Palpation in Identifying the Cricothyroid Membrane in Subjects with Poorly Defined Neck Landmarks: A Randomized Clinical Trial

The success of a cricothyrotomy depends on accurate localization of the cricothyroid membrane, which can be challenging when the conventional approach of external palpation is used. The hypothesis that ultrasound is more accurate in identifying the cricothyroid membrane than external palpation was tested in a randomized single-blinded study of 223 patients with poorly defined neck landmarks. Accurate identification of the cricothyroid membrane was defined as identification of a localization point within 5 mm of a point identified by a computed tomography image of the neck. Ultrasound correctly identified the cricothyroid membrane in 92 of 114 (81%) patients but external palpation made a correct identification in only 9 of 109 (8%) patients. The mean ± SD distance from the ultrasound point to the computed tomography point was 3.4 ± 3.3 mm, while that from the external palpation point to the computed tomography point was 16.6 ± 7.5 mm. *(Summary: M. J. Avram. Image: J. P. Rathmell.)*

1082 Patient Blood Management Program Improves Blood Use and Clinical Outcomes in Orthopedic Surgery

Recent American Association of Blood Banks (AABB)-endorsed transfusion guidelines recommend a hemoglobin trigger of 8 g/dl for orthopedic surgery patients, but a hemoglobin trigger of 7 g/dl for critically ill hospitalized patients. The hypothesis that after implementation of a patient blood management program encouraging a hemoglobin transfusion threshold of less than 7 g/dl, orthopedic patients would receive less allogeneic blood transfusions without an increase in adverse outcomes was tested in a retrospective analysis of 1,507 patients in the pre-blood management cohort and 2,402 patients in the post-blood management cohort. Between the pre- and post-blood management time periods the mean hemoglobin transfusion trigger decreased from 7.8 ± 1.0 (mean ± SD) to 6.8 ± 1.0 g/dl. The percentage of patients transfused red blood cells decreased from 16.1% to 9.4% and there was a 32.5% decrease in the number of red blood cell units per 1,000 patients. The composite outcome of any morbidity or mortality decreased by half. *See the accompanying Editorial View on **page 1060.** (Summary: M. J. Avram. Image: ©ThinkStock.)*

1149 Morbidity and Mortality of Crystalloids Compared to Colloids in Critically Ill Surgical Patients: A Subgroup Analysis of a Randomized Trial

The hypothesis that administration of colloids for fluid resuscitation alters 28-day mortality compared with administration of crystalloids was tested in critically ill surgical patients in an *a priori* defined secondary analysis of a large pragmatic trial comparing the administration of crystalloids and colloids in a general population of critically ill patients. Eligible patients required fluid resuscitation for acute hypovolemia and were randomly allocated to fluid resuscitation with products belonging to a broad family of fluids, either crystalloids or colloids; 356 patients were allocated to the crystalloids arm and 385 were allocated to the colloids arm. There was no difference between groups in the occurrence of death by day 28; 84 (23.6%) patients died in the crystalloids arm while 100 (26%) died in the colloids arm (adjusted odds ratio 0.86 [95% CI, 0.61 to 1.21]). *(Summary: M. J. Avram. Image: J. P. Rathmell.)*
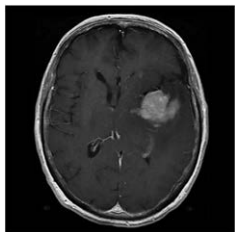
1111 Prediction Score for Postoperative Neurologic Complications after Brain Tumor Craniotomy: A Multicenter Observational Study

The primary objective of this study was to develop and validate a score that could predict severe postoperative neurosurgical complications in the first 24 h in the intensive care unit after elective brain tumor neurosurgery in order to improve intensive care unit triage and safely discharge patients to wards. The learning cohort consisted of 1,094 patients undergoing craniotomy for a brain tumor in one center between 2008 and 2012, 125 (11.4%) of whom presented with early postoperative neurosurgical complications. Eight factors were selected for the multivariable model, including Glasgow Coma Scale score before surgery ≤ 14, history of brain tumor surgery, greatest brain tumor diameter, and midline shift ≥ 3 mm. The prediction score based on these factors provided a probability of postoperative neurosurgical complications for each patient, expressed as a percentage. In the learning cohort, a 3% threshold had a sensitivity of 100%, a specificity of 6.2%, a positive predictive value of 12.1%, and a negative predictive value of 100%. *(Summary: M. J. Avram. Image: J. P. Rathmell.)*

1121 Hospital-, Anesthesiologist-, and Patient-level Variation in Primary Anesthesia Type for Hip Fracture Surgery: A Population-based Cross-sectional Analysis

There is substantial variation in the primary anesthesia type used for hip fracture surgery. A population-based cross-sectional analysis of 107,317 hip fracture surgery patients admitted to 80 different hospitals on a nonelective basis from 2002 to 2014 was conducted to determine the extent of practice variation in choice of anesthesia type attributable to hospital-, anesthesiologist-, and patient-level factors. Neuraxial anesthesia without concurrent general anesthesia was used in 57,080 (53.2%) patients. Patient factors accounted for 60.1% of the variation in neuraxial anesthesia use while 20.0% of the variation was attributable to the hospital level and 19.9% was attributable to the anesthesiologist. The median odds of a given patient receiving neuraxial anesthesia varied by more than 2.3-fold between any two randomly selected hospitals or anesthesiologists, independent of baseline patient illness, sociodemographic characteristics, or other factors that were postulated to influence a patient's probability of receiving neuraxial anesthesia. *(Summary: M. J. Avram. Image: J. P. Rathmell.)*

1101 Early Resumption of β Blockers Is Associated with Decreased Atrial Fibrillation after Noncardiothoracic and Nonvascular Surgery: A Cohort Analysis

The incidence of postoperative atrial fibrillation was determined in β-blocker users who had noncardiac surgery between 2008 and 2016, stayed at least two postoperative nights, were still at risk of developing atrial fibrillation at the end of postoperative day 1, and did and did not restart β blockers by the end of postoperative day 1. The incidence of postoperative atrial fibrillation was 4.2% for 7,095 patients who had already restarted β blockers and 7.1% for 994 patients who had not. To control for observed potential confounding variables, each patient who restarted β blockers after the end of postoperative day 1 was matched to a maximum of two patients who restarted by the end of postoperative day 1 using exact and propensity score matching. Within the subset of matched patients, 4.9% of 1,924 retaking β blockers by the end of postoperative day 1 experienced postoperative atrial fibrillation, as did 7.0% of 973 retaking after postoperative day 1 (odds ratio 0.69, 95% CI 0.50 to 0.95). *(Summary: M. J. Avram. Image: J. P. Rathmell.)*
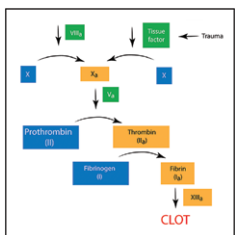
1171 Prothrombin Complex Concentrates for Perioperative Vitamin K Antagonist and Non–vitamin K Anticoagulant Reversal (Review Article)

Vitamin K antagonists, such as warfarin, are still widely used in patients with atrial fibrillation, venous thromboembolism, and mechanical heart valves. Because of the increased risk for bleeding associated with vitamin K antagonist therapy, current treatment guidelines recommend 4-factor prothrombin complex concentrates (containing coagulation factors II, VII, IX, and X), with concomitant intravenous vitamin K, as the preferred therapy for urgent vitamin K antagonist reversal in patients who require an emergency surgical procedure. Thirty-six articles published between 2008 and 2017 were reviewed to provide an update on the latest evidence for the use of prothrombin complex concentrates in patients requiring urgent vitamin K antagonist reversal for emergency surgery. The studies identified support current guideline recommendations. Prothrombin complex concentrates consistently and rapidly reduced patients' international normalized ratio, had greater clinical efficacy than plasma, and were associated with lower rates of fluid overload due to its lower infusion volume compared to plasma and no instances of viral transmission. *(Summary: M. J. Avram. Image: J. P. Rathmell.)*
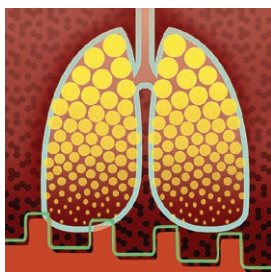
ANESTHESIOLOGY

ON THE COVER:

Intraoperative lung-protective ventilation can reduce postoperative pulmonary complications. The added protection of positive end-expiratory pressure (PEEP) remains uncertain. In this issue of ANESTHESIOLOGY, Pereira *et al*. demonstrate that PEEP requirements vary widely among patients. Individually-titrated PEEP during anesthesia reduces postoperative atelectasis while improving intraoperative oxygenation and driving pressures. In an accompanying Editorial View, Kacmarek and Villar discuss this new clinical trial in the context of previous trials evaluating the risks and benefits of using PEEP in the operating room.

● Pereira *et al*.: Individual Positive End-expiratory Pressure Settings Optimize Intraoperative Mechanical Ventilation and Reduce Postoperative Atelectasis, p. 1070

● Kacmarek and Villar: Lung-protective Ventilation in the Operating Room: Individualized Positive End-expiratory Pressure Is Needed! p. 1057

Quality of anesthesia care can be improved through measurement. We must take shared accountability for all surgical outcomes including cognitive recovery. We must move to listening to patient-oriented outcomes and satisfaction with our care.

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This Month's ANESTHESIOLOGY Journal-based CME Article

Read the article by Pereira *et al.* entitled "Individual Positive End-expiratory Pressure Settings Optimize Intraoperative Mechanical Ventilation and Reduce Postoperative Atelectasis" on page 1070, and the corresponding editorial by Kacmarek and Villar entitled "Lung-protective Ventilation in the Operating Room: Individualized Positive End-expiratory Pressure Is Needed!" on page 1057.

Learning Objectives

After successfully completing this activity, the learner will be able to describe the components of lung protective ventilation and their intended benefits; recognize potential effects of positive end-expiratory pressure (PEEP) application; and recognize the effects of PEEP in changing lung mechanics during open and laparoscopic procedures.

Disclosures

This journal article has been selected for and planned as a journal activity, which is designated for *AMA PRA Category 1 Credit.* The authors disclosed relationships in keeping with ANESTHESIOLOGY's requirements for all journal submissions. All relationships journal authors disclosed to ANESTHESIOLOGY are disclosed to learners, even those relationships that are not relevant financial relationships, per the ACCME's requirements for activities.

Editor-in-Chief: Evan D. Kharasch, M.D., Ph.D., has reported receiving consulting fees from TEN Healthcare.

CME Editors: Leslie C. Jameson, M.D., has reported no relevant financial relationships with commercial interests. Dan J. Kopacz, M.D., has reported holding an equity position with SoloDex, LLC.

Authors: Sérgio M. Pereira, M.D., Mauro R. Tucci, M.D., Ph.D., Caio C. A. Morais, P.T., M.Sc., Claudia M. Simões, M.D., Ph.D., Bruno F. F. Tonelotto, M.D., Michel S. Pompeo, M.D., Fernando U. Kay, M.D., Ph.D., Paolo Pelosi, M.D., F.E.R.S., Joaquim E. Vieira, M.D., Ph.D., Marcelo B. P. Amato, M.D., Ph.D., Robert M. Kacmarek, Ph.D., R.R.T., and Jesús Villar, M.D., Ph.D., have disclosed no relevant financial relationships with commercial interests.

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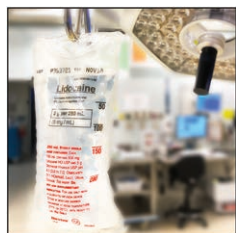
Perioperative lidocaine infusions for the prevention of chronic postsurgical pain: A systematic review and meta-analysis of efficacy and safety. Pain 2018; 159:1696–704.

Chronic postsurgical pain occurs in 12% of surgical populations and is a high priority for perioperative research. This systematic review synthesized the evidence linking lidocaine infusions and chronic postsurgical pain. The authors included trials that randomized adults without baseline pain to perioperative lidocaine infusion or placebo. The primary outcome was the presence of procedure-related pain at 3 months or longer after surgery. The authors included six trials with 5,420 patients from four countries. Perioperative lidocaine infusions significantly reduced the primary outcome (odds ratio, 0.29; 95% CI, 0.18 to 0.48). The difference in intensity of chronic postsurgical pain assessed by the short-form McGill Pain Questionnaire was not statistically significant (weighted mean difference, 21.55; 95% CI, 23.16 to 0.06). The authors identified trial design limitations and publication and other biases. Each study reported that no lidocaine-related adverse events occurred, but systematic safety surveillance strategies were absent. The authors concluded that current limited clinical trial data and biological plausibility support lidocaine infusions to prevent the development of chronic postsurgical pain without full assurances as to its safety. *(Article Selection: J. David Clark. Image: A. Pisansky.)*

Take home message: Limited clinical trial data support lidocaine infusions to prevent the development of chronic postsurgical pain but safety questions remain.
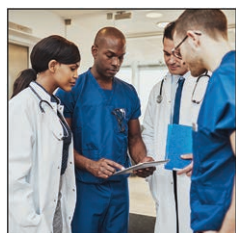
Ensuring equity, diversity, and inclusion in academic surgery: An American Surgical Association white paper. Ann Surg 2018; 268:403–7.

American Surgical Association leadership appointed a task force to address issues related to equity, diversity, and inclusion within academic surgery. Nine work groups reviewed the current literature, performed primary qualitative interviews, and distilled available guidelines and published primary source materials. The resulting handbook, Ensuring Equity, Diversity, and Inclusion in Academic Surgery, identifies challenges and develops a set of solutions and benchmarks to aid the academic surgical community in achieving diversity goals. The task force concluded that surgeons as a group must identify areas for improvement and work to correct past deficiencies. They note that this task requires the honest and ongoing identification and correction of implicit and explicit biases. Increasing diversity in surgical departments and residencies will improve patient care and enhance productivity. *(Article Selection: Beatrice Beck-Schimmer. Image: ©ThinkStock.)*

Take home message: Identification and correction of biases can lead to increased diversity, equity, and inclusion.

Assessment of the safety of discharging select patients directly home from the intensive care unit: A multicenter population-based cohort study. JAMA Intern Med 2018; 178:1390–9.

The safety of discharging adult patients recovering from critical illness directly home from the intensive care unit (ICU) is unknown. This retrospective population-based cohort study of adult ICU patients compared healthcare utilization and clinical outcomes for patients discharged directly home from the ICU with those of patients discharged home *via* the hospital ward. The primary outcome was readmission to the hospital within 30 days of hospital discharge. Of 6,732 patients included in the study, 922 (14%) were discharged directly home. In the 1,632-patient propensity score matched cohort, patients discharged directly home had median ICU stays of 3 days but significantly shorter length of hospital stay (median, 3.3 days *vs.* 9.2 days; *P* < 0.001). There were no significant differences between patients discharged directly home or home *via* the hospital ward for readmission to the hospital within 30 days of hospital discharge (10% [n = 81] *vs.* 11% [n = 92]; HR, 0.88; 95% CI, 0.64 to 1.20). The authors concluded that the common practice of discharging select adult patients directly home from the ICU is not associated with increased health care utilization or increased mortality. *(Article Selection: Martin J. London. Image: ©ThinkStock.)*

Take home message: Discharge of select patients directly to home from the ICU may not be associated with a higher risk of hospital readmission or mortality.

Effect of nitrous oxide as a treatment for subjective, idiopathic, nonpulsatile bothersome tinnitus: A randomized clinical trial. JAMA Otolaryngol Head Neck Surg 2018; 144:781–7.

Studies have suggested that *N*-methyl-D-aspartate receptor antagonists like nitrous oxide may help reduce tinnitus. This randomized, placebo-controlled crossover trial investigated whether nitrous oxide can reduce tinnitus. Adults with tinnitus of at least 6 months' duration (n = 40) were randomized to receive either placebo or nitrous oxide, then attend two interventional sessions at least 14 days apart. The sessions lasted for 40 min; the placebo session consisted of 50% nitrogen and 50% oxygen, and the treatment session consisted of 50% nitrous oxide and 50% oxygen. The authors assessed tinnitus before and after intervention, with the change in the Tinnitus Functional Index (TFI) as the primary outcome. The TFI after intervention was a mean (SD) of 1.8 (8.8) points lower in the placebo arm and a mean (SD) of 2.5 (11.0) points lower in the nitrous oxide arm. The within-participant mean difference in the change in the TFI of the placebo arm compared with the nitrous oxide arm was –1.1 points (95% CI, –5.6 to 3.4 points). The authors concluded that nitrous oxide was no more effective than placebo for the treatment of tinnitus. *(Article Selection: Deborah J. Culley. Image: J. P. Rathmell.)*

Take home message: Nitrous oxide appears to be ineffective for the treatment of tinnitus.

Six-month outcomes after restrictive or liberal transfusion for cardiac surgery. N Engl J Med 2018; 379:1224–33.

A previous publication demonstrated that a restrictive transfusion strategy in high-risk patients undergoing cardiac surgery was noninferior to a liberal strategy for the composite outcome of death from any cause, myocardial infarction, stroke, or new-onset renal failure by hospital discharge or 28 days after surgery in 5,243 patients. This publication reports on the same outcomes in this patient population 6 months after surgery. The primary composite outcome had occurred in 402 patients (17.4%) in the restrictive group and in 402 patients (17.1%) in the liberal group (absolute risk difference before rounding, 0.22 percentage points; 95% CI, –1.95 to 2.39; odds ratio, 1.02; 95% CI, 0.87 to 1.18; $P = 0.006$ for noninferiority). The authors concluded that a restrictive red-cell transfusion strategy was noninferior to a liberal strategy in high-risk patients undergoing cardiac surgery in terms of all-cause mortality, myocardial infarction, stroke, or new-onset renal failure at 6 months after surgery. *(Article Selection: Martin J. London. Image: J. P. Rathmell.)*

Take home message: Restrictive transfusion strategies in patients undergoing cardiac surgery may be noninferior to liberal transfusion strategies in the first 6 months after surgery.
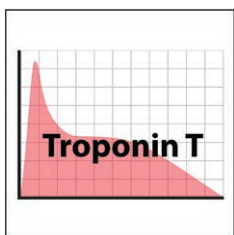
Fourth universal definition of myocardial infarction (2018). J Am Coll Cardiol 2018 Aug 23 [Epub ahead of print].

The European Society of Cardiology, American College of Cardiology Foundation, American Heart Association, and the World Heart Federation have published a revised definition of myocardial infarction. The term myocardial injury should be used when there is evidence of elevated cardiac troponin values (cTn) with at least one value above the 99th percentile of the upper reference limit (URL). The myocardial injury is considered acute if there is a rise and/or fall of cTn values. The term acute myocardial infarction should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischemia and detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and at least one of the following: symptoms of myocardial ischemia; new ischemic electrocardiographic changes; development of pathological Q waves; imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with ischemia; or identification of a coronary thrombus by angiography or autopsy. The definition also includes criteria for coronary procedure-related myocardial infarction and for prior or silent/unrecognized myocardial infarction. *(Article Selection: Martin J. London. Image: J. P. Rathmell.)*

Take home message: There is a revised definition of myocardial infarction from the European Society of Cardiology, American College of Cardiology Foundation, American Heart Association, and the World Heart Federation.
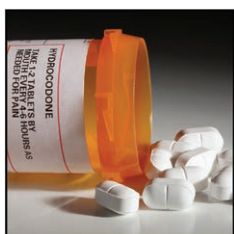
Persistent opioid use after wisdom tooth extraction. JAMA 2018; 320:504–6.

Opioid-naive patients are at risk for persistent opioid use after elective surgery, but the risk following dental procedures is unknown. This study investigated the association of filled perioperative opioid prescriptions with persistent use of prescription opioid medications following wisdom tooth extraction. The authors used a dental insurance claims database to identify filled prescriptions. The exposure was ≥ 1 filled perioperative opioid prescription and the primary outcome was persistent opioid use (≥ 1 opioid prescription filled during postprocedure days 4 to 90 and 91 to 365). Among 70,942 included patients, 56,686 patients filled a perioperative opioid prescription. Hydrocodone was the most common (70.3%), followed by oxycodone (24.3%). Patients who filled an opioid prescription were more often younger and female with higher rates of risk factors like chronic pain, depression, and anxiety. With a filled opioid prescription persistent opioid use occurred at an adjusted rate of 13 per 1,000 patients (95% CI, 9 to 19) compared with 5 per 1,000 patients (95% CI, 3 to 7) without a filled prescription. The authors noted that persistent use was not explained by patient characteristics or tooth impaction alone. *(Article Selection: J. David Clark. Image: ©ThinkStock.)*

Take home message: Patients who fill an opioid prescription following wisdom tooth extraction may have a higher rate of persistent opioid use.

Long-term quality of life in neonatal surgical disease. Ann Surg 2018; 268:497–505.

Quality of life in pediatric patients who receive surgery as neonates for complex congenital conditions is seldom explored longitudinally. This prospective observational study assessed postoperative quality of life for patients with congenital diaphragmatic hernia, esophageal atresia/tracheoesophageal fistula, Hirschsprung disease, gastroschisis, omphalocele, and necrotizing enterocolitis. The authors collected institutional clinical outcomes registry data from 241 patients. Aggregate physical, psychosocial, and overall quality of life scores were determined for each diagnosis. Physical scores trended up for all diagnoses except congenital diaphragmatic hernia and necrotizing enterocolitis beyond age 10. Psychosocial scores trended up for all diagnoses except necrotizing enterocolitis and esophageal atresia/tracheoesophageal fistula beyond age 10. Beyond age 12, quality of life is significantly impaired in necrotizing enterocolitis, moderately impaired in omphalocele and esophageal atresia/tracheoesophageal fistula, and within normal range for congenital diaphragmatic hernia, Hirschsprung disease, and gastroschisis patients. The authors concluded that variation exists in long-term quality of life scores after neonatal surgery for complex disease. These data may be helpful in prenatal and perioperative discussions with families. *(Article Selection: Beatrice Beck-Schimmer. Image: ©ThinkStock.)*

Take home message: Quantifying long-term quality of life measures in infants undergoing surgery for complex congenital conditions may aid in prenatal and perioperative counseling.
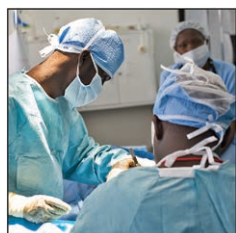
Global surgical, obstetric, and anesthetic task shifting: A systematic literature review. Surgery 2018; 164:553–8.

Task shifting is commonly used to expand the global surgical workforce, which is experiencing severe shortages. This systematic review examined the use of surgical, obstetric, and anesthetic task shifting worldwide. The authors extracted data for types of tasks, training, and levels of supervision, and compared these across regions and countries' income groups. They examined 55 relevant studies that included surgery data for 52 countries and anesthesia data for 147 countries. Surgical task shifting was documented in 19 countries and anesthetic task shifting in 119 countries. This practice was observed across all World Bank income groups. No nonphysician clinicians performed unsupervised surgical procedures in high-income countries. Independent anesthesia care by associate clinicians occurred in 3 of 19 countries with data. In low-income countries, associate clinicians performed surgical procedures independently in two of three countries and independent anesthesia care in 17 of 17 countries with data. The authors concluded that associate clinicians are ubiquitous among the global surgical workforce and should be considered in plans to scale up the surgical workforce. *(Article Selection: Beatrice Beck-Schimmer. Image: ©ThinkStock.)*

Take home message: Associate clinicians are ubiquitous in the global surgical workforce but are less common in high-income countries.
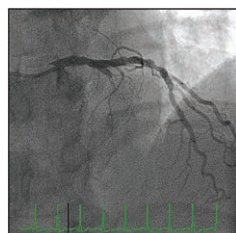
Drug-coated balloons for small coronary artery disease (BASKET-SMALL 2): An open-label randomised non-inferiority trial. Lancet 2018; 392:849–56.

Drug-coated balloons are a novel therapeutic strategy for the treatment of coronary artery disease. However, their safety and efficacy is poorly defined in comparison with drug-eluting stents. BASKET-SMALL 2 was a multicenter, open-label, randomized noninferiority trial. The authors randomized 758 patients with *de novo* lesions (less than 3 mm in diameter) in coronary vessels and an indication for percutaneous coronary intervention. Patients received either angioplasty with drug-coated balloon or implantation of a second-generation drug-eluting stent. The primary objective was to show noninferiority of balloons *versus* stents with regard to major adverse cardiac events (cardiac death, myocardial infarction, and target-vessel revascularization) after 1 yr. The noninferiority margin was an absolute difference of 4% in cardiac events. The authors found drug-coated balloons to be noninferior to drug-eluting stents because the 95% CI of the absolute difference in major cardiac events was below the predefined margin (–3.83% to 3.93%, $P = 0.0217$). After 12 months, the proportions of major cardiac events were also similar in both groups (7.5% for the balloon group *vs.* 7.3% for the stent group; hazard ratio, 0.97 [95% CI, 0.58 to 1.64], $P = 0.9180$). *(Article Selection: Martin J. London. Image: J. P. Rathmell.)*

Take home message: Angioplasty with drug-coated balloons may be noninferior to drug-eluting stents for the treatment of small lesion (less than 3 mm) coronary artery disease.
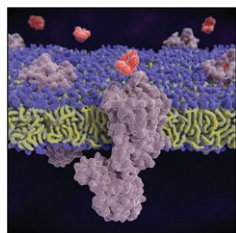
A bifunctional nociceptin and mu opioid receptor agonist is analgesic without opioid side effects in nonhuman primates. Sci Transl Med 2018; 10:eaar3483.

Misuse of prescription opioids, opioid addiction, and overdose underscore the urgent need for developing effective addiction-free medications for treating severe pain. Mu opioid peptide receptor agonists provide very effective pain relief. However, severe side effects limit their use in the clinical setting. Agonists of the nociceptin/orphanin FQ peptide receptor have been shown to modulate the antinociceptive and reinforcing effects of mu opioid peptide receptor agonists. The authors report the discovery and development of a bifunctional nociceptin/orphanin FQ peptide/mu opioid peptide receptor agonist, AT-121, which has partial agonist activity at both nociceptin/orphanin FQ peptide and mu opioid peptide receptors. AT-121 suppressed oxycodone's reinforcing effects and exerted morphine-like analgesic effects in nonhuman primates. AT-121 treatment did not induce side effects commonly associated with opioids, such as respiratory depression, abuse potential, opioid-induced hyperalgesia, and physical dependence. The authors conclude that their results in nonhuman primates suggest that bifunctional nociceptin/orphanin FQ peptide/mu opioid peptide agonists with the appropriate balance of nociceptin/orphanin FQ peptide and mu opioid peptide agonist activity may provide a dual therapeutic action for safe and effective pain relief and treatment of opioid abuse. *(Article Selection: J. David Clark. Image: ©ThinkStock.)*

Take home message: In nonhuman primates, a bifunctional nociceptin/orphanin FQ peptide and mu opioid peptide agonist may provide for safe and effective pain relief and treatment for opioid abuse.
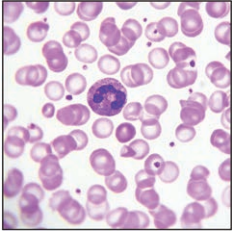
Impaired efferocytosis and neutrophil extracellular trap clearance by macrophages in ARDS. Eur Respir J 2018; 52:1702590.

Exaggerated release of neutrophil extracellular traps along with decreased clearance may contribute to sustained inflammation in acute respiratory distress syndrome (ARDS). This study investigated neutrophil and neutrophil extracellular trap clearance by macrophages from control and ARDS patients. Metformin and neutralizing antibody against high-mobility group box 1 were applied to improve efferocytosis and neutrophil extracellular trap clearance. Conversely, neutrophil extracellular trap formation was significantly enhanced in ARDS patients. Exposure of neutrophils to ARDS lavage fluid promoted neutrophil extracellular trap production, while control lavage fluid had no effect. Macrophage engulfment of neutrophil extracellular traps and apoptotic neutrophils was diminished in ARDS patients. Notably, activation of adenosine monophosphate-activated protein kinase in macrophages or neutralization of high-mobility group box 1 in lavage fluid improved efferocytosis and neutrophil extracellular trap clearance. The authors concluded that restoring adenosine monophosphate-activated protein kinase activity with metformin or specific neutralization of high-mobility group box 1 in lavage fluid are promising therapeutic strategies to decrease sustained lung inflammation during ARDS. *(Article Selection: Beatrice Beck-Schimmer. Image: ©ThinkStock.)*

Take home message: Restoring adenosine monophosphate-activated protein kinase activity with metformin or specific neutralization of high-mobility group box 1 in lavage fluid are promising therapeutic strategies to decrease lung inflammation in ARDS.
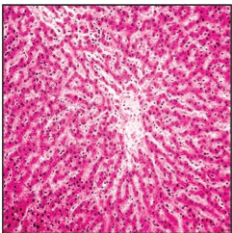
Hepatocyte spheroids as an alternative to single cells for transplantation after *ex vivo* gene therapy in mice and pig models. Surgery 2018; 164:473–81.

Autologous hepatocyte transplantation and gene therapy may be an alternative to liver transplantation in the setting of metabolic liver disease. This study evaluated *ex vivo* gene therapy followed by transplantation of single-cell or spheroid hepatocytes. The authors isolated and labeled pig and mouse hepatocytes and returned them to the liver as single cells or spheroids. Animals received portal vein infusion of autologous hepatocytes after *ex vivo* gene delivery. Differences in engraftment and expansion of *ex vivo* single-cell or spheroid hepatocytes were followed through histologic analysis and animals' ability to thrive off 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione. Positron emission tomography–computed tomography imaging showed spheroid hepatocytes with increased heterogeneity in biodistribution as compared with single cells, which spread more uniformly throughout the liver. Animals receiving spheroids experienced higher mean changes in portal pressure than animals receiving single cells ($P < 0.01$). The authors concluded that *ex vivo* gene correction of autologous hepatocytes in fumarylacetoacetate hydrolase–deficient pigs can be performed using hepatocyte spheroids or single-cell hepatocytes, with spheroids showing a more heterogeneous distribution within the liver and higher risks for portal vein thrombosis and increased portal pressures. *(Article Selection: Beatrice Beck-Schimmer. Image: ©ThinkStock.)*

Take home message: This study suggests that engraftment of *ex vivo* single cell hepatocytes may be associated with a more uniform spread of cells throughout the liver and lower portal pressure when compared to engraftment of spheroid hepatocytes.

ANESTHESIOLOGY

PERSONALIZED PEEP: Options for Getting It Just Right

Intraoperative lung protective ventilation includes[1]
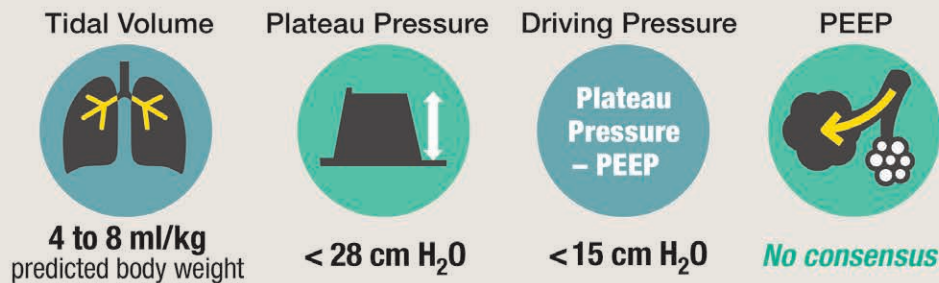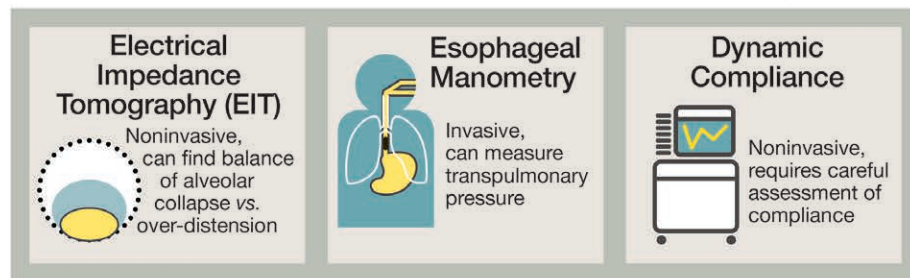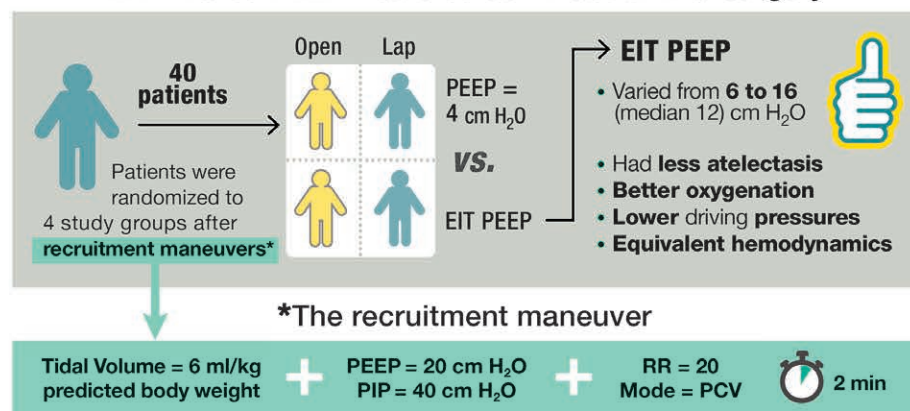
PCV, pressure control ventilation; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure; RR, respiratory rate.
Infographic created by Jonathan P. Wanderer, Vanderbilt University Medical Center and James P. Rathmell, Brigham and Women's Health Care/Harvard Medical School; illustration by Annemarie Johnson, Vivo Visuals. Address correspondence to Dr. Wanderer: jonathan.p.wanderer@vanderbilt.edu.

1. Kacmarek RM, Villar J. Lung-protective ventilation in the operating room: Individualized positive end-expiratory pressure is needed! ANESTHESIOLOGY 2018; 129:1057–9

2. Pereira SM, Tucci MR, Morais CCA, Simões CM, Tonelotto BFF, Pompeo MS, Kay FU, Pelosi P, Vieira JE, Amato MBP. Individual positive end-expiratory pressure settings optimize intraoperative mechanical ventilation and reduce postoperative atelectasis. ANESTHESIOLOGY 2018; 129:1070–81

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18-037

John (Iain) Glen Wins 2018 Lasker Prize for Development of Propofol

An Award for All of Anesthesiology

Margaret Wood, M.B., Ch.B., F.R.C.A., Ron Stark, M.D., Ph.D., F.R.C.P.

ON September 11, 2018, the Lasker Foundation announced the award recipients for 2018, with Iain Glen named winner of the Clinical Medical Research Award for his central role in the development of propofol. The Lasker Clinical Medical Research Award (www.laskerfoundation.org) is awarded annually to recognize individuals who have made innovative contributions to medical science that have improved the lives of many thousands of people. The Albert and Mary Lasker Foundation has made the awards since 1945 recognizing the most important discoveries in medical science, such that the awards are frequently described as "America's Nobels." Many Lasker recipients have subsequently received Nobel Prizes. It was our honor to nominate Iain Glen for this year's award in recognition of the vast number of patients who have benefited from the use of propofol.

When one of us (M.W.) graduated from medical school in 1970 and started specialty training in anesthesiology, thiopental was the intravenous anesthetic induction agent of choice, maintenance of anesthesia was with an inhalation anesthetic agent, and a frequent specialty board examination question was to discuss the relative complications of intravenous anesthetic induction agents. I (M.W.) vividly remember, as a young trainee, anesthetizing a patient for a repeat incision and drainage of a breast abscess and electing to administer *Althesin* for induction of anesthesia. Althesin was a mixture of two water-insoluble steroids—alphaxalone and alphadolone—that were solubilized in Cremophor EL. Immediately after administration, my patient became hypotensive and developed severe bronchospasm. Although my patient fully recovered, additional such anaphylactic reactions to Althesin eventually resulted in its removal from the market. Propanidid, another induction agent solubilized in Cremophor EL, was also withdrawn following the incidence of anaphylactoid reactions, although at the time, the relative contribution to the reaction of the drug itself or the Cremophor EL was hotly debated. In the 1970s, Dr. Glen, working at ICI Pharmaceuticals in Alderly Park, Cheshire, England, studied a large series of compounds to identify those with desirable anesthetic and hypnotic properties, eventually selecting 2,6-diisopropylphenol (propofol first tested on May 23, 1973)

to progress.[1] He chose propofol because of the characteristics that subsequently made it so widely used—limited effects on both the respiratory and cardiovascular system, rapid and complete recovery after administration, and lack of accumulation after multiple doses.[2] However, propofol is an oil and therefore, solubilization—a problem that others had tried to solve by solubilizing previous novel induction agents in Cremophor EL—was a problem. Solving this led to a more than 10-yr delay before the new agent could be introduced into anesthetic practice. It was initially hoped, and against Dr. Glen's advice, that propofol could be formulated in Cremophor EL. After clinical studies in 1,000 patients made it clear that the Cremophor EL formulation caused anaphylaxis, the clinical trials were stopped. At this stage the whole project might have been shelved and we would still be using thiopental in 2018. However, impressed by the promising clinical efficacy, Dr. Glen persuaded the company's management to continue the search for a formulation that would be safe. Dr. Glen was able to show that an emulsion formulation containing soybean oil and purified egg lecithin did not

Image: Ellen Jaffe.

This article has an audio podcast.

produce the anaphylaxis-like reaction in pigs—a species that had shown anaphylaxis-like reactions to Cremophor EL.[3,4] Thus, the "milky white" formulation that we know today was born. The clinical evaluation of the emulsion formulation of propofol began in 1983, and regulatory approvals for induction and short-term maintenance of anesthesia were received in 1986. Clinical anesthesiologists quickly recognized the potential for this new drug, and following clinical trials in a myriad of settings, subsequent approvals broadened the use of propofol to its ubiquitous use today. The successful development of propofol, like so many projects in life, required a visionary committed individual who was able to "stick with" the project in the face of challenges that frequently threatened to sink the project.

As is often the case, the development of one paradigm-changing discovery (propofol) made possible multiple other discoveries and innovations, which, though apparently independent, required the first innovation for their implementation and, importantly, could not have occurred without the first. The explosion of imaging technology in the 1980s and its subsequent widespread adoption in medical imaging was made possible by the ability to use propofol-induced sedation for diagnostic and therapeutic radiologic procedures; many of these studies would not have been possible without propofol. Of particular importance is the role that propofol has had in the safe use of imaging studies in young children. Such studies often require prolonged immobility for adequate imaging, and became possible in the large number of children undergoing such imaging only after propofol became available. The administration of propofol, using techniques developed by Dr. Glen, has saved and improved countless patient lives. In the procedural arena, screening colonoscopy and cataract extraction have a huge impact on the quality of life…and propofol is a major anesthetic for these two frequently performed procedures, allowing not only a reduction in patient morbidity and mortality but also an increased volume of procedures to be performed per session—improving patient access to life-enhancing procedures.

An additional impact of Dr. Glen's development of propofol is illustrated by the laryngeal mask airway, which was introduced by Dr. Archie Brain in 1983,[5] with the first commercial laryngeal mask airway made available in the United Kingdom in 1987. The laryngeal mask airway is a device that provides excellent airway patency, protects the airway, and has in large part replaced mask/inhalational anesthesia. When the airway cannot be secured due to difficulty in intubating the trachea, the laryngeal mask airway allows the patient to be rescued. However, the laryngeal mask airway could never have been introduced or used with only intravenous barbiturate agents available as anesthetic induction

agents. It was indeed serendipitous that both propofol and the laryngeal mask airway appeared on the scene at the same time in the mid-1980s. Propofol, with its special pharmacodynamic properties, allowed its safe and efficient use.

Propofol has revolutionized anesthesia throughout the world and affected countless patient lives. In the developed world, almost every person who undergoes a surgical procedure, screening colonoscopy, or complex imaging study may receive propofol—meaning that most of us have received, or will receive, propofol at some point in our lives. All of those who have undergone procedures—surgical, imaging, and screening—in the modern era have received propofol, perhaps without recognizing the enormous impact its discovery has had on medicine and the public's health. This impact was made possible by Dr. Glen's vision in recognizing the potential impact and importance of developing a novel anesthetic such as propofol. There are few families who have not benefitted from Dr. Glen's discovery. In spite of the challenges, it was Dr. Glen's vision, creativity, and persistent stewardship that gave us a drug whose advantages, safety, and ease of use have benefitted vast numbers of patients and remains a standard of care today. However, Dr. Glen did not do this alone. The notion that propofol could be more than an induction agent was carried forward by a successful collaboration between anesthesiologists and drug developers. This award underlines the importance of our specialty to medicine as a whole, and we both congratulate Dr. Glen on this award and celebrate our specialty and its contributions to medicine, science, and our patients.

Competing Interests

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

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References

1. James R, Glen JB: Synthesis, biological evaluation, and preliminary structure-activity considerations of a series of alkylphenols as intravenous anesthetic agents. J Med Chem 1980; 23:1350–7

2. Glen JB: Animal studies of the anaesthetic activity of ICI 35 868. Br J Anaesth 1980; 52:731–42

3. Glen JB, Davies GE, Thomson DS, Scarth SC, Thompson AV: An animal model for the investigation of adverse responses to i.v. anesthetic agents and their solvents. Br J Anaesth 1979; 51:819–27

4. Glen JB, Hunter SC: Pharmacology of an emulsion formulation of ICI 35 868. Br J Anaesth 1984; 56:617–26

5. Brain AI: The laryngeal mask–a new concept in airway management. Br J Anaesth 1983; 55:801–5

 M. Wood and R. Stark

Lung-protective Ventilation in the Operating Room

Individualized Positive End-expiratory Pressure Is Needed!

Robert M. Kacmarek, Ph.D., R.R.T., Jesús Villar, M.D., Ph.D.

CME This article has been selected for the ANESTHESIOLOGY CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

THE concept of lung-protective ventilation is well established in patients with acute lung injury and is now considered a fundamental approach when managing any patient under mechanical ventilation in an intensive care unit. The concept of lung-protective ventilation in the operating room has taken a little longer to develop, but data establishing the beneficial results of intraoperative lung-protective ventilation are increasing.[1–3] Regardless of location, it has become well accepted that tidal volume (V_T) should be maintained between 4 and 8 ml/kg of predicted body weight, that plateau pressure should be maintained at less than 28 cm H_2O, and that driving pressure (plateau pressure minus end-expiratory pressure [PEEP]) should be maintained at less than 15 cm H_2O.

> *"A small physiologic trial evaluate[d] the ability of titrated PEEP to prevent intraoperative atelectasis."*

However, the establishment of guidelines for the setting of PEEP in any of these settings has been very challenging. There are no guidelines for PEEP setting based on the results of randomized controlled trials. In fact, the current literature is nonconclusive. The only established guideline is that patients with moderate-to-severe acute respiratory distress syndrome require "high" PEEP levels, whereas patients with mild adult respiratory distress syndrome require "low" PEEP.

In this issue of the Journal, Pereira *et al.*[4] performed a small physiologic trial to evaluate the ability of titrated PEEP to prevent intraoperative atelectasis using electrical impedance tomography. Optimal PEEP was selected based on the specific response of the given patient's respiratory system. They selected 40 patients without previous lung disease undergoing elective abdominal surgery (20 under laparoscopy and 20 by open abdomen) admitted to the same institution during a 21-month period. All patients received a recruitment maneuver using pressure control ventilation to 40 cm H_2O. Upon completion of the recruitment maneuver and before the initiation of the surgical procedure, the patients were randomized to be ventilated with 4 cm H_2O PEEP or with the PEEP level that resulted in the least collapse and least overdistension using electrical impedance tomography. At the end of surgical anesthesia, patients in both arms were extubated without any adjustment of PEEP or fractional inspired oxygen tension; within 30 to 60 min of extubation, a chest computed tomography was performed. Compared with the 4 cm H_2O group, the PEEP by electrical impedance tomography group had a lower intraoperative driving pressure, better oxygenation, and equivalent hemodynamics. No other postoperative pulmonary complications were recorded, and no adverse events associated with the recruitment maneuver were reported.

Electrical impedance tomography is a portable, radiation-free imaging technique that can easily be used at the bedside. It provides real-time dynamic assessment of gas movement into and out of the respiratory system. As noted, it is very useful in identifying the PEEP level, resulting in minimal collapse and overdistension. The major problem with electrical impedance tomography is its availability. At present, no electrical impedance tomography device is commercially available in the United States. The only techniques that provide comparable information are the titration of PEEP postrecruitment using esophageal manometry or the best dynamic compliance PEEP.[5,6] These techniques require invasive placement of an esophageal balloon or the careful assessment of compliance as PEEP is decreased. Limited data are available comparing these techniques, but electrical impedance tomography appears more precise in identifying the optimal PEEP level.

Image: J. P. Rathmell.

Of concern is the fact that the results of the study by Pereira *et al.*[4] seem to differ from the recently published Spanish study by Ferrando *et al.*[7] The Spanish study did not find a difference in postoperative complications among groups.[7] The design of the Spanish study at first glance is similar to that of Pereira *et al.*[4] except (1) they enrolled 1,012 patients with healthy lungs scheduled for abdominal surgery in 21 hospitals during a 16-month period; (2) patients were randomly assigned to four arms, each evaluating different operative and postoperative ventilatory support strategies; and (3) the PEEP level in the control group was 5 cm H_2O, although 69 patients in the control group had their PEEP adjusted during surgery. Of interest is the fact that one of the groups had essentially the same intraoperative protocol as the recruitment maneuver used by Pereira *et al.*[4] followed by a decremental PEEP trial identifying optimal PEEP by best dynamic compliance. As we noted above, this should establish approximately the same PEEP level as with electrical impedance tomography. However, the PEEP levels applied to the open lung groups after the recruitment maneuver were different: median PEEP of 10 cm H_2O (interquartile range, 8 to 12 cm H_2O) in the Ferrando *et al.*[7] study (n = 479) *versus* the median PEEP of 12 cm H_2O (interquartile range, 10 to 14 cm H_2O) in the study by Pereira *et al.*[4] (n = 20). In addition, 50% of patients in the study by Pereira *et al.*[4] (n = 20) had laparoscopic surgery and 50% (n = 20) had open-abdomen surgery, whereas in the study by Ferrando *et al.*,[7] 60% of patients (n = 580) had open-abdomen surgery, and 40% (n = 364) had laparoscopic surgery. Of note, Ferrando *et al.*[7] reported the main surgical procedures performed in their study population, whereas Pereira *et al.*[4] did not.

The major difference between the two studies is that the primary outcome of interest in the study by Ferrando *et al.*[7] was the combined prevalence of pulmonary and systemic postoperative complications, not just postextubation atelectasis. In fact, their list of pulmonary complications included aspiration, pneumonitis, atelectasis, bronchospasm, dyspnea, pleural effusion, hypoxemia, pneumothorax, pneumonia, adult respiratory distress syndrome, and the need for reintubation and mechanical ventilation. In addition, they included surgical-site infection, anastomotic dehiscence, sepsis, cardiac failure, renal failure, and need for surgical reintervention. All of this was determined over the first 7 days after extubation. In the study by Pereira *et al.*,[4] patients had a computerized tomography scan performed 30 to 60 min after extubation, and the primary outcome of interest was the level of atelectasis postextubation. Pereira *et al.*[4] did not follow patients beyond the immediate postoperative period, and Ferrando *et al.*[7] only provided composite data, although as a secondary outcome, they found that the recruitment maneuver group had a significantly lower prevalence of combined pulmonary complications than the control PEEP groups. As a result, it is impossible to compare the outcomes of these two studies, and their outcome may have

been the same if their primary outcomes were the same. We hope that in a future secondary analysis, Ferrando *et al.*[7] will provide detailed analysis on each individual complication for comparison.

On the basis of current available literature and the study of Pereira *et al.*,[4] recruitment maneuvers with peak airway pressure of 40 cm H_2O are safe. The two primary concerns with recruitment maneuvers are pneumothorax and hemodynamic instability. The peak airway pressure obtained with bag mask ventilation can easily exceed 40 cm H_2O. Clinicians often do not precisely control and monitor airway pressure when they perform mask ventilation. Consequently, air pressures exceeding 40 cm H_2O in adults are common. Pneumothorax have only been reported occurring in association with recruitment maneuvers when peak airway pressures are 55 cm H_2O or more.[8,9] When peak recruitment maneuver airway pressures are 50 cm H_2O or less and patients are passively ventilated during the recruitment maneuver, pneumothorax is an extreme rarity. In the five most recent randomized controlled trials[4,7,8,10,11] in which recruitment maneuvers were used, pneumothorax was only associated with recruitment maneuvers in one of the trials,[8] and in that trial, recruitment maneuver peak pressure was set at 60 cm H_2O. Hemodynamic instability in another issue. Any patient may development hemodynamic instability during a recruitment maneuver. Before the recruitment maneuver, hemodynamic stability should be assured. However, even in the most hemodynamically stable patient, problems can occur. Clinicians must be ready to abort the recruitment maneuver and provide fluid or vasopressors to stabilize the patient unable to tolerate the recruitment maneuver. However, in a recent randomized controlled trial by Leme *et al.*,[11] the investigators found that recruitment maneuvers were well tolerated by postoperative cardiac surgical patients and had a positive effect on postoperative pulmonary complications and patient outcomes.

Pereira *et al.*[4] have examined the importance of an individualized approach to setting PEEP in abdominal surgery patients. However, the patients enrolled in their study were relatively homogenous. It is interesting to note that they indeed found a correlation between the body mass index and PEEP by electrical impedance tomography in spite of the range of body mass index in the studied patients being relatively small (29.5 ± 4.3). It is likely that the variation of PEEP by electrical impedance tomography in a patient population with greater body mass index is much larger. In addition, certain positioning may lead to higher and more variable PEEP by electrical impedance tomography, for instance during surgery of robotic assisted laparoscopic prostatectomy where abdominal insufflation and steep Trendelenburg position are applied. Although not the end of the story of setting PEEP in the operating room, their results provide essential pilot data for the development of future trials assessing the use of PEEP in the operating room. Most importantly, they have found that recruitment maneuvers and high levels of

PEEP can be safely used in the operating room and may have a positive impact on patient outcome.

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References

1. Severgnini P, Selmo G, Lanza C, Chiesa A, Frigerio A, Bacuzzi A, Dionigi G, Novario R, Gregoretti C, de Abreu MG, Schultz MJ, Jaber S, Futier E, Chiaranda M, Pelosi P: Protective mechanical ventilation during general anesthesia for open abdominal surgery improves postoperative pulmonary function. ANESTHESIOLOGY 2013; 118:1307–21

2. Futier E, Constantin JM, Paugam-Burtz C, Pascal J, Eurin M, Neuschwander A, Marret E, Beaussier M, Gutton C, Lefrant JY, Allaouchiche B, Verzilli D, Leone M, De Jong A, Bazin JE, Pereira B, Jaber S; IMPROVE Study Group: A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. N Engl J Med 2013; 369:428–37

3. Guldner A, Kiss T, Serpa Neto A, Hemmes SN, Canet J, Spieth PM, Rocco PR, Schultz MJ, Pelosi P, Gama de Abreu M: Intraoperative protective mechanical ventilation for prevention of postoperative pulmonary complications: A comprehensive review of the role of tidal volume, positive end-expiratory pressure, and lung recruitment maneuvers. ANESTHESIOLOGY 2015; 123:696–713

4. Pereira SM, Tucci MR, Morais CCA, Simoes CM, Tonelotto BFF, Pompeu MS, Kay FU, Pelosi P, Vieira JE, Amato MBP: Individual positive end-expiratory pressure settings optimize intraoperative mechanical ventilation and reduce postoperative atelectasis. ANESTHESIOLOGY 2018; 129:1070–81

5. Pirrone M, Fisher D, Chipman D, Imber DA, Corona J, Mietto C, Kacmarek RM, Berra L: Recruitment maneuvers and positive end-expiratory pressure titration in morbidly obese ICU patients. Crit Care Med 2016; 44:300–7

6. Fumagalli J, Berra L, Zhang C, Pirrone M, Santiago RRS, Gomes S, Magni F, Dos Santos GAB, Bennett D, Torsani V, Fisher D, Morais C, Amato MBP, Kacmarek RM: Transpulmonary pressure describes lung morphology during decremental positive end-expiratory pressure trials in obesity. Crit Care Med 2017; 45:1374–81

7. Ferrando C, Soro M, Unzueta C, Suarez-Sipmnn F, Canet J, Librero, Pozo N, Peiro S, Llombart A, Leon I, India I, Aldecoa C, Diaz-Cambronero O, Pestana D, Redondo FJ, Garutti I, Balust J, Garcia JI, Ibanez M, Granell M, Rodriguez A, Gallego L, de la Matta M, Gonzalez R, Brunelli A, Garcia J, Rovira L, Barrios F, Torres V, Hernandez S, Gracia E, Gine M, Garcia M, Garcia N, Miguel L, Sanchez S, Pineiro P, Pujol R, Garcia-del-Valle S, Valdivia J, Hernandez MJ, Padron O, Colas A, Puig J, Azparren G, Tusman G, Villar J, Belda J, on behalf of the Individualized PeRioperative Open-Lung Ventilation (iPROVE) Network: Individualised perioperative open-lung approach versus standard protective ventilation in abdominal surgery (iPROVE): A randomized controlled trial. Lancet 2018; 63:193–203

8. Cavalcanti AB, Suzumura EA, Laranjeira LN, Paisani DM, Damiani LP, Guimaraes HP, Romano ER, Regenga MM, Taniguchi LNT, Teixeira C, Pinheiro de Oliveira, Machado FR, Diaz-Quijano FA, Filho MSA IS, Caser EB, Filho WO, Borges MC, Martins PA, Matsui M, Ospina-Tascon GA, Giancursi TS, Giraldo-Ramirez ND, Vieira SRR, Assef MDGPL, Hasan MS, Szczeklik W, Rios F, Amato MBP, Berwanger O, Ribeiro de Carvalho CR: Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs. low PEEP on mortality in patients with acute respiratory distress syndrome: A randomized clinical trial. JAMA 2017; 318:1335–45

9. Borges JB, Okamoto VN, Matos GF, Caramez MP, Arantes PR, Barros F, Souza CE, Victorino JA, Kacmarek RM, Barbas CS, Carvalho CR, Amato MB: Reversibility of lung collapse and hypoxemia in early acute respiratory distress syndrome. Am J Respir Crit Care Med 2006; 174:268–78

10. Kacmarek RM, Villar J, Sulemanji D, Montiel R, Ferrando C, Blanco J, Koh Y, Soler JA, Martínez D, Hernández M, Tucci M, Borges JB, Lubillo S, Santos A, Araujo JB, Amato MB, Suárez-Sipmann F; Open Lung Approach Network: Open lung approach for the acute respiratory distress syndrome: A pilot, randomized controlled trial. Crit Care Med 2016; 44:32–42

11. Leme CA, Volpe M, Fukushima JT, De Santis Santiago RR, Osawa EA, Pinheiro de Almeida J, Gerent AM Franco RA, Feltrim Z, Nozawa E, de Moraes Coimbra VR, de Moraes Ianotti R, Hashizume CS, Filho RK, Auler JOC, Jatene FB, Galas RBG, Amato MBP: Effect of intensive vs. moderate alveolar recruitment strategies added to lung-protective ventilation on postoperative pulmonary complications: A randomized clinical trial. JAMA 2017; 317:1422–32

Observing Blood Management Programs through the Retrospectroscope

Richard J. Cook, B.Sc., M.Math, Ph.D., Richard B. Weiskopf, M.D.

IN this issue of ANESTHESIOLOGY, Gupta *et al.*[1] report on the results of a retrospective cohort study comparing transfusion practices and clinical outcomes before and after the implementation of a blood management program in orthopedic surgery at a single center. The motivation stems in part from interest in reducing the number of transfusions by the use of more restrictive hemoglobin triggers for red blood cell transfusions in orthopedic surgery patients. The authors observe that both lower utilization and comparable or improved patient outcomes followed implementation of the blood management program and conclude that a "hemoglobin threshold of 7 g/dl appears to be safe for many orthopedic patients." There is a clear need to understand the relationship between transfusion triggers and outcomes to ensure that limited resources are used judiciously, to minimize exposures of patients, and to optimize patient outcomes.

> *"Large databases are appealing to exploit for investigating focused scientific questions, but the data necessary for a rigorous analysis are often lacking ..."*

The study by Gupta *et al.*[1] offers a good illustration of the kinds of retrospective analyses often conducted based on data from large registries or administrative databases. There have been a number of studies in transfusion medicine which involved retrospective database analyses yielding findings that, when tested in prospective randomized trials, were not validated. For example, in a large retrospective analysis of 4,470 intensive care unit patients, Hébert *et al.*[2] observed an association between lower hemoglobin concentrations and death. However, when they tested this hypothesis in a subsequent randomized trial in 838 similar intensive care unit patients, there was no evidence of differences in mortality between the liberally and restrictively transfused groups that were transfused to hemoglobin concentrations of 10.7 and 8.5 g/dl.[3] In a retrospective analysis directed at the effect of red blood cell storage duration, Koch *et al.*[4] suggested that cardiac surgery patients transfused with red cells stored for longer periods of time experienced a higher mortality rate than did patients transfused with red cells having shorter storage durations; a subsequent larger retrospective analysis of all transfusions in Denmark and Sweden by Edgren *et al.*[5] showed different results. Exposure of patients with cardiovascular disease to red cells of particularly long storage duration was also associated with increased in-hospital mortality in a retrospective registry analysis by Eikelboom *et al.*,[6] but these findings were not validated in a subsequent analysis based on an expanded dataset.[7] Seven prospective randomized trials addressing this question did not substantiate the findings of Koch *et al.*, finding no difference between red cells storage duration and mortality, change in multiple organ dysfunction scores, composite morbidity, pulmonary and immune function, lactate clearance, and reversal of anemia-induced neurocognitive function in a wide range of populations: cardiac surgery, critically ill adults, children with severe anemia, low-weight premature infants, all hospitalized patients, and healthy volunteers.[8–14]

The current publication affords an opportunity to discuss some challenges arising in retrospective analyses, which are highlighted below. The themes include the *post hoc* definition exposure variables and the interpretation of their effects, the challenge of dealing completely and rigorously with the effect of confounding variables, incomplete data, and the use of composite outcomes. These, and other issues, are important to bear in mind when trying to explain conflicting findings between publications on different database analyses, and the results of randomized trials.

Post Hoc Definition of Exposure

Although a central theme of this work is examination of the effect of a new blood management program on red blood cell

use and outcome, some statements made by the authors suggest a causal effect of hemoglobin threshold on clinical outcome. The *post hoc* definition of hemoglobin threshold used here is "the lowest (nadir) hemoglobin concentration during the hospital stay." This crude summary of exposure over the course of a hospitalization may be reasonable for descriptive purposes, but there is danger in overinterpreting the relation between such an exposure summary and its association with the composite morbidity and mortality outcome. The principle reason is that this minimum hemoglobin concentration was simply an observed value over a period of time, with an unknown temporal relationship to any morbid event, rather than an actual predefined threshold as would be specified in a prospective randomized trial. The statement "[t]o our knowledge, ours is the first study in orthopedics to assess hemoglobin thresholds as low as 7 g/dl" and the concluding statement in the abstract are therefore inappropriate.

Ecological Fallacy and Confounding

Large databases are appealing to exploit for investigating focused scientific questions, but the data necessary for a rigorous analysis are often lacking; the lack of preoperative hemoglobin values is one such example in this article, but there is a myriad of factors influencing patient care, some of which are dynamic and responsive to early treatment. When a relatively small number of factors are adjusted for such as age, sex, hip fracture status, surgical procedure, and a case-mix index are used, concerns arise about whether the data are sufficient and the adjustments are adequate. A prospective observational study would have enabled collection of a more comprehensive set of variables enabling a more complete adjustment for potential confounders and findings more consistent with the prospective interpretation of real clinical interest. The rationale for many interventions is not generally available in databases; information on the reason for the transfusion would also be useful for causal analysis and would be easily collected in a prospective study. We also note that the propensity score used by the authors appears to include the same factors adjusted for in the multivariate regression analysis, so it does not represent a casual sensitivity analysis in the usual sense. Some principle advantages of propensity score analyses include the ability to adjust for a larger number of confounders while maintaining a relatively simply model for the outcome. This can be achieved by matching, stratification, or regression on the propensity score, or using inverse probability of exposure weights. The latter would yield estimates of the effect of the blood management program on the response more in line with what would be estimated in a randomized clinical trial.[15]

The selection criteria for potentially confounding variables to adjust for raises challenging issues. Confounding variables have an association with the outcome and the exposure variable, and although this is a relatively simple concept when dealing with cross-sectional studies, when exposure variables change over time in complex feedback systems,

identifying, selecting, and modeling the effect of confounding variables is a daunting challenge. Moreover, selection of variables to adjust for in causal analyses should be based on scientific context rather than statistical significance. We refer readers to a timely, sobering, and stimulating recent paper by Hernán,[16] from which one can learn to calibrate expectations and interpretations from registry-based studies.

Composite Outcomes

There is often compelling practical rationale for use of composite outcomes but these also introduce substantial challenges in interpretation of findings.[17] This challenge is particularly important when the components of a composite outcome are of unequal importance, when they represent quite different clinical outcomes, and when the relative weighting of the components is unclear in the final analysis. The magnitude of the effect reported on the composite outcome in Gupta *et al.* is striking, but for reasons stated earlier caution is warranted before attributing this large effect to a lower hemoglobin threshold. With such a large effect, however, it should be feasible to carry out a randomized clinical trial confirming this finding in the elderly population of orthopedic surgery patients. Some may consider that this had already been investigated in the prospective, randomized Transfusion Trigger Trial for Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS) trial, in which patients age 65 yr or more with a history of, or risk factors for, cardiovascular disease and undergoing surgical repair of hip fracture were randomly allocated to a liberal or restrictive transfusion protocol.[18] There were no differences in functional recovery or mortality found in this trial. Even such a randomized, clinical trial can have limitations, however: there was a highly significant increase in the use of "rescue" transfusion for cardiovascular symptoms (*i.e.*, red blood cell transfusion at a trigger greater than that specified by the protocol) in the restrictive group compared with the liberal group. Moreover, the population in the FOCUS trial was quite different than that analyzed by Gupta *et al.* We note that the numbers of patients experiencing even the composite outcome are quite low. To gain better insight into the nature of any effects, larger samples would be useful so that the effects could be explored in the component outcomes of the composite outcome in a meaningful way.[19] Finally, we note that the FOCUS trial is yet another example of a randomized trial yielding different results from the database analyses from which it was spawned.[20]

In many circumstances it is not possible to conduct randomized clinical trials, and other types of data are the best that can be obtained. Randomized trials are possible to test the hypothesis that less frequent red cell transfusion does not increase risk, and the results have been mixed, attesting to the challenges in conducting experimental research in complex settings. Comroe[21] in his book, *Retrospectroscope*, described the origins of some great discoveries in medicine. He did not envision his imaginary instrument being used for retrospective database examinations; in such settings the instrument's

lens can indeed be quite clouded. However, results generated from retrospective database analyses can be thought provoking, hypothesis generating, and help set the agenda for future investigations, as do the findings of Gupta *et al.*

Competing Interests

Dr. Cook consults for the following entities that have an interest in red cell transfusion: Canadian Blood Services (Ottawa, Canada), U.S. Food and Drug Administration (Silver Spring, Maryland), TerumoBCT (Lakewood, Colorado), HbO2 Therapeutics (Souderton, Pennsylvania). Dr. Weiskopf consults for the following entities that have an interest in red cell transfusion: U.S. Department of Defense (Arlington, Virginia), U.S. Food and Drug Administration, TerumoBCT, HbO2 Therapeutics.

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References

1. Gupta PB, DeMario VM, Amin RM, Gehrie EA, Goel R, Lee KHK, Yang WW, Khanuja HS, Sterling RS, Ness PM, Frank SM: Patient blood management program improves blood utilization and clinical outcomes in orthopedic surgery. Anesthesiology 2018; 129:1082–91

2. Hébert PC, Wells G, Tweeddale M, Martin C, Marshall J, Pham B, Blajchman M, Schweitzer I, Pagliarello G: Does transfusion practice affect mortality in critically ill patients? Transfusion Requirements in Critical Care (TRICC) Investigators and the Canadian Critical Care Trials Group. Am J Respir Crit Care Med 1997; 155:1618–23

3. Hébert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E: A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med 1999; 340:409–17

4. Koch CG, Li L, Sessler DI, Figueroa P, Hoeltge GA, Mihaljevic T, Blackstone EH: Duration of red-cell storage and complications after cardiac surgery. N Engl J Med 2008; 358: 1229–39

5. Edgren G, Kamper-Jørgensen M, Eloranta S, Rostgaard K, Custer B, Ullum H, Murphy EL, Busch MP, Reilly M, Melbye M, Hjalgrim H, Nyrén O: Duration of red blood cell storage and survival of transfused patients (CME). Transfusion 2010; 50:1185–95

6. Eikelboom JW, Cook RJ, Liu Y, Heddle NM: Duration of red cell storage before transfusion and in-hospital mortality. Am Heart J 2010; 159:737–43.e1

7. Heddle NM, Eikelboom J, Liu Y, Barty R, Cook RJ: Exploratory studies on the age of transfused blood and in-hospital mortality in patients with cardiovascular diagnoses. Transfusion 2015; 55:364–72

8. Steiner ME, Ness PM, Assmann SF, Triulzi DJ, Sloan SR, Delaney M, Granger S, Bennett-Guerrero E, Blajchman MA, Scavo V, Carson JL, Levy JH, Whitman G, D'Andrea P, Pulkrabek S, Ortel TL, Bornikova L, Raife T, Puca KE, Kaufman RM, Nuttall GA, Young PP, Youssef S, Engelman R, Greilich PE, Miles R, Josephson CD, Bracey A, Cooke R, McCullough J, Hunsaker R, Uhl L, McFarland JG, Park Y, Cushing MM, Klodell CT, Karanam R, Roberts PR, Dyke C, Hod EA, Stowell CP: Effects of red-cell storage duration on patients undergoing cardiac surgery. N Engl J Med 2015; 372:1419–29

9. Lacroix J, Hébert PC, Fergusson DA, Tinmouth A, Cook DJ, Marshall JC, Clayton L, McIntyre L, Callum J, Turgeon AF, Blajchman MA, Walsh TS, Stanworth SJ, Campbell H, Capellier G, Tiberghien P, Bardiaux L, van de Watering L, van der Meer NJ, Sabri E, Vo D; ABLE Investigators; Canadian Critical Care Trials Group: Age of transfused blood in critically ill adults. N Engl J Med 2015; 372:1410–8

10. Fergusson DA, Hébert P, Hogan DL, LeBel L, Rouvinez-Bouali N, Smyth JA, Sankaran K, Tinmouth A, Blajchman MA, Kovacs L, Lachance C, Lee S, Walker CR, Hutton B, Ducharme R, Balchin K, Ramsay T, Ford JC, Kakadekar A, Ramesh K, Shapiro S: Effect of fresh red blood cell transfusions on clinical outcomes in premature, very low-birth-weight infants: The ARIPI randomized trial. JAMA 2012; 308:1443–51

11. Heddle NM, Cook RJ, Arnold DM, Liu Y, Barty R, Crowther MA, Devereaux PJ, Hirsh J, Warkentin TE, Webert KE, Roxby D, Sobieraj-Teague M, Kurz A, Sessler DI, Figueroa P, Ellis M, Eikelboom JW: Effect of short-term vs. long-term blood storage on mortality after transfusion. N Engl J Med 2016; 375:1937–45

12. Dhabangi A, Ainomugisha B, Cserti-Gazdewich C, Ddungu H, Kyeyune D, Musisi E, Opoka R, Stowell CP, Dzik WH: Effect of transfusion of red blood cells with longer vs shorter storage duration on elevated blood lactate levels in children with severe anemia: The TOTAL randomized clinical trial. JAMA 2015; 314:2514–23

13. Kor DJ, Kashyap R, Weiskopf RB, Wilson GA, van Buskirk CM, Winters JL, Malinchoc M, Hubmayr RD, Gajic O: Fresh red blood cell transfusion and short-term pulmonary, immunologic, and coagulation status: A randomized clinical trial. Am J Respir Crit Care Med 2012; 185:842–50

14. Weiskopf RB, Feiner J, Hopf H, Lieberman J, Finlay HE, Quah C, Kramer JH, Bostrom A, Toy P: Fresh blood and aged stored blood are equally efficacious in immediately reversing anemia-induced brain oxygenation deficits in humans. Anesthesiology 2006; 104:911–20

15. Austin PC, Laupacis A: A tutorial on methods to estimating clinically and policy-meaningful measures of treatment effects in prospective observational studies: A review. Int J Biostat 2011; 7:6

16. Hernán MA: The C-word: Scientific euphemisms do not improve causal inference from observational data. Am J Public Health 2018; 108:616–9

17. Heddle NM, Cook RJ: Composite outcomes in clinical trials: What are they and when should they be used? Transfusion 2011; 51:11–3

18. Carson JL, Terrin ML, Noveck H, Sanders DW, Chaitman BR, Rhoads GG, Nemo G, Dragert K, Beaupre L, Hildebrand K, Macaulay W, Lewis C, Cook DR, Dobbin G, Zakriya KJ, Apple FS, Horney RA, Magaziner J; FOCUS Investigators: Liberal or restrictive transfusion in high-risk patients after hip surgery. N Engl J Med 2011; 365:2453–62

19. Freemantle N, Calvert M, Wood J, Eastaugh J, Griffin C: Composite outcomes in randomized trials: greater precision but with greater uncertainty? JAMA 2003; 289:2554–9

20. Lawrence VA, Silverstein JH, Cornell JE, Pederson T, Noveck H, Carson JL: Higher Hb level is associated with better early functional recovery after hip fracture repair. Transfusion 2003; 43:1717–22

21. Comroe JH: Retrospectroscope. Insights into Medical Discovery. Menlo Park, CA, Von Gehr Press, 1977

Quality Anesthesia

Medicine Measures, Patients Decide

Lee A. Fleisher, M.D.

ABSTRACT

Quality has been defined by six domains: effective, equitable, timely, efficient, safe, and patient centered. Quality of anesthesia care can be improved through measurement, either through local measures in quality improvement or through national measures in value-based purchasing programs. Death directly related to anesthesia care has been reduced, but must be measured beyond simple mortality. To improve perioperative care for our patients, we must take shared accountability for all surgical outcomes including complications, which has traditionally been viewed as being surgically related. Anesthesiologists can also impact public health by being engaged in improving cognitive recovery after surgery and addressing the opiate crisis. Going forward, we must focus on what patients want and deserve: improved patient-oriented outcomes and satisfaction with our care. By listening to our patients and being engaged in the entire perioperative process, we can make the greatest impact on perioperative care. (ANESTHESIOLOGY 2018; 129:1063-9)

QUALITY care is the goal of all clinicians and of health care. Quality was defined in the 2001 Institute of Medicine report titled "Crossing the Quality Chasm" as "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge."[1] In that report, the authors identified six domains of quality: effective, equitable, timely, efficient, safe, and patient centered (table 1). Anesthesiologists have been lauded for their accomplishments in the domain of patient safety, as well as being focused on the first four domains of quality. However, to ensure quality, we must increase our focus on patient-centeredness. The focus of this Rovenstine lecture was to describe the history and importance of quality measurement and the need to move to more measures of patient-oriented outcomes and patient satisfaction (table 2).

Measurement Is Critical to Improvement

Within the framework of measurement, Albert Einstein has been attributed with saying, "Not everything that counts can be counted, and not everything that can be counted counts," suggesting that we need to be careful to measure something of utility. However, W. Edwards Deming, the father of performance improvement, has been attributed with saying, "You can't improve what you don't measure." Therefore, to provide the best care, it is critical to choose outcomes carefully and use measurement to improve care.

The concept of measuring hospital performance was first established more than 150 yr ago. One of the first recorded hospital report cards was created by Florence Nightingale.[2] Rates of mortality varied between the hospitals in London and those in the countryside (fig. 1). Although the concept of reporting is important, it brings up the question of whether the differences in mortality observed by Florence Nightingale are a function of differences in quality of care or differences in the baseline risk of the patient population served. Today, most hospital report cards include risk-adjustment techniques to appropriately compare quality, a technique not available 150 yr ago.[3] A more detailed discussion of quality measurement, including the inclusion of risk adjustment, can be found elsewhere.[4]

The next major figure in quality measurement is Ernest Codman, a surgeon who lived from 1869 to 1940. He said, "Hospitals, if they wish to be sure of improvement, must find out what their results are, must analyze their results, and must compare their results with those of other hospitals."[5] Unfortunately, his ideas were not well accepted by his colleagues at the time, which led him to resign from the Massachusetts General Hospital, but his ideas were later accepted and eventually led to the founding of The Joint Commission. The epitaph on his gravestone, erected by the American College of Surgeons, reads, "It may take a hundred years for my ideas to be accepted." He was correct in his assumption.

Measurement has been a key component of modern anesthesia practice, with the initial focus being on anesthetic mortality. Shortly after the first reported use of an anesthetic, the first reported death from the administration of an anesthetic

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Table 1. Institute of Medicine: Six Domains of Quality

Domain	Description
Safe	Avoiding harm to patients from the care that is intended to help them
Effective	Providing services based on scientific knowledge to all who could benefit and refraining from providing services to those not likely to benefit (avoiding underuse and misuse, respectively)
Patient centered	Providing care that is respectful of and responsive to individual patient preferences, needs, and values and ensuring that patient values guide all clinical decisions
Timely	Reducing waits and sometimes harmful delays for both those who receive and those who give care
Efficient	Avoiding waste, including waste of equipment, supplies, ideas, and energy
Equitable	Providing care that does not vary in quality because of personal characteristics such as gender, ethnicity, geographic location, and socioeconomic status

Adapted from Reference 1.

occurred. According to burial documents, Hannah Greener died from the effects of chloroform.[6] However, it took almost a century before anesthetic mortality was measured in a large systematic study. Beecher and Todd[7] measured death directly attributable to anesthesia in 10 centers between the years 1948 to 1952 (fig. 2). The rate of mortality was shown to decrease dramatically between their initial report and subsequent studies with a currently frequently quoted rate of 1 in 185,096 based on data from 1982 from the Confidential Enquiries into Perioperative Deaths.[8] The field of anesthesiology's focus on developing systems of care and checklists clearly had a profound effect on mortality, particularly for healthy individuals. The accomplishments of the field of anesthesiology were lauded in the 1999 Institute of Medicine report titled, "To Err Is Human," which stated, "few professional societies or groups have demonstrated a visible commitment to reducing errors in health care and improving patient safety. … The exception most often cited is the work that has been done by anesthesiologists to improve safety and outcomes for patients."[9]

Anesthesiology has successfully reduced mortality directly attributable to anesthesia care from two deaths per 10,000 anesthetics administered in 1952 to one death per 200,000 to 300,000 anesthetics administered in 1982. The most recent rate of direct-anesthetic mortality is consistent with six-sigma quality. Although overall surgical mortality in healthy individuals has decreased, there continue to be high rates of anesthetic complications such as hospital-acquired infections, postoperative nausea and vomiting, and adverse drug events. However, Lagasse[10] has questioned the overall safety of anesthesia when additional studies and definitions of perioperative mortality are used. Nonetheless, high-quality anesthetic care can reduce these rates of complications and should be every practitioner's goal. As Ludwig Wittgenstein said, "Resting on your laurels is as resting when you are walking in the snow. You doze off and die in your sleep." Anesthesiologists should be cautious in remaining complacent with current complication rates and strive to improve all surgical outcomes.

Anesthesia-related Complications

In reviewing the history of measurement of anesthesia-related outcomes, Macario *et al.*[11] published a study asking anesthesiologists' expert opinion of those outcomes attributed to anesthesia care which patients value. They plotted the importance of the outcome against the frequency. For example, death and recall with pain are very important but of low frequency. Pain at the intravenous site is not very important but of high frequency. All of the outcomes cited were almost entirely within the control of the anesthesiologist.

In the United States, the National Quality Forum endorses measures that can be incorporated into federal value-based purchasing programs. National Quality Forum–endorsed measures represent a group of outcomes on which the field

	Number of Special Inmates on the 8th April, 1861.	Average Number of Inmates in each Hospital.	Number of Deaths registered in the Year 1861.	Mortality per Cent. on Inmates.
In 106 Principal Hospitals of England	12709	120	7227	56·87
24 London Hospitals	4214	176	3828	90·84
12 Hospitals in Large Towns	1870	156	1555	83·16
25 County and Important Provincial Hospitals	2248	90	886	39·41
30 Other Hospitals	1136	38	457	40·23
13 Naval and Military Hospitals	3000	231	470	15·67
1 Royal Sea Bathing Infirmary (Margate)	133	133	17	12·78
1 Dane Hill Metropolitan Infirmary (Margate)	108	108	14	12·96

Fig. 1. Rate of mortality in 106 hospitals in England, based on location, created by Florence Nightingale in 1863. Reproduced with permission from Reference 2.

Fig. 2. Beecher and Todd: *A Study of the Deaths Associated with Anesthesia and Surgery*. A copy of the monograph in the Dripps Library. In the public domain.

Fig. 3. Shared accountability is a function of patient, clinician, and system factors. QI, quality improvement; SES, socioeconomic status. Reproduced with permission from Peterson ED, Ho PM, Barton M, *et al.* ACC/AHA/AACVPR/AAFP/ANA concepts for clinician-patient shared accountability in performance measures: A report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. Journal of the American College of Cardiology 2014; 64:2133–45. Reproduced with permission.

of anesthesiology is willing to be measured. The anesthesiology measures were initially focused entirely on processes of care, such as the Surgical Care Improvement Project goals of antibiotics administered within 1 h before incision.[12] There initially was minimal willingness on the part of the American Society of Anesthesiologists House of Delegates to be measured on outcomes that can be shared with our surgical colleagues and the hospital, although shared outcome measures have been endorsed more recently. Most of these outcome measures represent postoperative complication rates as well as mortality. There are clearly some complications that can be attributed uniquely to the anesthesiologist, such as failed intubation, or attributed uniquely to the surgeon's skill, such as cutting through the bile duct, and each practitioner should be measured on those outcomes. With respect for more general morbidity, such as pneumonia or mortality, we should focus on what matters to patients and share the accountability for these outcomes with the surgeons.

The probability of developing a complication is determined in part by patient comorbidities. Clearly, the clinical skill of the anesthesiologist, nurse anesthetists, and anesthesia assistants in managing comorbidities is critical to outcome. Finally, anesthesiologists have been shown to positively impact the rate of failure to rescue or the likelihood of death after developing a complication. This likely reflects the anesthesiologist's role in the postanesthesia care unit, intensive care unit and ward.

Shared Accountability

Measuring individual anesthesiologist performance was first reported by Slogoff and Keats[13] in their paper on the relationship between the presence of preoperative myocardial ischemia and perioperative myocardial infarction and death.

One anesthesiologist, number 7 in the paper, had significantly higher rates of tachycardia and associated myocardial ischemia and infarction. Measuring outcome on an individual basis is critical for quality improvement, and education should be the first strategy for those providers who are outliers. One example of using local outcome metrics for quality and performance improvement is the Multicenter Perioperative Outcomes Group and the ASPIRE (Anesthesiology Performance Improvement and Reporting Exchange) quality initiative. Using data from the electronic medical record, the ASPIRE team is able to provide individual practitioners with their own dashboard of quality metrics and compare them with the rest of their department or national norms. They are currently going beyond process measures and using *International Classification of Diseases* (10th edition) codes and laboratory data to develop quality reports on outcomes such as perioperative myocardial injury and acute kidney injury.

If anesthesiologists are to be viewed as perioperative physicians, then they must be engaged in improving all aspects of surgical and anesthetic outcomes. As discussed earlier, anesthesiologists should be measured on intraoperative outcomes directly attributed to their care as well as be jointly accountable for postoperative outcomes. Essentially, perioperative care is a team sport, and shared accountability of all perioperative outcomes is key (fig. 3). Improvements in surgical morbidity and mortality occur when measurement and feedback is provided. The Veterans Administration National Surgical Quality Improvement Program was commissioned because of concerns regarding increased mortality associated with surgical care at the Veterans Administration Hospitals.

With implementation of National Surgical Quality Improvement Program outcome-based assessment and report card back to the hospitals, there was a marked improvement in both mortality and complication rates during the implementation phase.[14] During a period of increasing transparency of perioperative outcomes in nonfederal hospitals, Finks *et al.*[15] used Medicare data to demonstrate reductions in surgical mortality over a 10-yr period in major abdominal and thoracic procedures. Despite the improvement in the public and private sectors, 30-day mortality remained high in this group of high-risk surgeries, which suggests room for improvement, as opposed to the ambulatory surgery population where rates of complications are much lower. Because complications are a function of the interaction of patient factors, system factors, and clinical skills, it will require attention to all three domains to achieve optimal patient outcomes. If all groups assume joint ownership, including patients, hospitals, and providers, then outcomes will be improved.

The Journey from Anesthesiology to Perioperative Medicine

Anesthesiologists, as perioperative physicians, can impact care preoperatively, intraoperatively, and postoperatively to change the trajectory of the outcome. There are several strategies that have been implemented by anesthesiologists and anesthesiology departments to lead to improved outcome by being engaged in perioperative medicine. There are multiple such examples. The preoperative cardiovascular evaluation based on perioperative guidelines has been used in clinics as screening tools to optimize medical management, and strategies continue to evolve with the production of new evidence.[16] There is increasing evidence of the value of prehabilitation and exercise on outcomes after surgery, and prehabilitation clinics and protocols are being developed.[17] Anemia clinics and the use of preoperative erythropoietin and intravenous iron supplementation are other strategies that anesthesiologists can use in their preoperative clinic to improve perioperative outcomes.[18] Postoperative critical care has been an integral part of our departments since the development of the specialty.

Anesthesiologists can also impact patient care through efforts to address the opiate crisis. There is a great deal of attention on the risk of prolonged opiate use and the conversion to opiate substance disorder after surgery.[19] This concern has sparked a movement toward developing opiate-free or sparing techniques and the increasing use of regional anesthesia. Patients themselves are increasingly interested in more active participation during surgery, and patients are opting to be more awake, especially during orthopedic procedures. Globally, anesthesiologists are demonstrating leadership in developing postdischarge pain management strategies. For example, members of the faculty at the University of Pennsylvania Department of Anesthesiology and Critical Care are redefining discharge prescription order sets within the electronic medical record for opiates. The new order sets have

THE LANCET] **ORIGINAL**

ADVERSE CEREBRAL EFFECTS OF ANÆSTHESIA ON OLD PEOPLE*

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Fig. 4. The 1955 article by P.D. Bedford described postoperative delayed neurocognitive recovery after surgery in *The Lancet*. Reproduced with permission.

demonstrated similar patient satisfaction with pain management while reducing the number of dispensed, and therefore unnecessary, opiates.

A major area of interest, particularly in the elderly, is the issue of postoperative delayed neurocognitive recovery. There are stories of patients developing cognitive changes, delirium, and even hallucinations after surgery, with memory deficits for up to three months, or in some cases longer. There is interest in the role of neuroinflammation and the impact of surgery and potential impact of anesthesia in patients with a vulnerable brain who already demonstrate some degree of mild cognitive impairment.[20–22] The effects on cognition have been known for more than 60 yr and have been reported in the geriatric literature (fig. 4).[23,24] As described earlier, anesthesiologists should stop resting on their laurels and embrace new patient safety opportunities, hence the development of the American Society of Anesthesiologists Perioperative Brain Health Initiative. The mission of this Initiative is to arm anesthesiologists and other clinicians, hospitals, patients, and their families with tools and resources necessary to optimize the cognitive recovery and perioperative experience for adults 65 yr and older undergoing surgery. The Perioperative Brain Health Initiative website (www.asahq.org/brainhealthinitiative) includes tools and resources that clinicians can use to implement change locally. It includes a series of questions to ask patients preoperatively, which will help identify those at risk as well as remind patients to bring cognitive aids (*e.g.*, hearing devices, glasses) to the hospital (fig. 5). The Perioperative Brain Health Initiative is requesting that patients and providers submit stories of delirium and cognitive problems postoperatively as well as hospital-based improvement strategies so that these stories can be shared with others and allow anesthesiologists to lead through this patient safety initiative.

In the context of defining the cause and treatment of perioperative complications, it is critical that anesthesiologists continue to perform research that will help our patients. Without such innovative research, we will become extinct as a profession.[25] For example, anesthesiologists are actively engaged in both basic and clinical science, trying to understand the underlying pathophysiology as well as develop strategies to reduce the incidence and potential harm of postoperative delirium and delayed neurocognitive recovery.

Key Questions to Ask Your Patients
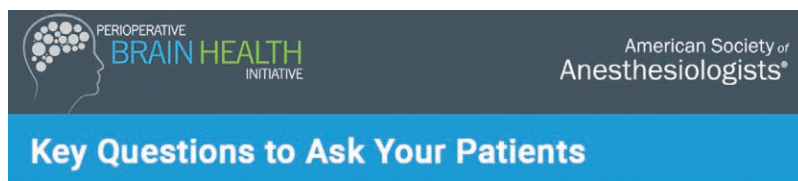
Below is a series of questions that providers need to ask their patients prior to surgery. M.E.D.I.A. refers to Memory, Episode, Drugs, Items and Aides.

A positive response to items 1-3 (M.E.D.) indicate risk for adverse cognitive outcomes and should trigger a preoperative cognitive evaluation, while items 4 and 5 are designed to reduce delirium.

1. Memory
Have you ever had a problem with your Memory or thinking ability after hospitalization or surgery before?

2. Episode
Have you ever had an Episode of confusion, or imagining things that were not real?

3. Drugs
Are you taking Drugs to help your thinking or memory such as Namenda (memantine) or Aricept (donepezil)?

4. Items
Are there personal Items, such as photos or a favorite music CD, that you can bring to remind you of home and family?

5. Aides
Do you have Aides, such as eyeglasses, hearing aides or dentures that you can bring to help you reorient after surgery?

Fig. 5. The American Society of Anesthesiologists Perioperative Brain Health Initiative includes numerous resources on the website. These include key questions that elderly patients should answer regarding memory issues and items and aids patients should bring to the hospital. Reproduced with permission.

Table 2. Key Messages

1. Measurement is good!
2. Anesthesiologists should be engaged in improving all surgical outcomes.
3. Anesthesiologists should take more ownership of the journey.
4. Patients' expectations have changed.

It will be important for the profession to advocate in the U.S. Congress to ensure continued funding and maintain interest in perioperative research through support for the National Institutes of Health budget.

Patient Expectations and Satisfaction with Care

Patients traditionally visit physicians and hospitals based on reputation and recommendations from colleagues and friends. Quality measurement and public reporting have been advocated by both consumers and insurers as a means of helping patients decide where to receive care. Multiple studies have shown that only a small percentage of patients actually look at quality ratings on websites, although this is changing, particularly with the publication of patient satisfaction ratings and comments.[26]

As these quality metrics are increasingly viewed by the public, the traditional medical metrics are being reevaluated. For example, readmission penalties are included in many value-based purchasing programs.[27] Although well-being and the incidence of being admitted after hospitalization is of concern to the patient, a more patient-centered outcome would be the number of days patients spend at home after surgery.[28] Using that metric, a short readmission is viewed very differently than a prolonged readmission. In addition, using other types of acute or postacute care besides the hospital are taken into account by such a measure.

It is clear that we are in an age of healthcare consumerism. Patients are looking for physicians to be more engaged in listening to their concerns. This can be accomplished through the development and assessment of measures that

matter, including those that are important and meaningful to the patients themselves. These measures can drive both the national aims as well as local quality improvement. By the National Quality Forum definition, a patient-reported outcome is any report on the status of a patient's health condition that comes directly from the patient, without interpretations of the patient's response by the clinician or anyone else.[29] Patient-reported outcomes are increasingly being used to evaluate and improve patient care and experience through assessing factors such as functional status. Patients also want to ensure that they understand their risk and have truly informed consent. This may include understanding the quality of their recovery and return to baseline function or improvement in their activities of daily living. The American Society of Anesthesiologists is engaged in furthering the development of measures as a member of The National Health Council Patient-Centered Value Model Rubric.

Patient satisfaction with care is another form of patient-reported outcome measure. Increasingly, patients are viewing patient comments on Yelp and are viewing Press–Ganey survey comments posted voluntarily on health system websites. The University of Utah has demonstrated the effect of publication of the Press–Ganey physician ratings and comments on their health system website and demonstrated that with public transparency the physician ratings markedly improved.

One clear example of using patient satisfaction in value-based care is the Geisinger Healthcare System (Danville, Pennsylvania) and its "Proven Experience" program. This program includes a "warranty" on the experience of care received within their system. If patients believe that an aspect of care did not meet expectations, they can open an app on their smart device and request a refund of a percentage of their copayments. Ashish Jha, M.D., M.P.H., a Harvard health policy expert, has suggested that a percentage of Medicare payments be linked to patient satisfaction with care measures.[30]

Are We Ready to Be Measured by Our Patients on Satisfaction with Care?

Measurement of satisfaction with anesthesia care has been proposed in academic publications, but such measurements have focused on defined procedures such as monitored anesthesia care for cataract surgery. One domain of satisfaction with anesthesiologists, certified registered nurse anesthetists, and anesthesia assistants is our level of empathy. As a specialty, are we ready to be measured by our patients on the empathy that we project? Many providers would feel a strong sense of vulnerability in such a paradigm. Brene Brown, Ph.D., L.M.S.W., has written extensively on the importance of vulnerability as the birthplace of creativity, innovation, and change. Candace Morrissey, M.D., M.S.P.H., an anesthesiologist at the University of Utah, wrote a piece for the *NEJM Catalyst* in which she said: "Countless eyes glazing over helped me realize that to explain what we do medically was not precious time well spent. Patients assumed I'd be technically competent. What they wanted to know was

that we cared."[31] Although the competency and excellence of the anesthesiologist remains paramount, Morrissey's essay emphasized the importance of empathy to many patients.

As an anesthesiologist, I am constantly amazed at how poorly focused the rest of the operating room personnel are on the patient during that period when they are awake before induction. How can empathy be taught? The Cleveland Clinic has produced a video that is internally facing for their providers to remind them of the importance of empathy for their patients, providers, and staff. I urge all to view it at https://www.youtube.com/watch?v=cDDWvj_q-o8.

Summary

In summary, medicine has moved from metrics of medical outcomes to patient-reported outcome measures and assessing patient satisfaction. As anesthesiologists, it is critical for us to continue to provide exemplary and safe care while also listening carefully to what our patients are interested in and deserve. We will remain relevant only if we ensure that we do both.

References

1. Committee on Quality Health Care in America IoM: Crossing the Quality Chasm: A New Health System for the 21st Century. Washington, D.C., National Academies Press, 2001
2. Nightingale F: Notes on Hospitals, 3rd edition. London, Longman, Green, Longman, Roberts and Green, 1863
3. Iezzoni LI: 100 apples divided by 15 red herrings: A cautionary tale from the mid-19th century on comparing hospital mortality rates. Ann Intern Med 1996; 124:1079–85
4. Hyder JA, Hebl JR: Performance measurement to demonstrate value. Anesthesiol Clin 2015; 33:679–96
5. Codman EA: A Study in Hospital Efficiency: As Demonstrated by the Case Report of the First Five Years of a Private Hospital. Boston, Thomas Todd, 1918
6. Knight PR 3rd, Bacon DR: An unexplained death: Hannah Greener and chloroform. ANESTHESIOLOGY 2002; 96:1250–3
7. Beecher HK, Todd DP: A study of the deaths associated with anesthesia and surgery: Based on a study of 599,548 anesthesias in ten institutions 1948–1952, inclusive. Ann Surg 1954; 140:2–35
8. Lunn JN, Mushin WW: Mortality associated with anesthesia. Anaesthesia 1982; 37:856

9. Kohn LT, Corrigan JM, Donaldson MS: To Err Is Human: Building a Safer Health System. Washington D.C., Institute of Medicine, 2000

10. Lagasse RS: Anesthesia safety: model or myth? A review of the published literature and analysis of current original data. ANESTHESIOLOGY 2002; 97:1609–17

11. Macario A, Weinger M, Truong P, Lee M: Which clinical anesthesia outcomes are both common and important to avoid? The perspective of a panel of expert anesthesiologists. Anesth Analg 1999; 88:1085–91

12. Hyder JA, Niconchuk J, Glance LG, Neuman MD, Cima RR, Dutton RP, Nguyen LL, Fleisher LA, Bader AM: What can the national quality forum tell us about performance measurement in anesthesiology? Anesth Analg 2015; 120:440–8

13. Slogoff S, Keats AS: Does perioperative myocardial ischemia lead to postoperative myocardial infarction? ANESTHESIOLOGY 1985; 62:107–14

14. Khuri SF, Daley J, Henderson W, Hur K, Demakis J, Aust JB, Chong V, Fabri PJ, Gibbs JO, Grover F, Hammermeister K, Irvin G 3rd, McDonald G, Passaro E Jr, Phillips L, Scamman F, Spencer J, Stremple JF: The Department of Veterans Affairs' NSQIP: The first national, validated, outcome-based, risk-adjusted, and peer-controlled program for the measurement and enhancement of the quality of surgical care. National VA Surgical Quality Improvement Program. Ann Surg 1998; 228:491–507

15. Finks JF, Osborne NH, Birkmeyer JD: Trends in hospital volume and operative mortality for high-risk surgery. N Engl J Med 2011; 364:2128–37

16. Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, Davila-Roman VG, Gerhard-Herman MD, Holly TA, Kane GC, Marine JE, Nelson MT, Spencer CC, Thompson A, Ting HH, Uretsky BF, Wijeysundera DN; American College of Cardiology; American Heart Association: 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: A report of the American College of Cardiology/ American Heart Association Task Force on practice guidelines. J Am Coll Cardiol 2014; 64:e77–137

17. Barberan-Garcia A, Ubré M, Roca J, Lacy AM, Burgos F, Risco R, Momblán D, Balust J, Blanco I, Martínez-Pallí G: Personalised prehabilitation in high-risk patients undergoing elective major abdominal surgery: A randomized blinded controlled trial. Ann Surg 2018; 267:50–6

18. Peters F, Ellermann I, Steinbicker AU: Intravenous iron for treatment of anemia in the 3 perisurgical phases: A review and analysis of the current literature. Anesth Analg 2018; 126:1268–82

19. Brummett CM, Waljee JF, Goesling J, Moser S, Lin P, Englesbe MJ, Bohnert ASB, Kheterpal S, Nallamothu BK: New persistent opioid use after minor and major surgical procedures in U.S. adults. JAMA Surg 2017; 152:e170504

20. Zheng B, Lai R, Li J, Zuo Z: Critical role of P2X7 receptors in the neuroinflammation and cognitive dysfunction after surgery. Brain Behav Immun 2017; 61:365–74

21. Tang JX, Mardini F, Janik LS, Garrity ST, Li RQ, Bachlani G, Eckenhoff RG, Eckenhoff MF: Modulation of murine Alzheimer pathogenesis and behavior by surgery. Ann Surg 2013; 257:439–48

22. Cascella M, Bimonte S: The role of general anesthetics and the mechanisms of hippocampal and extra-hippocampal dysfunctions in the genesis of postoperative cognitive dysfunction. Neural Regen Res 2017; 12:1780–5

23. Bedford PD: Adverse cerebral effects of anaesthesia on old people. Lancet 1955; 269:259–63

24. Racine AM, Fong TG, Gou Y, Travison TG, Tommet D, Erickson K, Jones RN, Dickerson BC, Metzger E, Marcantonio ER, Schmitt EM, Inouye SK: Clinical outcomes in older surgical patients with mild cognitive impairment. Alzheimers Dement 2018; 14:590–600

25. Todd MM, Fleisher LA: Avoiding professional extinction. ANESTHESIOLOGY 2014; 120:2–3

26. Ketelaar NA, Faber MJ, Flottorp S, Rygh LH, Deane KH, Eccles MP: Public release of performance data in changing the behaviour of healthcare consumers, professionals or organisations. Cochrane Database Syst Rev 2011: CD004538

27. VanLare JM, Conway PH: Value-based purchasing–national programs to move from volume to value. N Engl J Med 2012; 367:292–5

28. Myles PS, Shulman MA, Heritier S, Wallace S, McIlroy DR, McCluskey S, Sillar I, Forbes A: Validation of days at home as an outcome measure after surgery: A prospective cohort study in Australia. BMJ Open 2017; 7:e015828

29. National Quality Forum: Patient reported outcomes (PROs) in performance measurement, 2013. Available at https://www.qualityforum.org/publications/2012/12/patient-reported_outcomes_in_performance_measurement.aspx

30. Jha AK: Payment power to the patients. JAMA 2017; 318:18–9

31. Morrissey C: Patient satisfaction in anesthesiology matters. NEJM Catalyst, 2017. Available at: https://catalyst.nejm.org/patient-feedback-anesthesiology-matters/

Individual Positive End-expiratory Pressure Settings Optimize Intraoperative Mechanical Ventilation and Reduce Postoperative Atelectasis

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CME This article has been selected for the Anesthesiology CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

ABSTRACT

Background: Intraoperative lung-protective ventilation has been recommended to reduce postoperative pulmonary complications after abdominal surgery. Although the protective role of a more physiologic tidal volume has been established, the added protection afforded by positive end-expiratory pressure (PEEP) remains uncertain. The authors hypothesized that a low fixed PEEP might not fit all patients and that an individually titrated PEEP during anesthesia might improve lung function during and after surgery.

Methods: Forty patients were studied in the operating room (20 laparoscopic and 20 open-abdominal). They underwent elective abdominal surgery and were randomized to institutional PEEP ($4\,cm\,H_2O$) or electrical impedance tomography–guided PEEP (applied after recruitment maneuvers and targeted at minimizing lung collapse and hyperdistension, simultaneously). Patients were extubated without changing selected PEEP or fractional inspired oxygen tension while under anesthesia and submitted to chest computed tomography after extubation. Our primary goal was to individually identify the electrical impedance tomography–guided PEEP value producing the best compromise of lung collapse and hyperdistention.

Results: Electrical impedance tomography–guided PEEP varied markedly across individuals (median, $12\,cm\,H_2O$; range, 6 to $16\,cm\,H_2O$; 95% CI, 10–14). Compared with PEEP of $4\,cm\,H_2O$, patients randomized to the electrical impedance tomography–guided strategy had less postoperative atelectasis (6.2 ± 4.1 vs. $10.8 \pm 7.1\%$ of lung tissue mass; $P = 0.017$) and lower intraoperative driving pressures (mean values during surgery of 8.0 ± 1.7 vs. $11.6 \pm 3.8\,cm\,H_2O$; $P < 0.001$). The electrical impedance tomography–guided PEEP arm had higher intraoperative oxygenation (435 ± 62 vs. 266 ± 76 mmHg for laparoscopic group; $P < 0.001$), while presenting equivalent hemodynamics (mean arterial pressure during surgery of 80 ± 14 vs. 78 ± 15 mmHg; $P = 0.821$).

Conclusions: PEEP requirements vary widely among patients receiving protective tidal volumes during anesthesia for abdominal surgery. Individualized PEEP settings could reduce postoperative atelectasis (measured by computed tomography) while improving intraoperative oxygenation and driving pressures, causing minimum side effects. **(ANESTHESIOLOGY 2018; 129:1070-81)**

LUNG protective ventilation has been shown to improve outcomes in patients undergoing general anesthesia.[1–4] Anesthesia, paralysis, and mechanical ventilation under high concentrations of oxygen without adding positive end-expiratory pressure (PEEP) all result in persistent atelectasis, lung heterogeneities, and postoperative pulmonary complications.[2,5–7] High driving pressures (ΔP) during anesthesia have been associated with the development of postoperative pulmonary complications, including adult respiratory distress syndrome.[8,9] The presence of a high ΔP indicates cyclic lung overstress caused by atelectasis and lung heterogeneities, often exacerbated by suboptimal ventilator settings.[10,11] Thus, a lower intraoperative ΔP has been associated with a reduction in postoperative pulmonary complications.[8,9]

Editor's Perspective

What We Already Know about This Topic

- In patients with adult respiratory distress syndrome, physiologic tidal volume and positive end-expiratory pressure (PEEP) are protective
- In patients without lung diseases undergoing mechanical ventilation under general anesthesia, optimal PEEP is unknown

What This Article Tells Us That Is New

- Optimal positive end-expiratory pressure (PEEP) values for patients with normal lungs and under general anesthesia vary significantly
- Application of individualized optimal PEEP intraoperatively not only reduces driving pressure and improves respiratory compliance and oxygenation but also reduce the incidence and severity of postoperative atelectasis

Recent analyses of protective strategies have suggested the use of more physiologic tidal volumes (V_T; V_T = 6 to 8 ml/kg of ideal body weight) in combination with fixed, minimum PEEP levels, although with recommendations that vary from 2 up to 6 cm H_2O.[1–4] Although the protective role of more physiologic tidal volume (V_T) has been strongly suggested, no agreement exists on the value of optimal PEEP. A recent trial showed no benefit of high PEEP of 12 cm H_2O *versus* ≤ 2 cm H_2O, but harms including hemodynamic instability and increased requirement of fluid administration.[12] Therefore, low PEEP (≤ 2 cm H_2O) was recommended.[4,13] Meanwhile, others have suggested the use of moderate levels of PEEP (5 to 8 cm H_2O),[2,9,14] advocating its preventive role against postoperative atelectasis. Such lack of consensus occurs, in part, because PEEP is not typically individualized according to patient physiology. Evidence suggests that one fixed value of PEEP is unlikely to fit all patients, with large variability in PEEP requirements caused by individual characteristics, such as chest wall dimensions and shape, abdominal content, lung weights, and pleural pressures.[15–21]

This study evaluated the impact of the optimized PEEP guided by electrical impedance tomography (PEEP-EIT) *versus* fixed PEEP of 4 cm H_2O applied during the intraoperative period, in patients with healthy lungs and submitted to abdominal surgery. We hypothesized that PEEP-EIT would vary among different patients and that it would reduce postoperative atelectasis. Our primary goal was to individually identify the PEEP-EIT value that produced the best possible compromise of lung collapse and hyperdistention. Our secondary aim was to observe the effects of such PEEP-EIT on the postoperative atelectasis measured by computed tomography scan after extubation. Additional exploratory end points were the impact of PEEP selection (according to randomization) on pulmonary function and hemodynamics.

Materials and Methods

Between August 2014 and April 2016, 40 eligible patients undergoing elective abdominal surgery were included in the study after obtaining Institutional Review Board approval and written informed consent. This trial was registered at clinicaltrials.gov (trial registration: NCT02314845). All patients were submitted to anesthesia induction, ventilation with PEEP of 4 cm H_2O, first recruitment maneuver followed by PEEP titration, and second recruitment maneuver. Then, patients were randomized to one of two treatment arms: PEEP titrated by EIT (PEEP-EIT), within the range

from 4 to 20 cm H_2O or a fixed PEEP of 4 cm H_2O (PEEP4) (fig. 1A). The randomization was stratified by type of surgery. The inclusion criteria were abdominal surgery and age above 18 years old. Exclusion criteria were American Society of Anesthesiologists Physical Status III or greater and moderate/severe obstructive or restrictive pulmonary disease.

Intravenous anesthesia was induced with patients lying supine. After insertion of intravenous and arterial lines, an EIT belt was placed at the fifth intercostal space, and the EIT monitoring (Enlight 1800, Timpel, Brazil) was started with continuous recording. All patients were preoxygenated with 100% oxygen before intubation.

Mechanical ventilation was started under volume-controlled ventilation with fractional inspired oxygen tension (F_{IO_2}) = 0.5, PEEP = 4 cm H_2O, V_T = 6 to 7 ml/kg of predicted body weight,[22] an inspiratory pause of 30%, and respiratory rate was adjusted to maintain
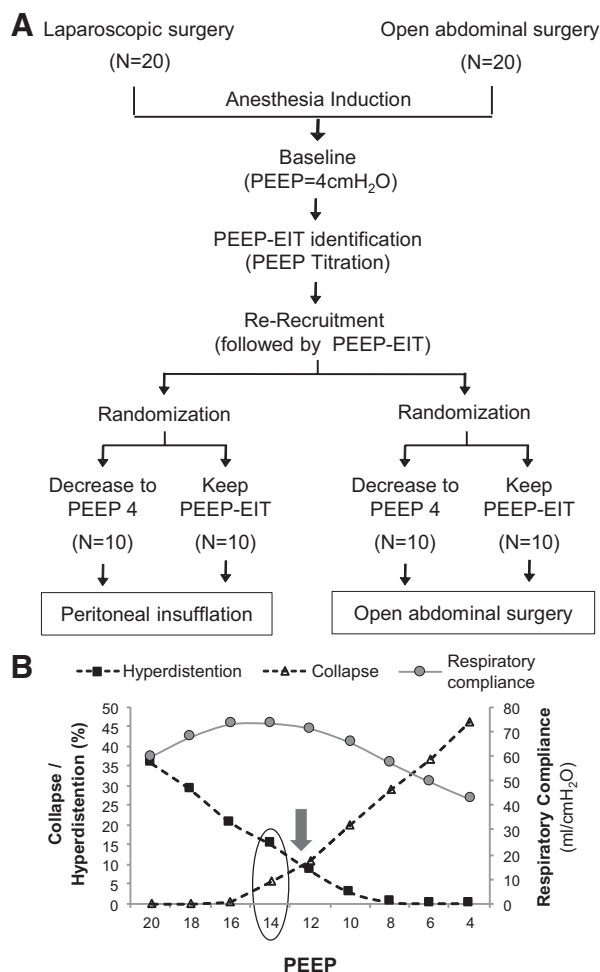
Fig. 1. *A*, Flowchart of the study. *B*, Criteria to choose positive end-expiratory pressure (PEEP) titrated by electrical impedance tomography (PEEP-EIT). PEEP-EIT was considered as the nearest PEEP above the crossing of the curves representing overdistension and collapse, indicating a mechanical compromise at which both lung collapse and hyperdistention were minimized.

end-tidal carbon dioxide between 35 and 45 mmHg. The synchronized pressure-flow sensor of the EIT monitor was connected to the proximal airway. After recording the baseline EIT signals, all patients (in both arms) were submitted to a recruitment maneuver in pressure-controlled ventilation mode with 20 cm H_2O of PEEP and inspiratory pressures reaching 40 cm H_2O for 2 min. At this PEEP level, a decremental PEEP-titration maneuver was started in volume-controlled ventilation mode, decreasing PEEP in steps of 2 cm H_2O every 40 s, and keeping constant respiratory rate (20 breaths/min), inspiratory pause of 30%, and V_T = 6 ml/kg. At the end of the procedure, the EIT monitor automatically plotted a graph showing the percentage of overdistended and collapsed lung units (corresponding to the percent mass of collapsed or overdistended lung-tissue) at each PEEP. PEEP-EIT was considered as the nearest PEEP above the crossing of the curves representing overdistension and collapse (fig. 1B), indicating a mechanical compromise where both lung collapse and overdistension were minimized.

After the decremental PEEP titration (performed in all patients before randomization), a new recruitment maneuver was performed, and PEEP-EIT was applied for 2 min, only for monitoring purposes. Subsequently, the patient was randomized and, according to group allocation, the PEEP-EIT was then maintained (PEEP-EIT arm) or reduced to 4 cm H_2O (PEEP4 arm). This randomized PEEP level was maintained throughout surgery, until extubation.

Data acquisition in laparoscopic and open abdominal surgery occurred in several time points: baseline (after intubation), during PEEP titration, after randomization, within 1 h of surgery, and before extubation. Data acquisition in patients undergoing laparoscopic surgery also occurred at the start of pneumoperitoneum and before pneumoperitoneum deflation. Mechanical ventilation, EIT, and hemodynamic data were collected. Arterial blood gas samples were also analyzed during surgery (fig. 2, A and B). Mechanical

ventilation parameters, such as RR and FIO_2, could be changed according to arterial blood gas results or SpO_2. Fluid administration, pain management, vasoactive drugs, and blood transfusion were implemented according to routine protocols.

Weaning was performed under pressure-support mode, keeping FIO_2 at 50% and maintaining PEEP according to the patient's randomization (*i.e.*, at 4 cm H_2O in controls, and at PEEP-EIT for the treatment arm). Thirty to 60 min after extubation, a chest computed tomography scan was obtained, during which patients were instructed to perform an expiratory hold at functional residual capacity. Ten slices were optimally selected to interpolate and calculate the percentage of nonaerated lung mass tissue (densities between −200 and +100 UH).[23]

The primary outcome of this trial was to identify the PEEP value, for each patient, that produced the best possible compromise of lung collapse and hyperdistention during a PEEP titration procedure using EIT. The secondary end point was to calculate the amount of atelectasis, as the percentage of lung mass, evaluated by chest computed tomography scan after extubation. Additional exploratory end points were the impact of PEEP selection (according to randomization) on pulmonary function and hemodynamics. Additional information on some procedures is provided in the Supplemental Digital Content, http://links.lww.com/ALN/B784.

Statistical Analysis

The sample size was estimated for our secondary end point, the amount of atelectasis. A previous study[24] observed, in patients ventilated with and without PEEP (=6 cm H_2O), a median area of atelectasis postoperatively of 5.2 cm² (range 1.6 to 12.2) *versus* 8.5 cm² (3–23.1). A sample size of 40 patients (20 patients in each PEEP arm) would be needed to observe this difference, assuming $\alpha = 0.05$ and power of 85%, using two-tailed Wilcoxon-Mann-Whitney
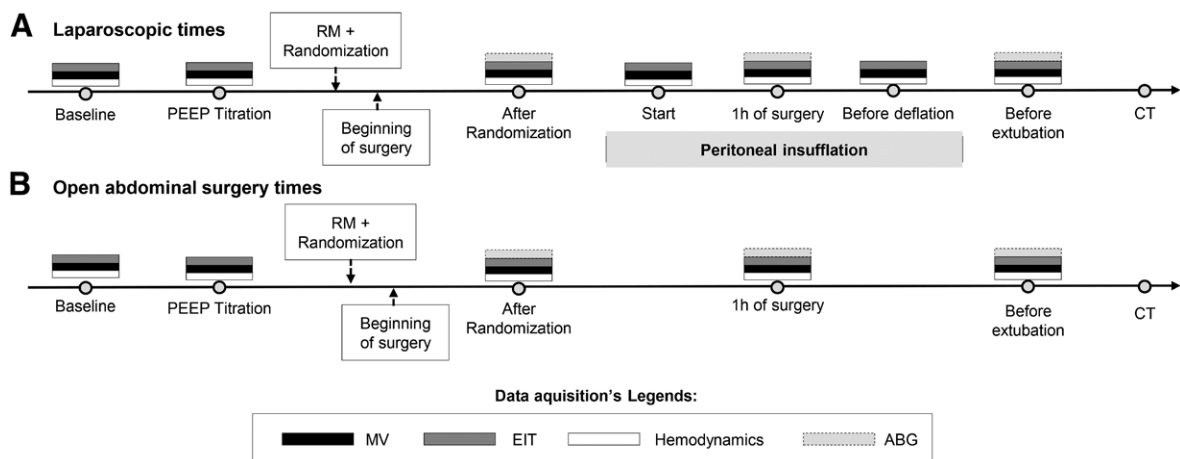
Fig. 2. Data collection times in laparoscopic (*A*) and open abdominal surgery (*B*). ABG, arterial blood gas; CT, computed tomography; EIT, electrical impedance tomography; MV, mechanical ventilation; PEEP, positive end-expiratory pressure; RM, recruitment maneuver.

test (asymptotic relative efficiency method) with software G*Power 3.1[25] and considering a data loss of 10%.

Normal distribution for continuous variables was determined using the Shapiro-Wilk test and, accordingly, the results were reported as mean ± SD and median (interquartile range). Unpaired *t* tests or Mann–Whitney tests were used for univariate analyses of continuous variables. For correlation between two variables, the Pearson correlation test was used.

For the analysis of variables collected at many time points during surgery and for computed tomography collapse, a mixed-model analysis, without random factors, was performed using the following variables as fixed factors: type of surgery (laparoscopic and open), time (from "PEEP-EIT," during PEEP titration, to "before extubation"), group (PEEP-EIT arm or PEEP4 arm), and the interaction between time and group. For comparisons between time points the Sidak correction test was used. Mean values for driving pressure, mean arterial pressure, PaO_2/FIO_2, and respiratory compliance after randomization were calculated for one or both types of surgery (laparoscopic and open), representing the average of three time points during surgery.

No data nor outlier values were excluded. The amount of missing data is less than 5%, in general, with no single variable presenting more than 15% of missing data. No data imputation was performed. SPSS 17 for Windows (SPSS Inc., USA) and GraphPad Prism V 6 (GraphPad Software, USA) were used for the statistical analyses and to plot the graphs. Statistically significant values were considered to have *P* values less than 0.05 using two-tailed tests.

Results

A total of 40 patients were included in this study. Patients' characteristics and comorbidities are summarized in table 1 and table E1 in the Supplemental Digital Content (http://links.lww.com/ALN/B784). No complication associated with the study was observed in any participant.

After anesthesia induction and intubation, when all patients received PEEP = 4 cm H_2O (before recruiting maneuvers), there were no statistically significant differences in respiratory variables between the two study arms (table 2). Equivalent respiratory variables were also observed after recruitment maneuver, when patients in both study arms were briefly submitted, during PEEP titration, to PEEP-EIT (table 2).

Primary Outcome: Identified PEEP

Before randomization, PEEP-EIT was assessed by for all patients after a recruiting maneuver. The median PEEP-EIT was 12 cm H_2O (10 to 14; 95% CI, 10–14; table 3 and fig. E1 in the Supplemental Digital Content (http://links.lww.com/ALN/B784)). Patients submitted to laparoscopic surgery exhibited statistically significantly higher PEEP-EIT than patients submitted to open surgery (13.5 ± 1.6 *vs.* 10.2 ± 2.3 cm H_2O; *P* < 0.001). Of note, PEEP

Table 1. Baseline Characteristics of the Patients

Demographic and Clinical Variables	All (n = 40)	PEEP4 (n = 20)	PEEP-EIT (n = 20)
Age, median (IQR), yr	52.5 (26–74)	54.2 (33–68)	50.7 (26–74)
Male sex, n (%)	18 (45.0)	8 (40.0)	10 (50.0)
Weight, mean ± SD, kg	77.9 ± 15.6	79 ± 15.9	76.8 ± 15.6
Predicted body weight, mean ± SD, kg	56.4 ± 9.5	54.3 ± 9.9	58.6 ± 8.8
Body mass index, mean ± SD, kg/m²	29.5 ± 4.3	30.6 ± 4.2	28.3 ± 4.2
Thoracic perimeter, mean ± SD, cm	100.4 ± 8.6	102 ± 9.0	99 ± 8.0
Type of Surgery			
Urology, n (%)	13 (32.5)	5 (25)	8 (40)
Gastric, n (%)	19 (47.5)	10 (50)	9 (45)
Gynecology, n (%)	8 (20)	5 (25)	3 (15)
ASA Physical Status I, n (%)	12 (30)	6 (30)	6 (30)
ASA Physical Status II, n (%)	28 (70)	14 (70)	14 (70)
Hypertension, n (%)	18 (45)	8 (40)	10 (50)
Hypothyroidism, n (%)	3 (7.5)	1 (5)	2 (10)
Diabetes, n (%)	7 (17.5)	2 (10)	5 (25)
Chronic kidney disease, n (%)	1 (2.5)	0 (0)	1 (5)
Smoking status			
Never, n (%)	27 (67.5)	16 (80)	11 (55)
Former, n (%)	5 (12.5)	2 (10)	3 (15)
Current, n (%)	8 (10)	2 (10)	6 (30)
Active cancer, n (%)	14 (35)	5 (25)	9 (45)
Chemotherapy, n (%)	0 (0)	0 (0)	0 (0)

Chronic kidney disease as defined according to Kidney Disease: Improving Global Outcomes. ASA, American Society of Anesthesiologists; IQR, interquartile range; PEEP4, PEEP of 4 cm H_2O; PEEP-EIT, PEEP guided by electrical impedance tomography.

requirements for the laparoscopic patients were assessed before abdominal insufflation of CO_2. There was some correlation (R^2 = 0.371, *P* < 0.001) between body mass index and PEEP-EIT (fig. 3), which partially explained such difference in PEEP-EIT (patients in the open surgery group had a lower body mass index, requiring a lower PEEP-EIT).

Secondary Outcome: Postoperative Collapse

After extubation and anesthesia recovery, the whole-lung computed tomography evaluation confirmed the reduction in atelectasis, with a significantly lower percentage of collapsed lung tissue in the PEEP-EIT arm (percent of nonaerated tissue = 6.2 ± 4.1% *vs.* 10.8 ± 7.1%; PEEP-EIT *vs.* PEEP4, respectively; *P* = 0.017; fig. 4). The amount of atelectasis in the two types of surgery was not different (*P* = 0.457). Representative images of computed tomography (after surgery) and EIT (during surgery) are shown in figure 5.

Exploratory Outcomes: PEEP, Body Mass Index, and Driving Pressure

When comparing ΔP before and after PEEP titration (*i.e.*, comparing ΔP at PEEP = 4 cm H_2O [after anesthesia induction] *vs.* the ΔP at the titrated-PEEP [after a recruiting

Table 2. Ventilation Parameters

Time of Acquisition	Parameters	Laparoscopic (n = 20) Randomized Group			Open Surgery (n = 20) Randomized Group		
		PEEP4 (n = 10)	PEEP-EIT (n = 10)	P Value	PEEP4 (n = 10)	PEEP-EIT (n = 10)	P Value
Baseline	V_T/Kg (ml/kg)	7 ± 0.7	6.4 ± 0.5	0.073	6.6 ± 0.5	6.2 ± 0.7	0.144
	PEEP (cmH$_2$O)	4.2 ± 0.3	4.1 ± 0.4		4.1 ± 0.1	4.4 ± 0.4	
	Plateau pressure (cmH$_2$O)	15.7 ± 2.4	13.9 ± 3.3	0.195	13.3 ± 2.5	13.4 ± 1.9	0.883
	Compliance (ml/cmH$_2$O)	33.5 ± 8.1	37.7 ± 9.7	0.317	42.1 ± 15.7	43.5 ± 7.9	0.807
	Driving pressure (cmH$_2$O)	11.6 ± 2.5	9.8 ± 3.1	0.188	9.3 ± 2.5	9.1 ± 1.7	0.869
	Collapse on EIT (%)	44.6 ± 15.4	41.7 ± 18.0	0.711	35 ± 16.1	31.3 ± 9.2	0.530
During titration (at PEEP-EIT)	V_T/Kg (ml/kg)	7.1 ± 0.5	6.7 ± 0.5	0.086	6.8 ± 0.5	6.5 ± 0.6	0.125
	PEEP (cmH$_2$O)	14.3 ± 1.5	12.9 ± 1.6		10.2 ± 2.3	10.3 ± 2.3	
	Plateau pressure (cmH$_2$O)	19.5 ± 2.0	18.1 ± 1.9	0.130	16.1 ± 3.1	16.8 ± 3.3	0.660
	Compliance (ml/cmH$_2$O)	77.1 ± 14.0	75.3 ± 8.6	0.742	75.9 ± 18.0	71.9 ± 15.7	0.601
	Driving pressure (cmH$_2$O)	5.3 ± 0.7	5.2 ± 0.7	0.796	6.0 ± 1.3	6.5 ± 1.1	0.336
	Collapse on EIT (%)	6.5 ± 5.6	4.5 ± 3.9	0.375	3.6 ± 1.8	5.4 ± 2.8	0.097
After randomization (selected PEEP)	V_T/Kg (ml/kg)	7.1 ± 0.7	6.5 ± 0.8	0.071	6.6 ± 0.4	6.3 ± 0.6	0.206
	PEEP (cmH$_2$O)	3.8 ± 0.3	13.2 ± 1.4	**<0.001**	3.9 ± 0.3	10.1 ± 2.0	**<0.001**
	Plateau pressure (cmH$_2$O)	13.7 ± 1.4	18.7 ± 2.0	**<0.001**	11.7 ± 1.4	16.6 ± 3.1	**<0.001**
	Compliance (ml/cmH$_2$O)	39.6 ± 7.2	67.6 ± 6.7	**<0.001**	48.8 ± 13.2	66.2 ± 14.2	**0.011**
	Driving pressure (cmH$_2$O)	9.8 ± 1.4	5.5 ± 0.8	**<0.001**	7.7 ± 1.5	6.5 ± 1.3	0.070
	Collapse on EIT (%)	42.5 ± 12.6	10.3 ± 10.2	**<0.001**	29.8 ± 14.2	8.5 ± 5.1	**<0.001**

Data are expressed as mean ± SD; V_T/Kg is expressed in ml/kg; PEEP, plateau pressure, and driving pressure are expressed in cmH$_2$O; Respiratory compliance is expressed in ml/cmH$_2$O; "Collapse on EIT": collapse on electrical impedance tomography is expressed as percentage of total lung mass; PEEP4, group randomized to PEEP of 4 cm H$_2$O; PEEP-EIT, group randomized to PEEP titrated by EIT. P (t test) for the difference between PEEP4 and PEEP-EIT in the same type of surgery (laparoscopic or open surgery). P values less than 0.05 are shown in bold.

EIT, electrical impedance tomography; PEEP, positive end-expiratory pressure; PEEP4, PEEP of 4 cm H$_2$O; PEEP-EIT, PEEP guided by electrical impedance tomography; V_T, tidal volume.

Table 3. Median Values of Titrated PEEP by Electrical Impedance Tomography

Criteria to Choose PEEP	All Patients (n = 40)	Laparoscopic (n = 20) Randomized Group		Open Surgery (n = 20) Randomized Group	
		PEEP4 (n = 10)	PEEP-EIT (n = 10)	PEEP4 (n = 10)	PEEP-EIT (n = 10)
PEEP-EIT, cmH$_2$O	12 (10–14)	14 (12–16)	14 (12–14)	10 (10–12)	10 (8–10)

Data are expressed as median (interquartile range).
EIT, electrical impedance tomography; PEEP, positive end-expiratory pressure; PEEP4, PEEP of 4 cm H$_2$O; PEEP-EIT, PEEP guided by electrical impedance tomography.

maneuver]), we observed a statistically significant reduction from 9.9 ± 2.6 to 5.7 ± 1.1 cm H$_2$O ($P < 0.001$). This reduction in ΔP was associated with a marked reduction in lung collapse (from an average of $38 \pm 15\%$ to $6 \pm 4\%$ of lung parenchyma; $P < 0.001$) and correlated with body mass index: the higher the body mass index, the greater the response to recruitment and the larger the reduction in ΔP (fig. 6; $R^2 = 0.454$, $P < 0.001$).

After randomization, PEEP was kept at the PEEP-EIT within the PEEP-EIT arm and decreased to 4 cm H$_2$O within the PEEP4 arm. Consequently, patients in the PEEP-EIT arm showed higher PEEP and higher plateau pressure (V_T was kept constant, table 2 and table E2 in the Supplemental Digital Content, http://links.lww.com/ALN/B784). During surgery, we observed a marked increase in ΔP in the PEEP4 arm when compared with PEEP-EIT: mean values for both types of surgeries of 11.6 ± 3.8 *versus* 8.0 ± 1.7 cm H$_2$O ($P < 0.001$ for the PEEP arm factor

of the mixed model analysis; fig. 7). Respiratory-system compliance decreased for the PEEP4 arm: mean values of 35.4 ± 13.4 *versus* 54.3 ± 13.9 ml/cmH$_2$O ($P < 0.001$ for the PEEP arm factor; fig. E2). Parallel to these changes, ventilation in dependent lung zones decreased (fig. E3 in the Supplemental Digital Content, http://links.lww.com/ALN/B784), and oxygenation worsened, especially in the laparoscopy group (fig. 8). These deteriorating changes were especially observed in the PEEP4 arm undergoing laparoscopic surgery and were associated with progressive, dependent lung collapse that persisted until the end of surgery, as shown by the EIT-derived estimates of lung collapse (table E2 in the Supplemental Digital Content, http://links.lww.com/ALN/B784). As for open abdominal surgery, within 1 h of surgery and before extubation, neither ΔP nor collapse on EIT was statistically different between groups (table E2 in the Supplemental Digital Content, http://links.lww.com/ALN/B784).
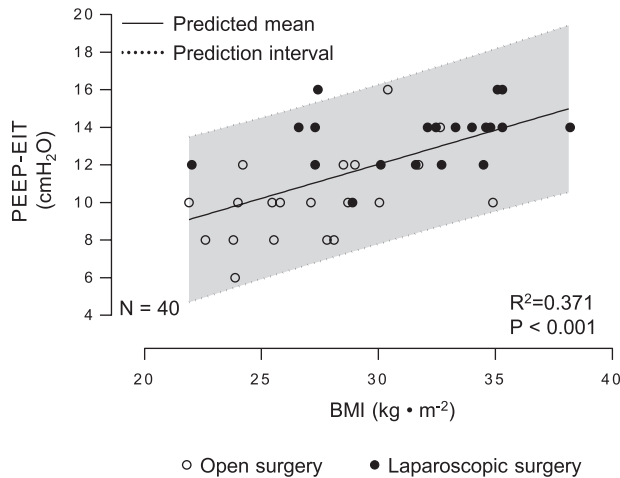
Fig. 3. Correlation and prediction interval of positive end-expiratory pressure titrated by electrical impedance tomography (PEEP-EIT) of all patients and body mass index (BMI). Open circles represent open surgery and closed circles represent laparoscopic surgery.

Fig. 4. Box plot (median with 25th and 75th percentiles) of nonaerated mass tissue on computed tomography after extubation. Gray boxes represent patients submitted to laparoscopic surgery, and white boxes represent patients submitted to open surgery. The positive end-expiratory pressure titrated by electrical impedance tomography (PEEP-EIT) arm had less atelectasis than PEEP4 arm after extubation. CT, computed tomography; PEEP4, PEEP of 4 cm H_2O.

Respiratory parameters were better preserved, with differences between arms exacerbated in the laparoscopic procedures. Minutes after peritoneal insufflation, the difference in ΔP between study arms reached 6.4 cm H_2O (95% CI, 3.4–9.4; $P = 0.001$), with the PEEP-EIT arm always presenting lower ΔP.

Along the intraoperative period, the differences in PaO_2/FIO_2 ratio mirrored the physiologic alterations described above. Patients in the PEEP-EIT arm presented higher PaO_2/FIO_2 ratios, with pronounced and statistically significant differences when considering the laparoscopic procedure (mean

of all samples along the surgery, PEEP-EIT $vs.$ PEEP4 arm, 435 ± 62 $vs.$ 266 ± 76 mmHg, $P < 0.001$; fig. 8). There is no difference in PaO_2/FIO_2 ratio between the two types of surgery ($P = 0.064$). FIO_2 was set at 0.5 throughout the surgery in all but one patient of the PEEP4 arm (submitted to open surgery), in which FIO_2 was increased to 0.6. The $PaCO_2$ was not significantly different between the study arms ($P = 0.805$ in laparoscopic surgery $vs.$ $P = 0.964$ in open surgery), but it
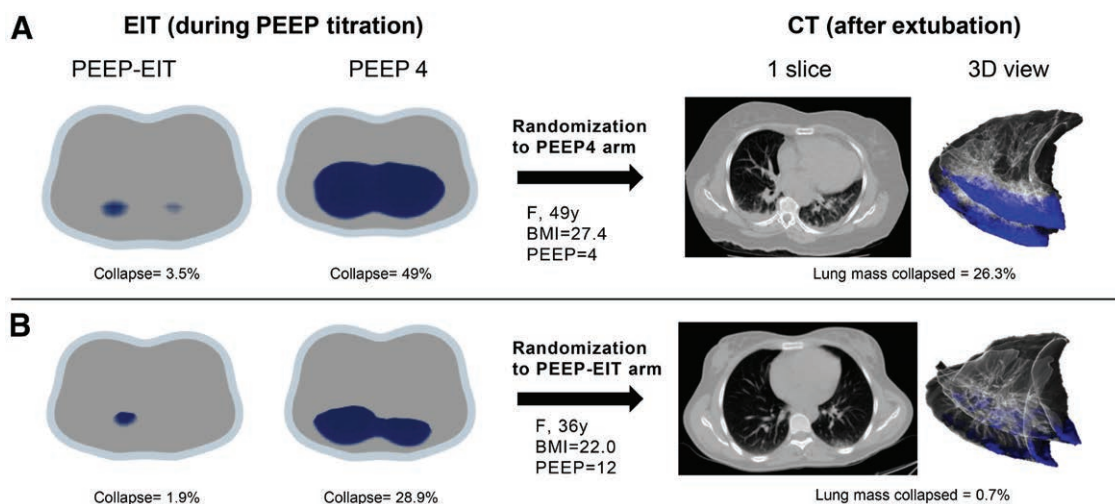
Fig. 5. Examples of electrical impedance tomography (EIT) images (at positive end-expiratory pressure guided by electrical impedance tomography [PEEP-EIT] and PEEP of 4 cm H_2O) and computed tomography images (after extubation) of two patients: in (*A*) a patient randomized for PEEP4 arm, and in (*B*) a patient randomized for PEEP-EIT arm. At left, EIT images show in blue the estimative of lung mass collapsed during PEEP titration in two values of PEEP (PEEP-EIT and PEEP of 4 cm H_2O). At right, one axial slice of the lung computed tomography and three-dimensional reconstruction of the lungs show the collapsed lung in blue (areas between −200 to +100 UH). BMI, body mass index; CT, computed tomography.
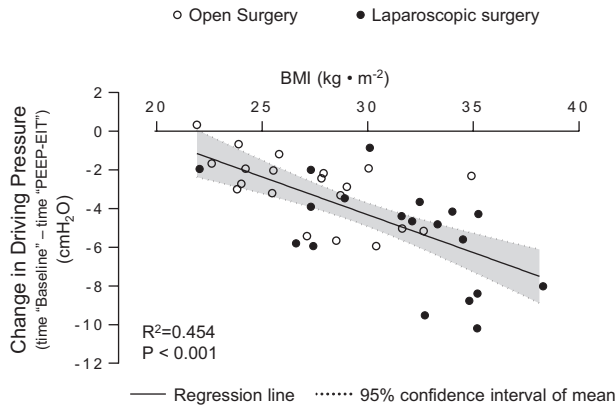
Fig. 6. Correlation of body mass index (BMI) and drop in driving pressure between time "baseline" (using positive end-expiratory pressure [PEEP] of 4 cm H_2O) and "during titration" (at PEEP titrated by electrical impedance tomography [PEEP-EIT]). Open circles represent open surgery, and closed circles represent laparoscopic surgery.

was consistently higher in the laparoscopic than in the open surgery procedure ($P = 0.014$; fig. E4 in Supplemental Digital Content, http://links.lww.com/ALN/B784).

Exploratory Outcomes: Anesthetic Management, Hemodynamics, and Length of Hospital Stay

The anesthetic management of patients is shown in table 4. In both types of surgery, a high percentage of patients needed vasoactive drugs during the recruitment maneuvers, but none needed continuous infusion throughout surgery. There were no differences between PEEP4 and PEEP-EIT arms in urine output or total fluids per hour in both types of surgery.

Patients submitted to open surgery were commonly submitted to neuroaxial anesthesia without any difference between the two study arms. No difference was observed in mean arterial pressure (mean of three time points during both types of surgery: PEEP-EIT of 80 ± 14 *vs.* PEEP4 of 78 ± 15 mmHg; $P = 0.821$) over time (fig. 9). Length of hospital stay was also not different between the two study arms (fig. E5 in Supplemental Digital Content, http://links.lww.com/ALN/B784). The length of both anesthesia and surgery, however, were longer in the PEEP4 arm when compared with the PEEP-EIT arm ($P = 0.013$ and $P = 0.009$, respectively).

Discussion

This pilot, randomized study tested the physiologic impact of individualized PEEP-EIT in anesthetized patients with healthy lungs receiving protective ventilation (V_T strictly lowered to 6 ml/kg, predicted body weight). The main findings were: (1) PEEP-EIT had a wide distribution among patients; (2) the beneficial effects persisted after extubation: those patients ventilated with PEEP-EIT presented less atelectasis on the chest computed tomography; (3) PEEP-EIT minimized lung collapse, reduced ΔP, and improved oxygenation and respiratory system compliance when compared with standard PEEP of 4 cm H_2O; (4) patients receiving PEEP-EIT did not present intraoperative hemodynamic instability nor did they require more vasoactive drugs or fluids.

Identified PEEP

The EIT has an algorithm that estimates recruitable alveolar collapse and hyperdistension during a decremental PEEP
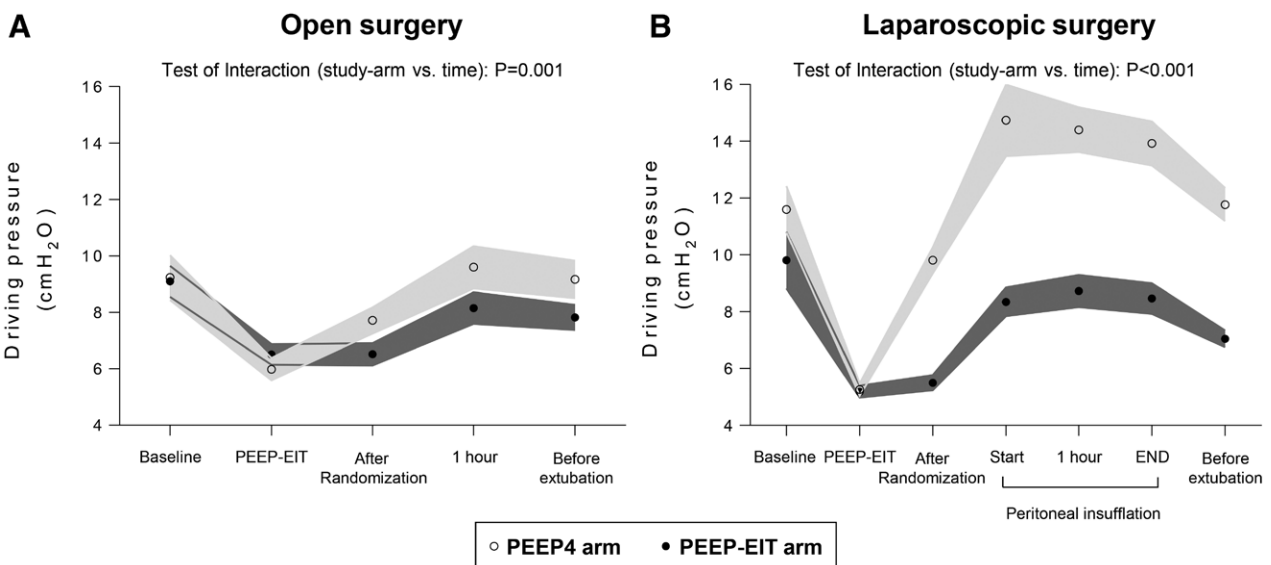
Fig. 7. Mean driving pressure during intraoperative period in open surgery (*A*) and laparoscopic surgery (*B*). Shaded areas represent standard error of mean. Closed circles represent positive end-expiratory pressure titrated by electrical impedance tomography (PEEP-EIT) arm, and open circles represent PEEP of 4 cm H_2O (PEEP4) arm. In both types of surgery, driving pressure was lower in PEEP-EIT arm.
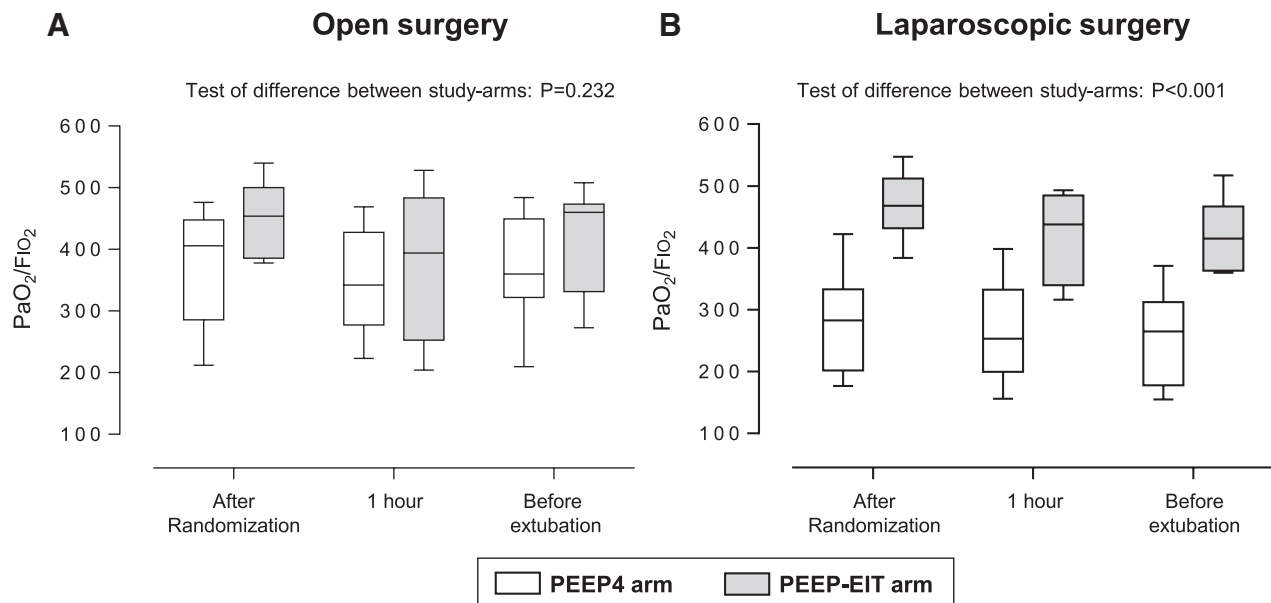
Fig. 8. Box plot (median with 25th and 75th percentiles) of PaO$_2$/FIO$_2$ ratio during intraoperative period in open surgery (*A*) and laparoscopic surgery (*B*). Gray boxes represent positive end-expiratory pressure titrated by electrical impedance tomography (PEEP-EIT) arm, and white boxes represent PEEP of 4 cm H$_2$O (PEEP4) arm.

Table 4. Anesthetic Management and Outcomes

	PEEP4 (n = 20)	PEEP-EIT (n = 20)	*P* Value
Anesthetic management			
Length of anesthesia, median (IQ), min	235 (220–248)	205 (175–240)	0.013
Length of surgery, median (IQ), min	180 (158–195)	138 (115–168)	0.009
Urine output per hour, median (IQ), ml	141 (77–223)	139 (75–175)	0.683
Total fluids per hour, median (IQ), ml	552 (444–619)	667 (491–720)	0.175
Neuraxial anesthesia			
Intradural (%)	4 (20)	6 (30)	
Epidural (%)	3 (15)	3 (15)	
Vasoactive drug			
During recruitment maneuver (%)	16 (80)	15 (75)	
Continuous (%)	0 (0)	0 (0)	
Outcome			
Length of hospital stay, median (IQ), days	3 (2–3)	3 (2–3)	0.138
Computed tomography after extubation			
Time to computed tomography, median (IQ), min	50 (45–59)	55 (39–62)	

Data are expressed as median (IQ [interquartile range]) or number of patients (percent). *P* (Mann–Whitney test) for the difference between PEEP 4 and PEEP-EIT (laparoscopic and open surgery together). PEEP4, PEEP of 4 cm H$_2$O; PEEP-EIT, PEEP guided by electrical impedance tomography.

titration.[26] High PEEP might result in more hyperdistension than collapse whereas low PEEP might result in more collapse than hyperdistension. Our data suggest that an individually adjusted PEEP—providing the optimum compromise between lung collapse and hyperdistension—presents wide between-patient variability (from 6 to 16 cm H$_2$O). Recent trials individualizing PEEP during general anesthesia also showed wide variability.[20,21,27] Such variability means that the use of a standardized PEEP for patients with "normal lungs" is problematic. For instance, when looking at our patients before randomization, when all were submitted to decremental PEEP titration, we observed that a fixed-PEEP

of 6 cm H$_2$O caused a wide range of lung collapse (from 3 to 33% of parenchymal collapse), whereas a fixed-PEEP of 16 cm H$_2$O caused 5 to 52% of parenchymal hyperdistension, with all of this variability depending exclusively on individual patient characteristics.

Some other aspects of this study are potentially relevant. We tested a method that has been shown to be fast (~5 min) and reproducible at the bedside.[16,26] When PEEP challenges are performed in a decremental fashion and in small steps, the new equilibrium of imaging and mechanics is quickly achieved, within just three to five ventilation cycles. Thus, the complete lung response to each PEEP step
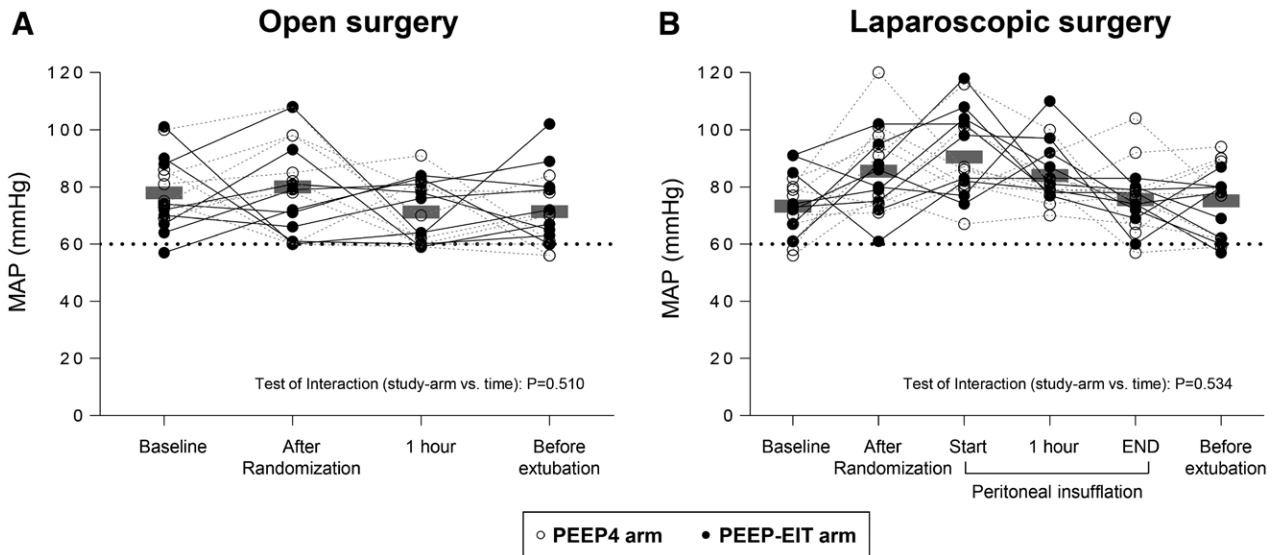
Fig. 9. Individual mean arterial pressure (MAP) and patients' mean during intraoperative period in open surgery (*A*) and laparoscopic surgery (*B*). Baseline was recorded after intubation. Closed circles represent patients ventilating under positive end-expiratory pressure titrated by electrical impedance tomography (PEEP-EIT), and open circles represent patients ventilating under positive end-expiratory pressure (PEEP) of 4 cm H_2O. There was no difference between groups in both types of surgery.

can be measured in just 20 to 30 s.[16] In contrast, when using blood gases, the equilibrium takes 4 to 10 min,[28] which is impractical. Recently, a new approach using pulse-oximetry (which takes only 1 or 2 min for each step) was proposed.[21] This procedure, however, could not offer any information about hyperdistension. In contrast, a key aspect of our EIT-based procedure is its high sensitivity to detect parenchymal hyperdistension or collapse,[26,29] providing objective parameters to accomplish a dual target during PEEP titration: minimal postoperative collapse, as confirmed by computed tomography after extubation, and minimal hyperdistension, as suggested by lower ΔP and good hemodynamic tolerance.

Of note, we tested individual PEEP settings applied to two relevant populations of patients: open abdominal surgery and laparoscopic surgery. The PEEP titration procedure was applied after recruitment and homogenization of the lungs in both populations, demonstrating not only that anesthesia induction promotes massive lung collapse (despite the application of a standard PEEP of 4 cm H_2O), but also that an objective improvement in lung function can be achieved for these two populations, with long-lasting effects after surgery and minimal side effects.

Lung Injury and Postoperative Collapse

Patients undergoing laparoscopic surgery and ventilated at PEEP-EIT had ΔP consistently less than 12.5 cm H_2O, a threshold associated with a lower incidence of postoperative pulmonary complications.[9] In contrast, patients allocated to PEEP4 frequently exceeded this threshold (fig. 7), thus being exposed to a higher risk of postoperative pulmonary complications.

We also demonstrated that optimal PEEP, compared with low fixed PEEP of 4 cm H_2O, not only reduces ΔP and improves compliance intraoperatively, but also reduces atelectasis in the postoperative period. The benefit is more profound for the patients in the laparoscopic than open surgery subgroup. Of note, in this study we did not evaluate the effect of the optimal intraoperative PEEP on the incidence and severity of postoperative pulmonary complications. In addition, the association of postoperative atelectasis with worse outcomes has not been a consensus.[30,31] However, a fair majority of studies suggests that postoperation atelectasis is harmful. It can last for several days after surgery,[32] increasing pulmonary complications, impairing respiratory function, and ultimately delaying patient discharge.[31,33]

It is convenient, therefore, that a single ventilator adjustment, such as PEEP-EIT, minimized the two main factors implicated in perioperative complications without increasing length of hospital stay (fig. E5 in Supplemental Digital Content, http://links.lww.com/ALN/B784). Nevertheless, the hypothesis that individualized PEEP could produce better outcome remains to be proven and, if proven, the methods to titrate PEEP should be accessible at the bedside. Of note, in a recent trial,[34] an individualized PEEP followed by individualized continuous positive airway pressure postoperatively did not reduce the primary end point (a composite of postoperative pulmonary and systemic complications) when compared with a standard PEEP of 5 cm H_2O and oxygen therapy, but it did improve secondary outcomes.

PEEP and Body Mass Index

A significant correlation between optimum individual PEEP with body mass index was observed (fig. 3, $P < 0.001$),

although we noticed a wide variation, suggesting that the consideration of body mass index could not replace the physiologic individualization of PEEP.

Previous research has shown that, during the intraoperative period, atelectasis is positively correlated with body mass index.[35] Also, recent physiologic studies identifying "optimum" PEEP by sequential measurements of respiratory system compliance or deadspace during anesthesia consistently showed a higher PEEP requirement in obese patients.[19,36] This higher PEEP requirement has been explained by increased pleural pressures during exhalation, strongly affected by the increased weight of chest-wall and abdominal structures.[10] The increased weight, however, does not affect the intrinsic compliance of the chest wall, causing only a continuous offset of pleural pressures, thus generating "negative" transpulmonary pressures and favoring end-expiratory lung collapse.[37] Consequently, higher mean PEEP was required in our population to counterbalance the highest compressive forces in those patients with the highest body mass index, especially in those submitted to laparoscopic surgery (fig. 3).

This correlation between body mass index and PEEP-EIT also explains the strong correlation between the drop in ΔP (from baseline to PEEP-EIT) and body mass index (fig. 6). The higher the body mass index, the higher the pleural pressures and the higher the PEEP needed to counterbalance this offset in transpulmonary pressures. Interestingly, after overcoming this high pressure-offset with PEEP, not only the chest wall but also the lung compliance was preserved after recruitment and, consequently, ΔP at the PEEP-EIT were similar in the obese and slim patients (fig. E6 in Supplemental Digital Content, http://links.lww.com/ALN/B784). This explains why the most expressive drop in ΔP (up to 12 cm H_2O after PEEP-EIT; fig. 6) was found in the most obese: in these patients, the difference in respiratory-system compliance between PEEP4 (with very negative transpulmonary pressures and massive atelectasis) and PEEP-EIT was maximal.

Hemodynamics

When comparing study arms, there were no differences in arterial pressures, cardiac rate, or use of fluids or continuous vasoactive drugs during the intraoperative period. Despite the requirement of vasoactive agents during the recruitment maneuver in most patients, none needed it continuously, a result that is in line with previous studies.[38] A recent large, randomized, clinical trial[34] showed similar results, corroborating that recruitment maneuvers are safe and the use of individualized higher PEEP might not necessarily lead to hemodynamic instability or increased fluid administration. Multiple factors are associated with good hemodynamic tolerance, including previous optimization of fluids before the maneuvers,[38] use of pressure-controlled breaths for recruitment (instead of sustained pressures or continuous positive airway pressure),[39] and individualized PEEP, probably lowering pulmonary vascular resistance and preserving right ventricular function.[40]

Study Limitations

The present study was a small, single-centered, physiologic proof-of-concept study, not powered to detect differences in hard outcomes. First, our number of patients was limited and heterogeneous. As expected, we did not detect significant differences in length of hospital stay or postoperative complications other than atelectasis. Second, our patients were graded American Society of Anesthesiologists Physical Status I or II. The use of recruitment maneuvers and titrated PEEP in more unstable patients was not tested and could increase the side effects of the strategy. Of note, a recent study testing an intensive recruiting strategy in vasoplegic patients after cardiac surgery[33] did not describe significant side effects. Third, the length of anesthesia and surgery were longer in the PEEP4 arm, which might have contributed to atelectasis formation in these patients. However, the computed tomography scan in this study was performed after extubation, and some patients might have performed uncontrolled recruitment maneuvers (by sighing or coughing), whereas others may have collapsed after falling asleep. Because most patients were fully awake during computed tomography, such confounding would only have decreased the chances of finding a significant difference in atelectasis. Performing computed tomography scans while patients were still under mechanical ventilation could have shown us the exact effect of PEEP, but it would not have provided the secondary outcome we were looking for (atelectasis after extubation). Fourth, the recruitment maneuver applied in this study lasted for 2 min. Because of the vasoplegia associated with anesthesia induction, many patients required vasoactive drugs during the first recruitment maneuver (table 4); in the second maneuver, however, such need was rare. It is possible that a shorter recruitment maneuver (15 to 30 s) might be used instead, showing preserved efficacy, but milder hemodynamic consequences as in a recent study.[41] EIT was used to set PEEP according to lung hyperdistention and collapse. Titrating PEEP in a decremental way according to driving pressure might lead to similar results, though we did not test for this hypothesis.

Conclusions

Optimal PEEP values vary widely in healthy patients ventilated with protective V_T during general anesthesia for abdominal surgery. The application of the optimal PEEP obtained with EIT for each individual patient improves intraoperative oxygenation, lowers ΔP, and minimizes incidence and severity of postoperative atelectasis with minimal side effects. Large randomized trials should be conducted to determine the effect of physiologic tidal volume together with individualized optimal PEEP on the patient.

Research Support

dination for the Improvement of Higher Level Personnel (CAPES), Brazil. This trial is registered at https://clinicaltrials.gov/ct2/show/NCT02314845 (NCT02314845).

Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available at: mrotucci@gmail.com. Raw data available at: mrotucci@gmail.com.

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References

1. Severgnini P, Selmo G, Lanza C, Chiesa A, Frigerio A, Bacuzzi A, Dionigi G, Novario R, Gregoretti C, de Abreu MG, Schultz MJ, Jaber S, Futier E, Chiaranda M, Pelosi P: Protective mechanical ventilation during general anesthesia for open abdominal surgery improves postoperative pulmonary function. ANESTHESIOLOGY 2013; 118:1307–21

2. Futier E, Constantin JM, Paugam-Burtz C, Pascal J, Eurin M, Neuschwander A, Marret E, Beaussier M, Gutton C, Lefrant JY, Allaouchiche B, Verzilli D, Leone M, De Jong A, Bazin JE, Pereira B, Jaber S; IMPROVE Study Group: A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. N Engl J Med 2013; 369:428–37

3. Ge Y, Yuan L, Jiang X, Wang X, Xu R, Ma W: [Effect of lung protection mechanical ventilation on respiratory function in the elderly undergoing spinal fusion]. Zhong Nan Da Xue Xue Bao Yi Xue Ban 2013; 38:81–5

4. Güldner A, Kiss T, Serpa Neto A, Hemmes SN, Canet J, Spieth PM, Rocco PR, Schultz MJ, Pelosi P, Gama de Abreu M: Intraoperative protective mechanical ventilation for prevention of postoperative pulmonary complications: A comprehensive review of the role of tidal volume, positive end-expiratory pressure, and lung recruitment maneuvers. ANESTHESIOLOGY 2015; 123:692–713

5. Brismar B, Hedenstierna G, Lundquist H, Strandberg A, Svensson L, Tokics L: Pulmonary densities during anesthesia with muscular relaxation: A proposal of atelectasis. ANESTHESIOLOGY 1985; 62:422–8

6. Tusman G, Böhm SH, Warner DO, Sprung J: Atelectasis and perioperative pulmonary complications in high-risk patients. Curr Opin Anaesthesiol 2012; 25:1–10

7. Lellouche F, Dionne S, Simard S, Bussières J, Dagenais F: High tidal volumes in mechanically ventilated patients increase organ dysfunction after cardiac surgery. ANESTHESIOLOGY 2012; 116:1072–82

8. Neto AS, Hemmes SN, Barbas CS, Beiderlinden M, Fernandez-Bustamante A, Futier E, Gajic O, El-Tahan MR, Ghamdi AA, Günay E, Jaber S, Kokulu S, Kozian A, Licker M, Lin WQ, Maslow AD, Memtsoudis SG, Reis Miranda D, Moine P, Ng T, Paparella D, Ranieri VM, Scavonetto F, Schilling T, Selmo G, Severgnini P, Sprung J, Sundar S, Talmor D, Treschan T, Unzueta C, Weingarten TN, Wolthuis EK, Wrigge H, Amato MB, Costa EL, de Abreu MG, Pelosi P, Schultz MJ; PROVE Network Investigators: Association between driving pressure and development of postoperative pulmonary complications in patients undergoing mechanical ventilation for general anaesthesia: A meta-analysis of individual patient data. Lancet Respir Med 2016; 4:272–80

9. Ladha K, Vidal Melo MF, McLean DJ, Wanderer JP, Grabitz SD, Kurth T, Eikermann M: Intraoperative protective mechanical ventilation and risk of postoperative respiratory complications: Hospital based registry study. BMJ 2015; 351:h3646

10. Chiumello D, Carlesso E, Brioni M, Cressoni M: Airway driving pressure and lung stress in ARDS patients. Crit Care 2016; 20:276

11. Amato MB, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld DA, Stewart TE, Briel M, Talmor D, Mercat A, Richard JC, Carvalho CR, Brower RG: Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med 2015; 372:747–55

12. Hemmes SN, Gama de Abreu M, Pelosi P, Schultz MJ, PROVE Network Investigators for the Clinical Trial Network of the European Society of Anaesthesiology: High versus low positive end-expiratory pressure during general anaesthesia for open abdominal surgery (PROVHILO trial): A multicentre randomised controlled trial. Lancet 2014; 384:495–503

13. Serpa Neto A, Hemmes SN, Barbas CS, Beiderlinden M, Biehl M, Binnekade JM, Canet J, Fernandez-Bustamante A, Futier E, Gajic O, Hedenstierna G, Hollmann MW, Jaber S, Kozian A, Licker M, Lin WQ, Maslow AD, Memtsoudis SG, Reis Miranda D, Moine P, Ng T, Paparella D, Putensen C, Ranieri M, Scavonetto F, Schilling T, Schmid W, Selmo G, Severgnini P, Sprung J, Sundar S, Talmor D, Treschan T, Unzueta C, Weingarten TN, Wolthuis EK, Wrigge H, Gama de Abreu M, Pelosi P, Schultz MJ; PROVE Network Investigators: Protective *versus* conventional ventilation for surgery: A systematic review and individual patient data meta-analysis. ANESTHESIOLOGY 2015; 123:66–78

14. Levin MA, McCormick PJ, Lin HM, Hosseinian L, Fischer GW: Low intraoperative tidal volume ventilation with minimal PEEP is associated with increased mortality. Br J Anaesth 2014; 113:97–108

15. Fumagalli J, Berra L, Zhang C, Pirrone M, Santiago RRS, Gomes S, Magni F, Dos Santos GAB, Bennett D, Torsani V, Fisher D, Morais C, Amato MBP, Kacmarek RM: Transpulmonary pressure describes lung morphology during decremental positive end-expiratory pressure trials in obesity. Crit Care Med 2017; 45:1374–81

16. Nakamura MAM, Hajjar LA, Galas FRbg, Ortiz TA, Amato MBP: Positive end expiratory pressure titration at bedside using electrical impedance tomography [abstract]. Intensive Care Med Exp 2016; 4:126–7

17. Maisch S, Reissmann H, Fuellekrug B, Weismann D, Rutkowski T, Tusman G, Bohm SH: Compliance and dead space fraction indicate an optimal level of positive end-expiratory pressure after recruitment in anesthetized patients. Anesth Analg 2008; 106:175–81, table of contents

18. Ferrando C, Soro M, Canet J, Unzueta MC, Suárez F, Librero J, Peiró S, Llombart A, Delgado C, León I, Rovira L, Ramasco F, Granell M, Aldecoa C, Diaz O, Balust J, Garutti I, de la Matta M, Pensado A, Gonzalez R, Durán ME, Gallego L, Del Valle SG, Redondo FJ, Diaz P, Pestaña D, Rodríguez A, Aguirre J, García JM, García J, Espinosa E, Charco P, Navarro J, Rodríguez C, Tusman G, Belda FJ; iPROVE investigators (Appendices 1 and 2): Rationale and study design for an individualized perioperative open lung ventilatory strategy (iPROVE): Study protocol for a randomized controlled trial. Trials 2015; 16:193

19. Pirrone M, Fisher D, Chipman D, Imber DA, Corona J, Mietto C, Kacmarek RM, Berra L: Recruitment maneuvers and positive end-expiratory pressure titration in morbidly obese ICU patients. Crit Care Med 2016; 44:300–7

20. Nestler C, Simon P, Petroff D, Hammermüller S, Kamrath D, Wolf S, Dietrich A, Camilo LM, Beda A, Carvalho AR, Giannella-Neto A, Reske AW, Wrigge H: Individualized positive end-expiratory pressure in obese patients during general anaesthesia: A randomized controlled clinical trial using electrical impedance tomography. Br J Anaesth 2017; 119:1194–205

21. Ferrando C, Tusman G, Suarez-Sipmann F, León I, Pozo N, Carbonell J, Puig J, Pastor E, Gracia E, Gutiérrez A, Aguilar G, Belda FJ, Soro M: Individualized lung recruitment maneuver guided by pulse-oximetry in anesthetized patients undergoing laparoscopy: A feasibility study. Acta Anaesthesiol Scand 2018; 62:608–19

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

23. Reske AW, Reske AP, Gast HA, Seiwerts M, Beda A, Gottschaldt U, Josten C, Schreiter D, Heller N, Wrigge H, Amato MB: Extrapolation from ten sections can make CT-based quantification of lung aeration more practicable. Intensive Care Med 2010; 36:1836–44

24. Edmark L, Auner U, Hallén J, Lassinantti-Olowsson L, Hedenstierna G, Enlund M: A ventilation strategy during general anaesthesia to reduce postoperative atelectasis. Ups J Med Sci 2014; 119:242–50

25. Faul F, Erdfelder E, Buchner A, Lang AG: Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. Behav Res Methods 2009; 41:1149–60

26. Costa EL, Borges JB, Melo A, Suarez-Sipmann F, Toufen C Jr, Bohm SH, Amato MB: Bedside estimation of recruitable alveolar collapse and hyperdistension by electrical impedance tomography. Intensive Care Med 2009; 35:1132–7

27. Ferrando C, Suarez-Sipmann F, Tusman G, León I, Romero E, Gracia E, Mugarra A, Arocas B, Pozo N, Soro M, Belda FJ: Open lung approach *versus* standard protective strategies: Effects on driving pressure and ventilatory efficiency during anesthesia - A pilot, randomized controlled trial. PLoS One 2017; 12:e0177399

28. Borges JB, Okamoto VN, Matos GF, Caramez MP, Arantes PR, Barros F, Souza CE, Victorino JA, Kacmarek RM, Barbas CS, Carvalho CR, Amato MB: Reversibility of lung collapse and hypoxemia in early acute respiratory distress syndrome. Am J Respir Crit Care Med 2006; 174:268–78

29. Franchineau G, Bréchot N, Lebreton G, Hekimian G, Nieszkowska A, Trouillet JL, Leprince P, Chastre J, Luyt CE, Combes A, Schmidt M: Bedside contribution of electrical impedance tomography to setting positive end-expiratory pressure for extracorporeal membrane oxygenation-treated patients with severe acute respiratory distress syndrome. Am J Respir Crit Care Med 2017; 196:447–57

30. Pelosi P, Ball L, de Abreu MG, Rocco PR: General anesthesia closes the lungs: Keep them resting. Turk J Anaesthesiol Reanim 2016; 44:163–4

31. Hedenstierna G, Edmark L: Protective ventilation during anesthesia: Is it meaningful? ANESTHESIOLOGY 2016; 125:1079–82

32. Lindberg P, Gunnarsson L, Tokics L, Secher E, Lundquist H, Brismar B, Hedenstierna G: Atelectasis and lung function in the postoperative period. Acta Anaesthesiol Scand 1992; 36:546–53

33. Costa Leme A, Hajjar LA, Volpe MS, Fukushima JT, De Santis Santiago RR, Osawa EA, Pinheiro de Almeida J, Gerent AM, Franco RA, Zanetti Feltrim MI, Nozawa E, de Moraes Coimbra VR, de Moraes Ianotti R, Hashizume CS, Kalil Filho R, Auler JO Jr, Jatene FB, Gomes Galas FR, Amato MB: Effect of intensive vs moderate alveolar recruitment strategies added to lung-protective ventilation on postoperative pulmonary complications: A randomized clinical trial. JAMA 2017; 317:1422–32

34. Ferrando C, Soro M, Unzueta C, Suarez-Sipmann F, Canet J, Librero J, Pozo N, Peiró S, Llombart A, León I, India I, Aldecoa C, Díaz-Cambronero O, Pestaña D, Redondo FJ, Garutti I, Balust J, García JI, Ibáñez M, Granell M, Rodríguez A, Gallego L, de la Matta M, Gonzalez R, Brunelli A, García J, Rovira L, Barrios F, Torres V, Hernández S, Gracia E, Giné M, García M, García N, Miguel L, Sánchez S, Piñeiro P, Pujol R, García-Del-Valle S, Valdivia J, Hernández MJ, Padrón O, Colás A, Puig J, Azparren G, Tusman G, Villar J, Belda J; Individualized PeRioperative Open-lung VEntilation (iPROVE) Network: Individualised perioperative open-lung approach *versus* standard protective ventilation in abdominal surgery (iPROVE): A randomised controlled trial. Lancet Respir Med 2018; 6:193–203

35. Strandberg A, Tokics L, Brismar B, Lundquist H, Hedenstierna G: Constitutional factors promoting development of atelectasis during anaesthesia. Acta Anaesthesiol Scand 1987; 31:21–4

36. Tusman G, Groisman I, Fiolo FE, Scandurra A, Arca JM, Krumrick G, Bohm SH, Sipmann FS: Noninvasive monitoring of lung recruitment maneuvers in morbidly obese patients: The role of pulse oximetry and volumetric capnography. Anesth Analg 2014; 118:137–44

37. Loring SH, Behazin N, Novero A, Novack V, Jones SB, O'Donnell CR, Talmor DS: Respiratory mechanical effects of surgical pneumoperitoneum in humans. J Appl Physiol (1985) 2014; 117:1074–9

38. Bohm SH, Thamm OC, von Sandersleben A, Bangert K, Langwieler TE, Tusman G, Strate TG, Standl TG: Alveolar recruitment strategy and high positive end-expiratory pressure levels do not affect hemodynamics in morbidly obese intravascular volume-loaded patients. Anesth Analg 2009; 109:160–3

39. Lim SC, Adams AB, Simonson DA, Dries DJ, Broccard AF, Hotchkiss JR, Marini JJ: Transient hemodynamic effects of recruitment maneuvers in three experimental models of acute lung injury. Crit Care Med 2004; 32:2378–84

40. Gernoth C, Wagner G, Pelosi P, Luecke T: Respiratory and haemodynamic changes during decremental open lung positive end-expiratory pressure titration in patients with acute respiratory distress syndrome. Crit Care 2009; 13:R59

41. Arnal JM, Paquet J, Wysocki M, Demory D, Donati S, Granier I, Corno G, Durand-Gasselin J: Optimal duration of a sustained inflation recruitment maneuver in ARDS patients. Intensive Care Med 2011; 37:1588–94

Patient Blood Management Program Improves Blood Use and Clinical Outcomes in Orthopedic Surgery

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ABSTRACT

Background: Although randomized trials show that patients do well when given less blood, there remains a persistent impression that orthopedic surgery patients require a higher hemoglobin transfusion threshold than other patient populations (8 g/dl *vs.* 7 g/dl). The authors tested the hypothesis in orthopedic patients that implementation of a patient blood management program encouraging a hemoglobin threshold less than 7 g/dl results in decreased blood use with no change in clinical outcomes.

Methods: After launching a multifaceted patient blood management program, the authors retrospectively evaluated all adult orthopedic patients, comparing transfusion practices and clinical outcomes in the pre- and post-blood management cohorts. Risk adjustment accounted for age, sex, surgical procedure, and case mix index.

Results: After patient blood management implementation, the mean hemoglobin threshold decreased from 7.8 ± 1.0 g/dl to 6.8 ± 1.0 g/dl (*P* < 0.0001). Erythrocyte use decreased by 32.5% (from 338 to 228 erythrocyte units per 1,000 patients; *P* = 0.0007). Clinical outcomes improved, with decreased morbidity (from 1.3% to 0.54%; *P* = 0.01), composite morbidity or mortality (from 1.5% to 0.75%; *P* = 0.035), and 30-day readmissions (from 9.0% to 5.8%; *P* = 0.0002). Improved outcomes were primarily recognized in patients 65 yr of age and older. After risk adjustment, patient blood management was independently associated with decreased composite morbidity or mortality (odds ratio, 0.44; 95% CI, 0.22 to 0.86; *P* = 0.016).

Conclusions: In a retrospective study, patient blood management was associated with reduced blood use with similar or improved clinical outcomes in orthopedic surgery. A hemoglobin threshold of 7 g/dl appears to be safe for many orthopedic patients. (ANESTHESIOLOGY 2018; 129:1082-91)

BLOOD transfusions are the most frequently performed hospital procedure in the United States,[1] and according to the Joint Commission in 2012, they are also one of the top five overused procedures.[2] Because of the risks, costs, and adverse outcomes associated with blood transfusions,[3–8] recent studies have focused on investigating methods to reduce the number of unnecessary transfusions performed. According to the AABB (formerly the American Association of Blood Banks), erythrocyte transfusions in hospital settings nationwide have significantly decreased (by approximately 25%) during the past 5 yr.[9,10] In particular, patient blood management programs implementing techniques such as restrictive hemoglobin triggers, clinical decision support, educational efforts, and technologic advances in surgery and blood conservation across hospitals and health systems have been effective in decreasing blood use.[11–20]

A number of reports, including nine landmark randomized controlled trials,[21–29] have investigated clinical outcomes in patients after decreased blood transfusions. These studies

Editor's Perspective

What We Already Know about This Topic

- A transfusion threshold of 8 g/dl of hemoglobin is considered safe for asymptomatic orthopedic surgery patients, but lower thresholds have not been tested

What This Article Tells Us That Is New

- A blood management program using a hemoglobin transfusion threshold of 7 g/dl in asymptomatic orthopedic patients reduces blood use by 32.5% and results in similar or improved clinical outcomes
- Improved outcomes occurred primarily in patients 65 yr of age and older

demonstrate that giving less blood through restrictive hemoglobin triggers results in similar outcomes for most patients or improved outcomes for some subgroups of patients. Only one of these nine studies, however, the Functional Outcomes in Cardiovascular Patients Undergoing Surgical Repair of Hip Fracture (FOCUS) trial,[27] specifically enrolled

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This article is featured in "This Month in Anesthesiology," page 1A. Corresponding article on page 1060. This article has a visual abstract available in the online version.

orthopedic surgery patients, and these patients were elderly with hip fracture and high-risk with a high prevalence (more than 60%) of cardiovascular disease. Based primarily on this study, and several others that also included elderly high-risk patients,[30–33] recent AABB-endorsed transfusion guidelines recommend a hemoglobin trigger of 8 g/dl for orthopedic surgery patients (strong recommendation, moderate quality evidence), but a hemoglobin trigger of 7 g/dl even for critically ill hospitalized patients (also strong recommendation, moderate quality evidence[34]). The guidelines recognize, however, that a hemoglobin trigger of 7 g/dl is likely comparable to 8 g/dl, but not enough evidence is available for orthopedic patients to make this determination.

In light of this suggestion that orthopedic patients may require more liberal transfusion than other patients, and thus may be vulnerable at lower hemoglobin levels, we were specifically interested in the effect of a patient blood management program on orthopedic surgery patients. During the past 5 yr, in alignment with recent trends in blood management, our health system instituted a comprehensive patient blood management program with an aim to decrease unnecessary blood transfusion across the health system. The various methods we endorse are evidence-based best practices that result in reduced overall transfusions, and in the interest of safety and quality, we want to ensure that we are not putting our orthopedic patients at risk by giving them less blood than is needed. Therefore, we did a retrospective analysis to test the hypothesis that after implementation of a patient blood management program, orthopedic patients would receive fewer allogeneic blood transfusions without an increase in adverse outcomes.

Materials and Methods

Institutional review board approval with a waiver for written informed consent was obtained to assess changes in blood use and clinical outcomes across The Johns Hopkins Health System. The patient blood management database with clinical outcomes covers the period from January 2013 to May 2017. At The Johns Hopkins Bayview Medical Center (Baltimore, Maryland), the primary orthopedic center at our institution, the patient blood management program was phased in over time; however, for the purposes of this study, patient blood management was considered to be initiated in January 2015, when the majority of patient blood management efforts were implemented. Further details on the timing of individual interventions are outlined in the section, "Phasing In of Patient Blood Management Interventions." These methods were implemented as part of larger health system-wide patient blood management program. All patients aged 18 and over admitted to the orthopedic surgery service during this period were included in the current study. Categories of surgical procedure included hip fracture repair, hip and knee arthroplasty (primary and revision), and "other" (all patients except those mentioned). Spine surgery was not included because orthopedic spine cases are done at another hospital in our health system.

Patient Blood Management Program

The patient blood management program employed several strategies outlined in table 1, which included (1) obtaining support from hospital leadership; (2) assembling multidisciplinary teams of stakeholders and holding monthly meetings; (3) providing education based on rigorous peer-reviewed studies; (4) implementing transfusion guidelines; (5) implementing clinical decision support with best-practice advisory alerts; (6) performing data acquisition and analytics[35]; (7) creating blood use electronic dashboards[35]; (8) providing transfusion guideline compliance audit reports with feedback[15]; and (9) enacting specific methods to decrease blood use, including a "Why Give 2 When 1 Will Do?" Choosing Wisely campaign,[16] use of intraoperative antifibrinolytics (primarily tranexamic acid), anesthetic management such as controlled hypotension and maintaining normothermia, surgical methods such as newer cautery techniques,[36] topical hemostatics, and reduction of phlebotomy blood loss by using smaller tubes and reducing unnecessary laboratory test ordering. Diagnosis and treatment of preoperative anemia was not emphasized, and there was no preoperative anemia clinic in the pre- or post-patient blood management time periods.

Phasing In of Patient Blood Management Interventions

For the purposes of describing the incremental onset of our patient blood management program, we have defined four stages over time, which are (1) pre-patient blood management, before any activities began; (2) early patient blood management, when education on evidence-based transfusion practice at The Johns Hopkins Hospital campus began, and tranexamic acid at The Johns Hopkins Bayview campus

Table 1. Methods for Implementing the Patient Blood Management Program

1. Obtain support from health system leadership
2. Assemble multidisciplinary team with monthly meetings
3. Education (with emphasis on the randomized control trials supporting restrictive transfusion)
4. Implement transfusion guidelines
5. Decision support with best-practice advisories
6. Data acquisition and analytics
7. Blood management data dashboards
8. Transfusion guideline compliance audits with feedback (reports) to providers
9. Methods to improve blood use
   Evidence-based transfusion triggers
   "Why Give 2 When 1 Will Do?" Choosing Wisely campaign for erythrocytes
   Antifibrinolytics (tranexamic acid)
   Anesthetic management (*e.g.,* controlled hypotension, normothermia)
   Surgical methods (*e.g.,* newer cautery methods, topical hemostatics, and sealants)
   Reduce phlebotomy blood loss (smaller tubes, eliminate unnecessary testing)

Table is modified from Frank SM, *et al.* Anesthesiology 2017; 127:754–64.[20]

was introduced; (3) post-patient blood management, when harmonized transfusion guidelines across the health system, a "Why Give 2 When 1 Will Do?" single-unit transfusion campaign, data dashboards, audits for transfusion guideline compliance with feedback, and an early version of clinician decision support for hemoglobin triggers were implemented; and (4) enhanced patient blood management, when the Epic (USA) electronic record was launched with improved decision support and best-practice advisories notifying clinicians

about out-of-guideline orders, as well as enhanced guideline compliance audits with feedback sent to all departments and providers. These patient blood management intervention phases are illustrated in figure 1.

Data Collection and Clinical Outcomes

Transfusion and laboratory data were collected from two platforms of electronic medical records (Meditech [USA] before September 2015, and Epic thereafter). Quality
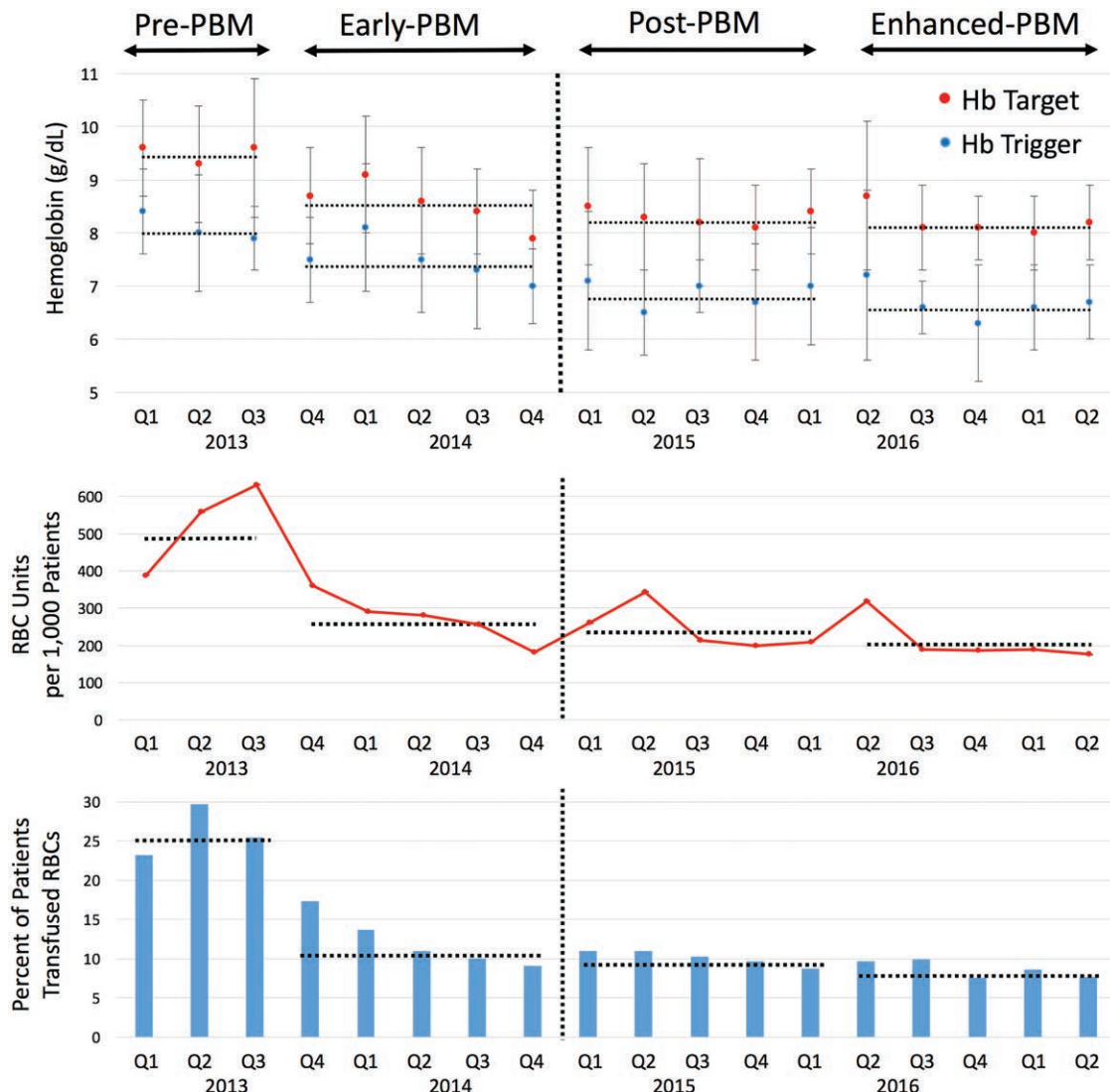
Fig. 1. Changes in hemoglobin trigger and target, number of units per 1,000 patients, and percentage of patients transfused erythrocytes are shown over time. The *vertical dotted line* divides the pre- and post-patient blood management (PBM) periods that were compared in the analysis. The *horizontal dotted lines* are averages over the four periods, which are (1) pre-PBM, before patient blood management began; (2) early PBM, when education on evidence-based transfusion practice at The Johns Hopkins Hospital campus began, and tranexamic acid at The Johns Hopkins Bayview campus was implemented; (3) post-PBM, when harmonized transfusion guidelines, a "Why Give 2 When 1 Will Do?" single-unit transfusion campaign,[16] data dashboards,[35] audits for transfusion guidelines compliance with feedback,[15] and an early version of clinician decision support for Hb triggers were implemented in the electronic record system; and (4) enhanced PBM, when the Epic (USA) electronic record was launched with improved decision support and best-practice advisories notifying clinicians about out-of-guideline orders, as well as enhanced guideline compliance audits with feedback sent to all departments and providers.[35] Of note is the decrease in mean Hb trigger from above 7 g/dl over the first two periods to less than 7 g/dl over the latter two periods. Hb, hemoglobin; RBC, erythrocyte; Q, calendar year quarter (3-month intervals). Hb concentration shown as mean ± SD.

control for these two sources was confirmed by our Clinical Analytics team and by an outside consultant, and the data were consolidated onto our blood management dashboard, as previously described.[35] Blood use data were verified by comparison with blood bank records. Clinical outcomes, as described below, were assessed with administrative data obtained from our health system's administrative database.

The primary clinical outcome assessed was composite morbidity or mortality. Secondary outcomes included (1) composite morbidity, (2) mortality (during the hospitalization), (3) length of stay, and (4) 30-day readmissions. Composite morbidity was defined as the occurrence of any of the following hospital-acquired morbid events, defined by International Classification of Diseases, Ninth Revision, or International Classification of Diseases, Tenth Revision, codes, as we have previously described.[37] Morbid events included (1) infection (*Clostridioides difficile,* sepsis, surgical site infection, or drug-resistant infection), (2) thrombotic event (deep venous thrombosis, pulmonary embolus, or disseminated intravascular coagulation), (3) kidney injury, (4) respiratory event, and (5) ischemic event (myocardial infarction, transient ischemic attack, or cerebrovascular injury). Conditions that were flagged as present on admission were not considered to be hospital-acquired morbid events.

Assessment of Blood Use

For erythrocyte-transfused patients, the lowest (nadir) hemoglobin concentration during the hospital stay was used to define the hemoglobin trigger, and the last measured hemoglobin concentration before discharge was used to define the hemoglobin target, as we have previously described.[38] Preoperative hemoglobin concentrations were unavailable in our database. Blood use was assessed two ways: (1) the percentage of patients receiving any erythrocyte units, and (2) the number of units transfused per 1,000 patients during their entire hospital stay.

Data and Statistical Analysis

The analysis was designed as a pre- and post-patient blood management comparison, comparing two periods: (1) January 2013 to December 2014, and (2) January 2015 to May 2017. The methods of analysis were planned before accessing the data, and the sample size needed was estimated on the basis of experience with morbid event rates from our previous outcome studies.[39–41] In an effort to reduce bias, analysis of blood use and clinical outcomes was first performed for the entire patient population and then by preplanned subgroup analyses with two age-defined subgroups (younger than 65 yr and 65 yr of age and older). The subgroup analysis was done to determine whether older orthopedic surgery patients showed differing results compared to younger patients, given that several previous orthopedic surgery studies made their conclusions based on elderly patients alone.

We performed a multivariable logistic regression to assess the risk-adjusted effect of the patient blood management program on adverse outcomes (any morbidity or mortality). The independent variables entered into the model for risk adjustment were age, case mix index (weighted All Patients Refined–Diagnosis-Related Groups), hip fracture, surgical procedure, and sex. We chose the weighted All Patients Refined–Diagnosis-Related Groups since this variable accounts for both complexity of procedure and severity of illness, and it correlates with both transfusion requirements[42] and clinical outcomes.[43] The logistic regression model included those independent variables that were (1) the design variable in the study (pre- and post-patient blood management), (2) variables that have been linked to outcomes in previous studies, or (3) variables with $P < 0.1$ on univariate analysis.

Continuous data are given as mean ± SD or median (interquartile range) if normally or not normally distributed, respectively. Ordinal and nominal values are given as percentages. Means were compared by unpaired Student's t tests, and medians by Mann–Whitney U tests, while percentages were compared by chi-square tests or the Fisher exact test when the numerator had five or fewer patients or events. Analyses were generated with JMP version 12.1.0 and SAS version 9.4.2 (SAS Institute, USA). For all analyses, $P < 0.05$ (two-tailed) was considered significant.

Sensitivity Analysis

To further control for confounding, we performed a sensitivity analysis using a propensity score, derived for each individual on the basis of the predictor variables from a multivariable logistic regression as the probability of being in the post-patient blood management group. These variables included age, sex, case mix index, hip fracture, and hip or knee arthroplasty. After adjustment, by forcing propensity score into the multivariable model, the association of patient blood management with composite morbidity or mortality was recalculated.

Results

There were 1,507 patients in the pre-patient blood management cohort and 2,402 patients in the post-patient blood management cohort. The clinical characteristics between the two groups are shown in table 2. Mean age was 1 yr older in the post-patient blood management cohort, and there was no change in male and female sex distribution. Case mix index assessed by median weighted All Patients Refined–Diagnosis-Related Groups was slightly but significantly decreased in the post-patient blood management cohort, indicating a small decrease in aggregate severity of illness and/or complexity of procedure. The percentage of patients requiring surgery for hip fracture was similar in the two periods. The percentage of patients undergoing total hip arthroplasty increased in the post-patient blood management period. The percentage of revision total joint

Table 2. Patient Characteristics before and after Patient Blood Management (All Patients)

Parameter	Pre-patient Blood Management (n = 1,507)	Post-patient Blood Management (n = 2,402)	P Value
Age, yr, mean ± SD	61 ± 16	62 ± 15	0.010
Age ≥ 65 yr, n (%)	620 (41.1)	1,042 (43.4)	0.17
Sex, n (% male)	685 (45.5)	1,114 (46.4)	0.57
CMI, median (IQR)	1.89 (1.65–1.98)	1.84 (1.53–1.98)	< 0.0001
Patient category, n (%)			
Hip fracture	124 (8.2)	194 (8.1)	0.87
Total hip	321 (21.3)	647 (26.9)	< 0.0001
Total knee	490 (32.5)	818 (34.1)	0.32
Total hip revision	49 (3.3)	81 (3.4)	0.84
Total knee revision	39 (2.6)	48 (2.0)	0.23
Other orthopedic	484 (32.1)	614 (25.6)	< 0.0001

CMI, case mix index (All Patient Refined–Diagnosis-Related Groups).

Table 3. Blood Use and Clinical Outcomes before and after Patient Blood Management (All Patients)

Parameter	Pre-patient Blood Management (n = 1,507)	Post-patient Blood Management (n = 2,402)	P Value
Trigger Hb, g/dl*, mean ± SD	7.8 ± 1.0	6.8 ± 1.0	< 0.0001
Target Hb, g/dl*, mean ± SD	9.0 ± 1.1	8.3 ± 1.0	< 0.0001
% Tx RBC, n (%)	242 (16.1)	226 (9.4)	< 0.0001
RBC units/1,000 patients	338	228	0.0007
LOS, days, median (IQR)	3 (1–4)	2 (1–3)	< 0.0001
Morbidity, n (%)	20 (1.3)	13 (0.54)	0.01
Mortality, n (%)	2 (0.13)	6 (0.25)	0.72
Morbidity or mortality, n (%)	22 (1.5)	18 (0.75)	0.035
30-day readmit†, n (%)	133 (9.0)	135 (5.8)	0.0002

*Trigger is defined as the nadir Hb during the hospital stay, and target as the last measured Hb before discharge. †Twenty-six patients in the pre-patient blood management period and 79 patients in the post-patient blood management period had missing data for this outcome.

Hb, hemoglobin; LOS, length of stay; RBC, erythrocyte; Tx, transfused.

arthroplasty patients was similar in the two cohorts. The number of patients having "other" procedures decreased in the post-patient blood management cohort.

The phasing in of different patient blood management program interventions over time along with changes in hemoglobin trigger and target, percentage of patients transfused, and mean number of units per patient are shown in figure 1. There was an incremental stepwise decrease in each parameter shown for each of the four periods. The changes shown in the early patient blood management phase are likely due to education at The Johns Hopkins Hospital campus, which carried over to the Bayview campus (as they share staff), and perioperative tranexamic acid use. Of significance is the average hemoglobin trigger, which was more than 7 g/dl during the first two periods and less than 7 g/dl during the second two periods.

Changes in blood use between the pre- and post-patient blood management time periods are shown in table 3. The mean hemoglobin transfusion trigger decreased by 1 g/dl, and the mean hemoglobin target decreased by 0.7 g/dl (both $P <$ 0.0001). The percentage of patients transfused erythrocytes decreased from 16.1% to 9.4% ($P < 0.0001$), and there was a 32.5% decrease in the number of erythrocyte units per 1,000 patients ($P = 0.0007$). The percentages of patients transfused plasma (pre-patient blood management 1.6% *vs.* post-patient blood management 1.4%; $P = 0.66$) and platelets (pre-patient blood management 0.53% *vs.* post-patient blood management 0.37%; $P = 0.48$) were low and unchanged.

Clinical outcomes comparing the pre- and post-patient blood management periods are also shown in table 3. The composite outcome of any morbidity or mortality (primary outcome) decreased by half ($P = 0.035$). The median (interquartile range) length of stay decreased by 1 day ($P < 0.0001$). The morbid event rate decreased by more than half ($P = 0.01$), and mortality was unchanged ($P = 0.72$). The 30-day readmission rate significantly decreased from 9.0% to 5.8% ($P = 0.0002$). In the pre- and post-patient

blood management periods, 26 patients and 79 patients had missing readmission data, respectively. In summary, when all adult orthopedic patients are included (both young and old cohorts), the implementation of patient blood management was associated with improvement in all measured outcomes, except for mortality, which remained unchanged.

Clinical characteristics for the younger and older subgroups are shown in table 4. Mean age was approximately 25 yr greater in the older (65 yr old and older) subgroup. Median case mix index was slightly but significantly decreased in the post-patient blood management period for both age subgroups. The percentage of patients requiring surgery for hip fracture was similar in the pre- and post-patient blood management periods for both subgroups. The percentage of patients undergoing total hip arthroplasty increased in the post-patient blood management period for both subgroups.

Changes in blood use and clinical outcomes are shown for the younger and older subgroups in table 5. The percentage of patients transfused decreased post-patient blood management in both subgroups; however, erythrocyte use (erythrocyte units per 1,000 patients) decreased significantly in the older subgroup only (by 43%; $P < 0.0001$). Median length of stay decreased by 1 day for both the younger and older subgroups in the post-patient blood management period (both $P < 0.0001$). Morbidity was unchanged in the younger subgroup but decreased in the older subgroup in the post-patient blood management period ($P = 0.039$). Mortality remained unchanged in both younger and older subgroups, as did the composite outcome (morbidity or mortality). The 30-day readmission rate was unchanged in the younger subgroup, but for the older subgroup, there was a decrease in readmission rate post-patient blood management ($P < 0.0001$). In summary, the improved outcomes with patient blood management were more apparent in the

Table 4. Patient Characteristics before and after Patient Blood Management (Younger and Older Subgroups)

Parameter	Younger Patients (<65 yr; n = 2,247)			Older Patients (≥65 yr; n = 1,662)		
	Pre-patient Blood Management (n = 887)	Post-patient Blood Management (n = 1,360)	P Value	Pre-patient Blood Management (n = 620)	Post-patient Blood Management (n = 1,042)	P Value
Age, yr, mean ± SD	51 ± 12	52 ± 11	0.009	75 ± 8	75 ± 8	0.93
Sex, n (% male)	488 (55.0)	701 (51.5)	0.11	197 (31.8)	412 (39.6)	0.001
CMI, median (IQR)	1.84 (1.65–1.98)	1.70 (1.51–1.98)	< 0.0001	1.89 (1.65–2.04)	1.84 (1.58–1.98)	< 0.0001
Patient category, n (%)						
Hip fracture	25 (2.8)	46 (3.4)	0.45	99 (16.0)	148 (14.2)	0.31
Total hip	207 (23.3)	396 (29.1)	0.002	114 (18.4)	251 (24.1)	0.006
Total knee	279 (31.5)	435 (32.0)	0.79	211 (34.0)	383 (36.8)	0.26
Total hip revision	30 (3.4)	41 (3.0)	0.63	19 (3.1)	40 (3.8)	0.40
Total knee revision	20 (2.3)	26 (1.9)	0.58	19 (3.1)	22 (2.1)	0.23
Other orthopedic	326 (36.8)	416 (30.6)	0.003	158 (25.5)	198 (19.0)	0.002

CMI, case mix index (All Patients Refined–Diagnosis-Related Groups).

Table 5. Blood Use and Clinical Outcomes before and after Patient Blood Management (Younger and Older Subgroups)

Parameter	Younger Patients (<65 yr; n = 2,247)			Older Patients (≥65 yr; n = 1,662)		
	Pre-patient Blood Management (n = 887)	Post-patient Blood Management (n = 1,360)	P Value	Pre-patient Blood Management (n = 620)	Post-patient Blood Management (n = 1,042)	P Value
Trigger Hb, g/dl*, mean ± SD	7.9 ± 1.0	6.7 ± 0.9	< 0.0001	7.8 ± 1.0	6.9 ± 1.1	< 0.0001
Target Hb, g/dl*, mean ± SD	9.0 ± 1.3	8.1 ± 0.9	< 0.0001	9.0 ± 1.1	8.3 ± 1.0	< 0.0001
% Tx RBC, n (%)	89 (10.0)	86 (6.3)	0.0015	153 (24.5)	139 (13.4)	<0.0001
RBC units/1,000 patients	192	163	0.39	547	313	0.0001
LOS, days, median (IQR)	2 (1–3)	1 (1–3)	< 0.0001	3 (2–4)	2 (1–4)	< 0.0001
Morbidity, n (%)	8 (0.9)	5 (0.4)	0.15	12 (1.9)	8 (0.8)	0.039
Mortality, n (%)	1 (0.1)	1 (0.1)	1.0	1 (0.2)	5 (0.5)	0.42
Morbidity or mortality, n (%)	9 (1.0)	6 (0.4)	0.11	13 (2.1)	12 (1.2)	0.13
30-day readmit†, n (%)	62 (7.1)	74 (5.6)	0.15	71 (12)	61 (6.1)	< 0.0001

In the older patient cohort, 17 patients in the pre-patient blood management period and 38 patients in the post-patient blood management period had missing data for this outcome.

*Trigger is defined as the nadir Hb during the hospital stay, and target as the last measured Hb before discharge. †In the younger patient cohort, 9 patients in the pre-patient blood management period and 41 patients in the post-patient blood management period had missing data for this outcome.

Hb, hemoglobin; LOS, length of stay; RBC, erythrocyte; Tx, transfused.

older patient subgroup (age 65 yr or older), whereas in the younger patients, the outcomes were unchanged.

In the multivariable model with risk adjustment for age, case mix index, sex, hip fracture, and type of surgery, there were reduced odds of an adverse outcome (composite morbidity or mortality; odds ratio, 0.44; 95% CI, 0.22 to 0.86; P = 0.016) in the post-patient blood management period than in the pre-patient blood management period (table 6). Case mix index, hip fracture, and total joint arthroplasty were also independent predictors of adverse outcomes, but age and sex were not. These findings indicate that patient blood management was associated with improvement in clinical outcomes even after adjustment for these potential confounders. On sensitivity analysis using risk adjustment with propensity scores in the logistic regression model, the results remained robust, and patient blood management remained associated

Table 6. Multivariable Logistic Regression—Predictors of Adverse Outcome (Morbidity or Mortality)

Parameter	Odds Ratio	95% CI	P Value
Age, <65 yr/≥65 yr	1.57	(0.74–3.38)	0.24
Sex, male/female	0.92	(0.45–1.90)	0.82
CMI, per unit change in regressor	3.66	(2.59–5.32)	< 0.0001
Hip fracture	3.28	(1.39–7.81)	0.0067
Total joint arthroplasty	0.31	(0.13–0.74)	0.008
Pre- / Post-patient blood management	0.44	(0.22–0.86)	0.016

On sensitivity analysis when adding propensity score into the above model, the results remained robust, and patient blood management was associated with a decrease in the composite adverse outcome (morbidity or mortality; odds ratio, 0.37; 95% CI, 0.18–0.74; P = 0.005).

CMI, case mix index (All Patients Refined–Diagnosis-Related Groups).

with a decrease in the composite outcome (morbidity or mortality; odds ratio, 0.37; 95% CI, 0.18 to 0.74; P = 0.005).

Discussion

The results of this study demonstrate that for orthopedic surgery patients, a comprehensive patient blood management program is a successful method for significantly reducing blood use, while maintaining or improving clinical outcomes. Even after age and risk adjustment in the post-patient blood management cohort, patients did just as well or better with a lower hemoglobin trigger and target, resulting in an overall decrease in the percentage of patients transfused and erythrocyte units transfused per patient. Importantly, morbidity, length of stay, and readmission rates all improved, while mortality was unchanged. It is likely that with the overall low incidence of mortality (about 2 per 1,000 patients), the sample size was too small and/or the patients too healthy to assess mortality. Regarding age, the older patients showed more benefit than younger patients with the changes in transfusion practice, perhaps because both morbidity and readmissions occurred with about half the frequency at baseline in the younger subgroup. The finding that older patients do as well or better with a restrictive transfusion strategy than with a liberal strategy is also supported by clinical trials in orthopedic[27] and cardiac surgery.[29]

The FOCUS trial,[27] published in 2011, enrolled more than 2,000 hip fracture patients, who were randomized to hemoglobin triggers of 8 or 10 g/dl, and the primary result was no difference in any of the major outcomes. Our study also included orthopedic patients, although the mean age of our patients was about 20 yr younger than the mean age in the FOCUS trial (61 yr vs. 83 yr). This age difference is likely because elderly patients are more prone to hip fractures, and the FOCUS inclusion criteria specified a history of risk factors for cardiovascular disease. Our study's results are in agreement with the results of the FOCUS trial,[27] in that a restrictive transfusion strategy is safe in orthopedic patients, with the caveat (from both studies) that symptomatic anemia and not just hemoglobin concentration be used as criteria for transfusion. However, our results differ from the FOCUS results because we describe a decrease to an even lower hemoglobin threshold for transfusion (less than 7 g/dl rather than less than 8 g/dl). Our results also differ in that we showed improvement in some clinical outcomes. Even the older subgroup in our analysis had the same or better outcomes with this lower hemoglobin threshold. Granted, even our older subgroup (mean age 75 yr) was still younger than the average FOCUS patient (83 yr), but our findings suggest that a blanket statement for orthopedic patients to be transfused at a hemoglobin trigger of 8 g/dl is overstated.

The findings in the current study have implications regarding the most recent AABB transfusion guidelines,[34] where 8 g/dl is suggested as the ideal trigger for orthopedic patients, with a statement recognizing that 7 g/dl versus 8 g/dl has not been compared. Of interest is the average hemoglobin trigger above 7 g/dl, decreasing to less than 7 g/dl, in what we defined as the pre- and post-patient blood management periods in our study (fig. 1). It should be recognized that before blood management, approximately one third of all erythrocyte transfusions at our institution were ordered with a preceding hemoglobin concentration between 7 and 8 g/dl.[15,35] Thus, when Choosing Wisely and AABB guidelines recommend a hemoglobin threshold between 7 and 8 g/dl,[34,44] this leaves a substantial number of transfusions that could potentially be avoided with preceding hemoglobin levels between 7 and 8 g/dl. Perhaps the best conclusion is that we treat the whole patient, and not just their laboratory values. In fact, the FOCUS trial allowed transfusion in the restrictive group even when the hemoglobin was more than 8 g/dl, if symptoms of anemia were present (cardiac chest pain, congestive heart failure, or tachycardia or hypotension unresponsive to fluid), and our hospital guidelines are similar. In fact, about 15% of patients assigned to the FOCUS trial restrictive group were transfused for such symptoms. The same criteria would be important to consider as indications for transfusion if a hemoglobin threshold of 7 g/dl was to be used for orthopedic patients.

Other studies that describe a before and after patient blood management analysis of outcomes include the study by Goodnough et al.,[45] who retrospectively investigated clinical outcomes across all patients hospital-wide after starting a blood management program. These investigators noted similar trends but slightly different results than ours, with an improvement in mortality rates and unchanged readmission rates, yet a similar reduction in mean erythrocyte units per patient (≈25 to 30%). Another recent study by Leahy et al.[19] retrospectively examined blood use and patient outcomes after a health system–wide patient blood management program. In this study, which also included all hospitalized patients, they noted a decrease in erythrocyte transfusions (≈40%), as well as a decrease in hemoglobin trigger and length of stay; however, they also noted a decrease in mortality. A patient blood management program specifically for hip and knee arthroplasty patients showed a 30 to 50% decrease in percentage of patients transfused, along with a decreased length of stay.[46] Interestingly, their patient blood management methods included postoperative blood salvage and postoperative intravenous iron, which were not included in our patient blood management program. Tranexamic acid was also used.

Other orthopedic studies on transfusion triggers have assessed ability to ambulate,[47] quality of life,[48] delirium,[32] cardiac ischemia,[49] and infections,[31] and these studies almost universally found no benefit to liberal transfusion; however, the hemoglobin transfusion triggers ranged from 8 to 11.3 g/dl. To our knowledge, ours is the first study in orthopedics to assess hemoglobin thresholds as low as 7 g/dl. Given the potential risk of anemia from undertransfusion in the era of patient blood management, our findings are reassuring in this regard. Certainly, monitoring for undertransfusion should be considered in a patient blood management program,

since severe anemia can result in impaired oxygen delivery with an increase in ischemic events and/or mortality.[50,51]

There are some limitations that should be recognized in our study. In a retrospective observational analysis, controlling for multiple confounding variables that change over time or issues such as missing data is challenging, and identifying a true causal effect of a patient blood management program on blood use and clinical outcomes is not possible. There may have also been unreported changes, such as quality improvement efforts in surgical practice, some of which are designed, for example, to decrease length of stay. Cohort characteristics were relatively similar before and after patient blood management, with the exceptions of an increase in the proportion of total hip replacements, a small increase in age, and a small decrease in case mix index. Furthermore, since all adult orthopedic inpatients were included, there were likely a considerable number of low-risk (primarily younger) patients in our study population. Interestingly, however, there appeared to be more improvement for clinical outcomes in the older subgroup of patients (65 yr and older). Thus, we can only say that in the setting of our current orthopedic care standards, patient blood management was associated with decreased blood use and similar or better outcomes, without a clear causal relationship to outcomes. In addition, after adding surgical procedure (total joint and hip fracture) to the multivariable model, the risk-adjusted odds ratio showing decreased adverse clinical outcome remained significant. The exact beginning of patient blood management is difficult to determine because there were 10 or more methods that were implemented in a gradual, stepwise fashion (fig. 1). For the purposes of the outcomes analysis, we chose to define the start as when pre-patient blood management activities were completed and the majority of the primary interventions had been initiated. Of note is the mean hemoglobin trigger, decreasing from above to less than 7 g/dl when our pre- and post-time periods are compared. Regarding the various different patient blood management methods, we cannot clearly determine the most impactful initiatives because many of them were implemented as a "bundle." Because preoperative anemia is associated with increased transfusion and adverse outcomes,[52] but was not specifically addressed in our study, we are unable to comment on the importance of anemia management. Tranexamic acid for total joints was phased in gradually at least 1 yr before these interventions. The single-center nature of this study is also a limitation, as results in other centers may differ from ours. Other centers may have sicker or older patients, such as those with hip fractures, which result in a higher-risk population, like that in the FOCUS trial. In fact, our overall adverse event rates were lower than those reported in other studies.

In conclusion, our results suggest that patient blood management is efficacious for orthopedic patients and that a hemoglobin trigger of 7 g/dl rather than 8 g/dl is well tolerated, even by elderly patients on an orthopedic service. Our study adds to the growing body of literature regarding the efficacy of patient blood management programs on reducing transfusion overuse while maintaining good outcomes. By reducing risks and costs while improving outcomes, we can promote high-value practice with effective patient blood management programs.

Competing Interests

Dr. Frank has been on advisory boards for Haemonetics (Braintree, Massachusetts) and Medtronic (Minneapolis, Minnesota). The other authors declare no competing interests.

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References

1. Pfuntner A, Wier LM, Stocks C: Most frequent procedures performed in U.S. hospitals, 2011. Available at: https://www.hcup-us.ahrq.gov/reports/statbriefs/sb165.pdf. Accessed March 9, 2018

2. Joint Commission T, American Medical Association-Convened Physician Consortium for Performance Improvement: Proceedings from the National Summit on Overuse: September 24, 2012. Available at: https://www.jointcommission.org/assets/1/6/National_Summit_Overuse.pdf. Accessed March 9, 2018

3. Vamvakas EC, Blajchman MA: Transfusion-related mortality: The ongoing risks of allogeneic blood transfusion and the available strategies for their prevention. Blood 2009; 113:3406–17

4. Engoren MC, Habib RH, Zacharias A, Schwann TA, Riordan CJ, Durham SJ: Effect of blood transfusion on long-term survival after cardiac operation. Ann Thorac Surg 2002; 74:1180–6

5. Rawn J: The silent risks of blood transfusion. Curr Opin Anaesthesiol 2008; 21:664–8

6. Ferraris VA, Davenport DL, Saha SP, Bernard A, Austin PC, Zwischenberger JB: Intraoperative transfusion of small amounts of blood heralds worse postoperative outcome in patients having noncardiac thoracic operations. Ann Thorac Surg 2011; 91:1674–80; discussion 1680

7. Shishehbor MH, Madhwal S, Rajagopal V, Hsu A, Kelly P, Gurm HS, Kapadia SR, Lauer MS, Topol EJ: Impact of blood transfusion on short- and long-term mortality in patients with ST-segment elevation myocardial infarction. JACC Cardiovasc Interv 2009; 2:46–53

8. Goodnough LT: Risks of blood transfusion. Crit Care Med 2003; 31(12 suppl):S678–86

9. Sapiano MRP, Savinkina AA, Ellingson KD, Haass KA, Baker ML, Henry RA, Berger JJ, Kuehnert MJ, Basavaraju SV: Supplemental findings from the National Blood Collection and Utilization Surveys, 2013 and 2015. Transfusion 2017; 57 Suppl 2:1599–624

10. Whitaker B, Rajbhandary S, Kleinman S, Harris A, Kamani N: Trends in United States blood collection and transfusion: Results from the 2013 AABB Blood Collection, Utilization, and Patient Blood Management Survey. Transfusion 2016; 56:2173–83

11. Tokin C, Almeda J, Jain S, Kim J, Henderson R, Nadim M, Sher L, Selby RR: Blood-management programs: A clinical and administrative model with program implementation strategies. Perm J 2009; 13:18–28

12. Waters JH, Ness PM: Patient blood management: A growing challenge and opportunity. Transfusion 2011; 51:902–3

13. Yang WW, Thakkar RN, Gehrie EA, Chen W, Frank SM: Single-unit transfusions and hemoglobin trigger: Relative impact on red cell utilization. Transfusion 2017; 57:1163–70

14. Sikorski RA, Rizkalla NA, Yang WW, Frank SM: Autologous blood salvage in the era of patient blood management. Vox Sang 2017; 112:499–510

15. Thakkar RN, Lee KH, Ness PM, Wintermeyer TL, Johnson DJ, Liu E, Rajprasad A, Knight AM, Wachter PA, Demski R, Frank SM: Relative impact of a patient blood management program on utilization of all three major blood components. Transfusion 2016; 56:2212–20

16. Podlasek SJ, Thakkar RN, Rotello LC, Fleury TA, Demski RJ, Ness PM, Frank SM: Implementing a "Why give 2 when 1 will do?" Choosing Wisely campaign. Transfusion 2016; 56:2164

17. Oliver JC, Griffin RL, Hannon T, Marques MB: The success of our patient blood management program depended on an institution-wide change in transfusion practices. Transfusion 2014; 54(10 pt 2):2617–24

18. Leahy MF, Roberts H, Mukhtar SA, Farmer S, Tovey J, Jewlachow V, Dixon T, Lau P, Ward M, Vodanovich M, Trentino K, Kruger PC, Gallagher T, Koay A, Hofmann A, Semmens JB, Towler S; Western Australian Patient Blood Management Program: A pragmatic approach to embedding patient blood management in a tertiary hospital. Transfusion 2014; 54:1133–45

19. Leahy MF, Hofmann A, Towler S, Trentino KM, Burrows SA, Swain SG, Hamdorf J, Gallagher T, Koay A, Geelhoed GC, Farmer SL: Improved outcomes and reduced costs associated with a health-system-wide patient blood management program: A retrospective observational study in four major adult tertiary-care hospitals. Transfusion 2017; 57:1347–58

20. Frank SM, Thakkar RN, Podlasek SJ, Ken Lee KH, Wintermeyer TL, Yang WW, Liu J, Rotello LC, Fleury TA, Wachter PA, Ishii LE, Demski R, Pronovost PJ, Ness PM: Implementing a health system-wide patient blood management program with a clinical community approach. ANESTHESIOLOGY 2017; 127:754–64

21. Hajjar LA, Vincent JL, Galas FR, Nakamura RE, Silva CM, Santos MH, Fukushima J, Kalil Filho R, Sierra DB, Lopes NH, Mauad T, Roquim AC, Sundin MR, Leão WC, Almeida JP, Pomerantzeff PM, Dallan LO, Jatene FB, Stolf NA, Auler JO Jr: Transfusion requirements after cardiac surgery: The TRACS randomized controlled trial. JAMA 2010; 304:1559–67

22. Hébert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E: A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med 1999; 340:409–17

23. Villanueva C, Colomo A, Bosch A, Concepción M, Hernandez-Gea V, Aracil C, Graupera I, Poca M, Alvarez-Urturi C, Gordillo J, Guarner-Argente C, Santaló M, Muñiz E, Guarner C: Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med 2013; 368:11–21

24. Holst LB, Haase N, Wetterslev J, Wernerman J, Guttormsen AB, Karlsson S, Johansson PI, Aneman A, Vang ML, Winding R, Nebrich L, Nibro HL, Rasmussen BS, Lauridsen JR, Nielsen JS, Oldner A, Pettilä V, Cronhjort MB, Andersen LH, Pedersen UG, Reiter N, Wiis J, White JO, Russell L, Thornberg KJ, Hjortrup PB, Müller RG, Møller MH, Steensen M, Tjäder I, Kilsand K, Odeberg-Wernerman S, Sjøbø B, Bundgaard H, Thyø MA, Lodahl D, Mærkedahl R, Albeck C, Illum D, Kruse M, Winkel P, Perner A; TRISS Trial Group; Scandinavian Critical Care Trials Group: Lower versus higher hemoglobin threshold for transfusion in septic shock. N Engl J Med 2014; 371:1381–91

25. Murphy GJ, Pike K, Rogers CA, Wordsworth S, Stokes EA, Angelini GD, Reeves BC; TITRe2 Investigators: Liberal or restrictive transfusion after cardiac surgery. N Engl J Med 2015; 372:997–1008

26. Lacroix J, Hébert PC, Hutchison JS, Hume HA, Tucci M, Ducruet T, Gauvin F, Collet JP, Toledano BJ, Robillard P, Joffe A, Biarent D, Meert K, Peters MJ; TRIPICU Investigators; Canadian Critical Care Trials Group; Pediatric Acute Lung Injury and Sepsis Investigators Network: Transfusion strategies for patients in pediatric intensive care units. N Engl J Med 2007; 356:1609–19

27. Carson JL, Terrin ML, Noveck H, Sanders DW, Chaitman BR, Rhoads GG, Nemo G, Dragert K, Beaupre L, Hildebrand K, Macaulay W, Lewis C, Cook DR, Dobbin G, Zakriya KJ, Apple FS, Horney RA, Magaziner J; FOCUS Investigators: Liberal or restrictive transfusion in high-risk patients after hip surgery. N Engl J Med 2011; 365:2453–62

28. Robertson CS, Hannay HJ, Yamal JM, Gopinath S, Goodman JC, Tilley BC, Baldwin A, Rivera Lara L, Saucedo-Crespo H, Ahmed O, Sadasivan S, Ponce L, Cruz-Navarro J, Shahin H, Aisiku IP, Doshi P, Valadka A, Neipert L, Waguspack JM, Rubin ML, Benoit JS, Swank P; Epo Severe TBI Trial Investigators: Effect of erythropoietin and transfusion threshold on neurological recovery after traumatic brain injury: A randomized clinical trial. JAMA 2014; 312:36–47

29. Mazer CD, Whitlock RP, Fergusson DA, Hall J, Belley-Cote E, Connolly K, Khanykin B, Gregory AJ, de Médicis É, McGuinness S, Royse A, Carrier FM, Young PJ, Villar JC, Grocott HP, Seeberger MD, Fremes S, Lellouche F, Syed S, Byrne K, Bagshaw SM, Hwang NC, Mehta C, Painter TW, Royse C, Verma S, Hare GMT, Cohen A, Thorpe KE, Jüni P, Shehata N; TRICS Investigators and Perioperative Anesthesia Clinical Trials Group: Restrictive or liberal red-cell transfusion for cardiac surgery. N Engl J Med 2017; 377:2133–44

30. Vuille-Lessard E, Boudreault D, Girard F, Ruel M, Chagnon M, Hardy JF: Red blood cell transfusion practice in elective orthopedic surgery: A multicenter cohort study. Transfusion 2010; 50:2117–24

31. Gregersen M, Damsgaard EM, Borris LC: Blood transfusion and risk of infection in frail elderly after hip fracture surgery: The TRIFE randomized controlled trial. Eur J Orthop Surg Traumatol 2015; 25:1031–8

32. Fan YX, Liu FF, Jia M, Yang JJ, Shen JC, Zhu GM, Zhu SH, Li WY, Yang JJ, Ji MH: Comparison of restrictive and liberal transfusion strategy on postoperative delirium in aged patients following total hip replacement: A preliminary study. Arch Gerontol Geriatr 2014; 59:181–5

33. Hovaguimian F, Myles PS: Restrictive versus liberal transfusion strategy in the perioperative and acute care settings: A context-specific systematic review and meta-analysis of randomized controlled trials. ANESTHESIOLOGY 2016; 125:46–61

34. Carson JL, Guyatt G, Heddle NM, Grossman BJ, Cohn CS, Fung MK, Gernsheimer T, Holcomb JB, Kaplan LJ, Katz LM, Peterson N, Ramsey G, Rao SV, Roback JD, Shander A, Tobian AA: Clinical practice guidelines from the AABB: Red blood cell transfusion thresholds and storage. JAMA 2016; 316:2025–35

35. Wintermeyer TL, Liu J, Lee KH, Ness PM, Johnson DJ, Hoffman NA, Wachter PA, Demski R, Frank SM: Interactive dashboards to support a patient blood management program across a multi-institutional healthcare system. Transfusion 2016; 56:1480–1

36. Frank SM, Wasey JO, Dwyer IM, Gokaslan ZL, Ness PM, Kebaish KM: Radiofrequency bipolar hemostatic sealer reduces blood loss, transfusion requirements, and cost for patients undergoing multilevel spinal fusion surgery: A case control study. J Orthop Surg Res 2014; 9:50

37. Johnson DJ, Scott AV, Barodka VM, Park S, Wasey JO, Ness PM, Gniadek T, Frank SM: Morbidity and mortality after high-dose transfusion. ANESTHESIOLOGY 2016; 124:387–95

38. Frank SM, Resar LM, Rothschild JA, Dackiw EA, Savage WJ, Ness PM: A novel method of data analysis for utilization of red blood cell transfusion. Transfusion 2013; 53:3052–9

39. Gani F, Cerullo M, Ejaz A, Gupta PB, DeMario VM, Johnston FM, Frank SM, Pawlik TM: Implementation of a blood management program at a tertiary care hospital. Ann Surg 2017 Nov 2 [Epub ahead of print]

40. Goel R, Johnson DJ, Scott AV, Tobian AA, Ness PM, Nagababu E, Frank SM: Red blood cells stored 35 days or more are associated with adverse outcomes in high-risk patients. Transfusion 2016; 56:1690–8

41. Kim Y, Spolverato G, Lucas DJ, Ejaz A, Xu L, Wagner D, Frank SM, Pawlik TM: Red cell transfusion triggers and postoperative outcomes after major surgery. J Gastrointest Surg 2015; 19:2062–73

42. Stonemetz JL, Allen PX, Wasey J, Rivers RJ, Ness PM, Frank SM: Development of a risk-adjusted blood utilization metric. Transfusion 2014; 54(10 pt 2):2716–23

43. Averill RF, Goldfield N, Hughes JS, Bonazelli J, McCullough EC, Steinbeck BA, Mullin R, Tang AM, Muldoon J, Turner L, Gay J. All patient refined diagnosis related groups (APR-DRGs). Available at: https://www.hcup-us.ahrq.gov/db/nation/nis/APR-DRGsV20MethodologyOverviewandBibliography.pdf. Accessed December 3, 2017

44. Callum JL, Waters JH, Shaz BH, Sloan SR, Murphy MF: The AABB recommendations for the Choosing Wisely campaign of the American Board of Internal Medicine. Transfusion 2014; 54:2344–52

45. Goodnough LT, Maggio P, Hadhazy E, Shieh L, Hernandez-Boussard T, Khari P, Shah N: Restrictive blood transfusion practices are associated with improved patient outcomes. Transfusion 2014; 54(10 pt 2):2753–9

46. Albinarrate A, López-Picado A, Oiartzabal I, López-Ariznabarreta C, Molano J, Barrachina B: Assessment of the introduction of a blood management program in orthopaedic surgery. Rev Esp Anestesiol Reanim 2015; 62:443–9

47. Foss NB, Kristensen MT, Jensen PS, Palm H, Krasheninnikoff M, Kehlet H: The effects of liberal versus restrictive transfusion thresholds on ambulation after hip fracture surgery. Transfusion 2009; 49:227–34

48. Gregersen M, Borris LC, Damsgaard EM: Blood transfusion and overall quality of life after hip fracture in frail elderly patients—The transfusion requirements in frail elderly randomized controlled trial. J Am Med Dir Assoc 2015; 16:762–6

49. Grover M, Talwalkar S, Casbard A, Boralessa H, Contreras M, Boralessa H, Brett S, Goldhill DR, Soni N: Silent myocardial ischaemia and haemoglobin concentration: A randomized controlled trial of transfusion strategy in lower limb arthroplasty. Vox Sang 2006; 90:105–12

50. Carson JL, Noveck H, Berlin JA, Gould SA: Mortality and morbidity in patients with very low postoperative Hb levels who decline blood transfusion. Transfusion 2002; 42:812–8

51. Weiskopf RB, Viele MK, Feiner J, Kelley S, Lieberman J, Noorani M, Leung JM, Fisher DM, Murray WR, Toy P, Moore MA: Human cardiovascular and metabolic response to acute, severe isovolemic anemia. JAMA 1998; 279:217–21

52. Spahn DR: Anemia and patient blood management in hip and knee surgery: A systematic review of the literature. ANESTHESIOLOGY 2010; 113:482–95

Comparison of Two Major Perioperative Bleeding Scores for Cardiac Surgery Trials

Universal Definition of Perioperative Bleeding in Cardiac Surgery and European Coronary Artery Bypass Grafting Bleeding Severity Grade

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ABSTRACT

Background: Research into major bleeding during cardiac surgery is challenging due to variability in how it is scored. Two consensus-based clinical scores for major bleeding: the Universal definition of perioperative bleeding and the European Coronary Artery Bypass Graft (E-CABG) bleeding severity grade, were compared in this substudy of the Transfusion Avoidance in Cardiac Surgery (TACS) trial.

Methods: As part of TACS, 7,402 patients underwent cardiac surgery at 12 hospitals from 2014 to 2015. We examined content validity by comparing scored items, construct validity by examining associations with redo and complex procedures, and criterion validity by examining 28-day in-hospital mortality risk across bleeding severity categories. Hierarchical logistic regression models were constructed that incorporated important predictors and categories of bleeding.

Results: E-CABG and Universal scores were correlated (Spearman ρ = 0.78, $P < 0.0001$), but E-CABG classified 910 (12.4%) patients as having more severe bleeding, whereas the Universal score classified 1,729 (23.8%) as more severe. Higher E-CABG and Universal scores were observed in redo and complex procedures. Increasing E-CABG and Universal scores were associated with increased mortality in unadjusted and adjusted analyses. Regression model discrimination based on predictors of perioperative mortality increased with additional inclusion of the Universal score (c-statistic increase from 0.83 to 0.91) or E-CABG (c-statistic increase from 0.83 to 0.92). When other major postoperative complications were added to these models, the association between Universal or E-CABG bleeding with mortality remained.

Conclusions: Although each offers different advantages, both the Universal score and E-CABG performed well in the validity assessments, supporting their use as outcome measures in clinical trials. (**ANESTHESIOLOGY** 2018; 129:1092-100)

EXCESSIVE perioperative blood loss requiring transfusion is a common and clinically important complication of cardiac surgery.[1,2] Despite its importance, there is significant variability in how this outcome is scored across clinical trials.[1,2] Adoption of consensus-based outcome scoring methods has been advocated as a means for better standardizing endpoints in clinical trials.[3–6] They offer consistency across clinical trials, help simplify the interpretation of trials with conflicting results, and facilitate evidence synthesis.[7,8]

Two such consensus-based scores for clinically important blood loss in cardiac surgery have recently been proposed, namely the Universal definition of perioperative bleeding[9]

Editor's Perspective

What We Already Know about This Topic

- Major bleeding can occur during cardiac surgery. Although different scoring systems exist, the assessment of bleeding can be variable, and the reliability of these scoring systems has not been determined.

What This Article Tells Us That Is New

- Two consensus-based scoring systems for assessing bleeding were compared in a substudy of the Transfusion Avoidance in Cardiac Surgery trial. Both the Universal score and European Coronary Artery Bypass Graft scores performed well and may be used as validated outcome measures in future clinical trials.

Table 1. Bleeding Categories Defined by Two Different Consensus-based Bleeding Scores Designed for Use in Cardiac Surgery Clinical Trials

	Sternal Closure Delayed	Postoperative Chest Tube Blood Loss within 12 h (ml)	Erythrocytes (units)	FFP (units)	PLT (units)	Cryoprecipitate	PCCs	rFVIIa	Reexploration/ Tamponade
Universal Definition of Perioperative Bleeding in Adult Cardiac Surgery*[9]									
Bleeding class									
Class 0 (insignificant)	No	< 600	0*	0	0	No	No	No	No
Class 1 (mild)	No	601–800	1	0	0	No	No	No	No
Class 2 (moderate)	No	801–1000	2–4	2–4	Yes	Yes	Yes	No	No
Class 3 (severe)	Yes	1001–2000	5–10	5–10	N/A	N/A	N/A	No	Yes
Class 4 (massive)	N/A	> 2000	> 10	> 10	N/A	N/A	N/A	Yes	N/A
E-CABG grading and additive score†[10]									
Grades		Intervention for Treatment of Bleeding							
Grade 0		No use of blood products with the exception of 1 unit of erythrocytes							
Grade 1		Transfusion of platelets; transfusion of fresh frozen plasma or prothrombin complex concentrates; Transfusion of 2–4 units of erythrocytes							
Grade 2		Transfusion of 5–10 units of erythrocytes; reoperation for bleeding							
Grade 3		Transfusion of >10 units of erythrocytes							

*If clinical events occurring to a patient indicate more than one bleeding category, the worst category applies, including if transition between categories is based on one more severe item. The Universal definition of perioperative bleeding is scored based on events occurring during surgery or within the first postoperative day. Preoperative transfusions are not included. †This classification included any transfusion of erythrocytes, platelets, and fresh frozen plasma that occurred during the operation and postoperatively during the same in-hospital stay. Preoperative transfusions are not included.

E-CABG, European Coronary Artery Bypass Graft; FFP, fresh frozen plasma; N/A, not applicable; PCC, prothrombin complex concentrate; PLT, platelet concentrate; rFVIIa, recombinant activated factor VII.

and the European Coronary Artery Bypass Graft (E-CABG) bleeding severity grade (table 1).[10,11] The Universal score is based on nine clinically important events that occur during surgery or within the first postoperative day. It was designed to capture significant bleeding independent of its source or clinical management decisions (table 1).[9] Conversely, the E-CABG score is based on interventions that indirectly quantify perioperative blood loss (*i.e.*, blood product transfusion, reoperation for bleeding) and occur at any point from surgery to the end of hospitalization (table 1).[11]

Precise quantification of bleeding during the perioperative period is difficult and prone to error. Direct estimation of surgical blood loss, even by experienced staff, is often inaccurate and unreliable.[12,13] In addition, ongoing bleeding may be concealed or unrecognized until it leads to changes in hemodynamic stability or laboratory parameters. As such, these consensus-based scores were designed to grade bleeding using multiple items rather than relying on directly observed blood loss. Recognizing that multiple items are combined to create a construct for bleeding, such scores are often compared and evaluated to provide evidence of their validity prior to use in clinical trials.[14–16]

There has been no prior comparison of E-CABG and the Universal score for their intended purpose, which is as clinical trial endpoints. We therefore conducted a substudy of the Transfusion Avoidance in Cardiac Surgery (TACS) trial,[17] which was a stepped-wedge clustered randomized controlled trial evaluating point-of-care hemostatic testing for transfusion avoidance at 12 hospitals, to compare the Universal and E-CABG scoring systems with respect to their content, construct, and criterion validity.

Content validity is whether all important domains of a given construct are included and was assessed by examining the individual items graded by the Universal score and E-CABG. Construct validity is whether a measurement tool captures the phenomenon it claims to measure and was assessed by examining whether patients who underwent procedures known to be associated with higher blood loss correspondingly had higher Universal and E-CABG scores. Last, criterion validity, which is the extent to which a score is related to an important outcome, was assessed by examining whether higher blood loss as assessed by either score was predictive of early postoperative mortality.

We hypothesize that both E-CABG and the Universal score will have evidence of content, criterion, and construct validity but expect that the Universal score may have better measurement properties overall given the greater number of clinically relevant events captured in the perioperative period.

Materials and Methods

Study Setting and Population

This substudy was based on data prospectively collected in the TACS trial, which included all patients who underwent elective, urgent, and emergent cardiac surgical procedures with cardiopulmonary bypass at 12 Canadian study sites from October 6, 2014, to May 1, 2015. Institutional research ethics board approval for this substudy was obtained from the University Health Network in Toronto, Canada. All authors had full access to all the data in the study and were responsible for its integrity and the data analysis. If a

patient was readmitted for additional operations requiring cardiopulmonary bypass during the study period, only data from the first admission were used. The eligible patient sample included all 7,402 patients included in the TACS trial.

Predictor and Outcome Definitions

The primary outcome was 28-day in-hospital all-cause mortality. In the TACS trial, major bleeding was scored using the Universal definition of perioperative bleeding, but E-CABG could be readily scored using variables already collected in the trial data set. Other events of interest included acute kidney injury (defined as an at least twofold postoperative increase in creatinine concentration or new need for renal replacement therapy, which corresponds to Kidney Disease Improving Global Outcomes stage 2 or 3),[18] sepsis, sternal infection, myocardial infarction, return to the operating room for reexploration, and cerebrovascular accident. In-hospital follow-up for complications was censored at postoperative day 28.

Important confounders for potential inclusion in risk-adjustment models were selected based on a review of published cardiac risk scores, as well as the literature examining the association between preoperative factors and postcardiac surgery outcomes.[19–29] These potential confounders included demographics (age, sex); procedure urgency (elective, urgent, emergent); redo procedure; preoperative intraaortic balloon pump; preoperative hemoglobin concentration (g/l); preoperative renal dysfunction, which was defined as an estimated glomerular filtration rate of less than 60 ml/min (calculated using the Cockcroft–Gault Equation)[30] or preoperative dialysis; diabetes mellitus; extracardiac arteriopathy, which was defined as stroke, transient ischemic events, or peripheral arterial disease; chronic obstructive pulmonary disease; coronary artery disease; liver disease; heart failure; hypertension; and procedure complexity.[20] Procedure complexity was classified as simple, which was defined as isolated coronary artery bypass graft (CABG) or single valve procedure, or complex (all other procedures).

Statistical Analysis

The data set had at most 2% missing data; hence, missing data were not replaced or imputed. Initially, descriptive statistics (mean, SD, median, interquartile range, counts, proportion) were used to characterize the overall cohort, strata based on the presence *versus* absence of the primary outcome, and strata delineated by the E-CABG and Universal scores. Statistical significance was defined by a two-sided *P* value less than 0.05. All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., USA).

Content Validity. Content validity refers to whether a measure reasonably represents all aspects of a given construct. The items graded by each score, as well as items incorporated into one score but not the other, were assessed for how they contributed to assigning patients to a given category of blood loss. Chest tube output was specifically examined because it

could upgrade bleeding severity in the Universal score alone and thereby could result in discrepancies between the Universal score and E-CABG. The correlation between E-CABG and Universal scores was characterized using the Spearman statistic.

Construct Validity. Construct validity refers to whether the Universal score and E-CABG behave as would be expected if they are representing measures of perioperative blood loss. We examined whether procedure types known to have higher rates of blood loss, such as complex and redo procedures, were associated with higher blood loss severity as graded by either score.

Criterion Validity. An important component of criterion validity is whether increased severity of blood loss (as assessed by the Universal score or E-CABG) is associated with future events, such as increasing postoperative mortality. We measured the adjusted association between the Universal score and E-CABG with in-hospital 28-day all-cause mortality using multivariable logistic regression modeling. We accounted for clustering by using hierarchical models that incorporated site random effects and patient-level factors as fixed effects. Both the Universal score and E-CABG were each treated as ordinal variables, with progressively increasing scores treated as higher severity categories. Model assumptions were verified, including linearity of continuous variables. Age was modeled using a b-spline method to provide a robust and flexible way of modeling nonlinearity to the logit. Hemoglobin was treated as an untransformed continuous variable because it did not demonstrate significant nonlinearity. All other variables were binary or categorical.

A series of nested models were constructed for both the Universal score and E-CABG. Model 1 was used as the baseline model that only incorporated parsimonious predictive variables, which were initially identified from the literature and published predictive indices. Bootstrapping was used to select relevant variables for inclusion in the model from this initial list. Random sampling with replacement was used to generate a sample of 5,000 in 300 bootstrapped replicates, and covariates included in more than 50% of bootstrapped replicates were retained. Site was empirically retained in the model. Model 2 included all predictor variables in model 1 plus Universal score categories. Model 3 incorporated all predictor variables in model 2 plus major perioperative complications as predictors. This process was then repeated for E-CABG bleeding severity grades. Model 4 was composed of all predictor variables in model 1 plus E-CABG bleeding severity grades. Model 5 incorporated all predictor variables in model 4 plus major perioperative complications. Model calibration was examined using the Hosmer–Lemeshow statistic, whereas discrimination was characterized using the area under the curve for the receiver-operating-characteristic curve.

Using SAS version 9.4, the Glimmix procedure was used to create hierarchical models. The output data from the Glimmix procedure was subsequently used in the logistic

procedure to obtain the area under the curve and receiver-operating-characteristic curve for each model. Using Glimmix output, the logistic procedure receiver-operating-characteristic contrast command was used to compare differences in area under the curve values between the models. The output data sets from the Glimmix procedure were ranked according to deciles, and the Hosmer–Lemeshow statistic was calculated for each hierarchical model. In addition, internal model validation was conducted for all adjusted models *via* bootstrapping to obtain the model optimism, which was subsequently used to adjust the c-statistic and obtain a 95% CI using the Harrell Optimism SAS macro.

Results

The primary outcome, 28-day in-hospital mortality, occurred in 190 (2.6%) patients. The characteristics of patients stratified by mortality are presented in table 2. The Universal score could be fully calculated for 7,281 (98.4%) patients, of whom 168 (2.3%) died. E-CABG could be fully calculated for 7,347 (99.3%) of patients, of whom 190 (2.6%) died.

Content Validity

Universal score classes and E-CABG grades were moderately correlated with each other (Spearman ρ = 0.78, P < 0.0001). Only 910 (12.4%) patients were classified as having more severe bleeding (grade 2 or 3) when E-CABG was used, whereas 1,729 (23.8%) of patients were classified as having more severe bleeding (class 3 or 4) by the Universal score. Individual items in each scale were evaluated to explain this discrepancy. In total, 857 (11.9%) patients were classified by E-CABG as having lower severity bleeding (E-CABG grades 0 and 1) but classified as higher severity bleeding by the Universal score (Universal score class 3 and 4). Out of these individuals, 700 (81.7%) patients were classified as higher severity bleeding by the Universal score based solely on high chest tube output. Mortality risk among patients classified into higher severity bleeding categories due to chest tube output alone was low, with 0.9% (n = 6) of these patients experiencing death. In contrast, patients classified as higher severity by the Universal score due to factors other than or in addition to chest tube output had much higher mortality, with 12.6% (n = 130) experiencing death. No patients classified as lower severity bleeding by the Universal score (class 0 to 2) were scored as higher bleeding by E-CABG (grade 2 and 3).

Construct Validity

There were higher numbers of complex and redo procedures within each increasing category of bleeding severity for both scores (fig. 1).

Criterion Validity

When blood loss severity increased as graded by either score, there was a corresponding increase in mortality (fig. 2). In unadjusted logistic regression analyses, increasing Universal

Table 2. Patient Characteristics Stratified by In-hospital 28-day All-cause Mortality

Variable	Patients Alive (n = 7,212)	Patients with Primary Outcome (Death) (n = 190)
Age	67 (59, 74)	72 (63, 80)
Sex (female)	1,791 (24.83)	64 (33.68)
Procedure urgency		
Elective	4,543 (63.57)	77 (41.40)
Urgent	2,165 (30.29)	61 (32.80)
Emergent	439 (6.14)	48 (25.81)
Redo operation	417 (5.84)	31 (16.49)
Preoperative IABP	131 (1.82)	17 (8.95)
Procedure complexity	2,050 (28.42)	108 (56.84)
Preoperative hemoglobin concentration (g/l)	136 (123, 146)	121 (105, 137)
Comorbidities		
Diabetes	2,395 (33.21)	73 (38.42)
Extracardiac arteriopathy	1,216 (16.86)	62 (32.63)
COPD	880 (12.20)	31 (16.32)
Renal dysfunction	1,767 (24.98)	104 (58.10)
Coronary artery disease	5,266 (73.02)	123 (64.74)
Heart failure	1,445 (20.04)	78 (41.05)
Liver disease	158 (2.19)	13 (6.84)
Hypertension	5,554 (77.01)	144 (75.79)
Perioperative events		
Reexploration/return to operating room	333 (4.62)	66 (34.74)
AKI	43 (0.61)	8 (4.76)
CVA	112 (1.55)	34 (17.89)
Sternal infection	96 (1.33)	10 (5.26)
Acute MI	28 (0.39)	10 (5.26)
Postoperative sepsis	75 (1.04)	31 (16.32)
Universal definition of perioperative bleeding category		
Class 0	2,196 (30.87)	3 (1.79)
Class 1	1,200 (16.87)	9 (5.36)
Class 2	2,124 (29.86)	20 (11.90)
Class 3	1,325 (18.63)	76 (45.24)
Class 4	268 (3.77)	60 (35.71)
E-CABG grade		
Grade 0	4,090 (57.15)	17 (8.95)
Grade 1	2,295 (32.07)	35 (18.42)
Grade 2	715 (9.99)	115 (60.53)
Grade 3	57 (0.80)	23 (12.11)

The values shown are frequencies (%) or medians (Q1, Q3).
AKI, acute kidney injury; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; E-CABG, European Coronary Artery Bypass Graft; IABP, intraaortic balloon pump; MI, myocardial infarction.

and E-CABG scores were associated with increasing mortality (table 3). When used as the only predictor for the outcome of mortality, the Universal score and E-CABG did not differ in their discrimination, with the Universal score having an area under the curve of 0.84 (95% CI 0.81 to 0.87), and E-CABG having an area under the curve of 0.85 (95% CI 0.82 to 0.88). These two areas under the curve did not differ significantly (P = 0.25).

Percent Complex and Redo Procedures by Universal Definition of Perioperative Bleeding Class

	Class 0	Class 1	Class 2	Class 3	Class 4
Patients in Class (%)	30.28	16.66	29.36	19.22	4.48
Redo Procedures (%)	3.16	2.83	6.56	9.38	19.81
Complex Procedures (%)	17.92	18.36	32.7	42.33	62.2

Percent Complex and Redo Procedures by E-CABG Grade

	Grade 0	Grade 1	Grade 2	Grade 3
Patients in Grade (%)	56.06	31.6	11.24	1.1
Redo Procedures (%)	2.94	7.7	15.16	31.25
Complex Procedures (%)	18.31	38.07	53.86	73.75

Fig. 1. Redo and complex procedure proportions shown for each bleeding severity category. E-CABG, European Coronary Artery Bypass Graft.

Similar results were found in subsequent adjusted analyses. In the hierarchical logistic regression model that incorporated important confounders but not bleeding events or other complications (model 1), the area under the curve for predicting 28-day in-hospital mortality was 0.84. In model 2, Universal classes were added, and the area under the curve increased to 0.91. In model 3, the further addition of other important complications increased the area under the curve to 0.94. Adding E-CABG grade as a predictor to model 1 similarly increased the area under the curve to 0.92. Further addition of other important complications to the model with E-CABG grades increased the area under the curve to 0.94. In each of the models, bleeding severity regardless of the score used, whether assessed by the Universal score or E-CABG, demonstrated a statistically significant association with 28-day in-hospital mortality. The details of the models can be found in Supplemental Digital Content 1, http://links.lww.com/ALN/B671. Detailed model calibration results can be found in Supplemental Digital Content 2, http://links.lww.com/ALN/B672.

Discussion

This study compared the Universal definition of perioperative bleeding and E-CABG bleeding severity scores and attempted to provide evidence of construct, criterion, and content validity in a high-quality data set from a multicenter clinical trial of patients undergoing cardiac surgery. Our findings indicate that the Universal score and E-CABG are both valid and acceptable scoring systems for use as bleeding endpoints in cardiac surgery clinical trials.

The Universal definition of perioperative bleeding has been studied in various patient samples since its development. It was tested in an 1,144 patient single-institution adult European cardiac surgical database, where it was shown that increasing classes demonstrated an independent association with 30-day mortality.[9] The Universal score was further validated in an institutional cardiac surgery data set of 2,764 patients in Finland, where increasing classes were significantly associated with worse immediate and late outcomes.[19]

E-CABG has also been studied in a variety of patient samples. It was evaluated in a 7,491 patient sample drawn from

Patient Distribution and Death within Universal Definition of Perioperative Bleeding Classes

	Class 0 (n=2199)	Class 1 (n=1209)	Class 2 (n=2144)	Class 3 (n=1401)	Class 4 (n=328)
Percent Total Patients within Bleeding Grade (%)	30.2	16.6	29.45	19.24	4.5
Percent Death within Bleeding Class (%)	0.14	0.74	0.93	5.42	18.29

Patient Distribution and Death Rate Across E-CABG Bleeding Grades

	Grade 0 (n=4107)	Grade 1 (n=2330)	Grade 2 (n=830)	Grade 3 (n=80)
Percent Total Patients within Bleeding Grade (%)	55.9	31.71	11.3	1.09
Percent Death within Bleeding Grade (%)	0.41	1.5	13.86	28.75

Fig. 2. The distribution of patients across Universal definition of perioperative bleeding classes and European Coronary Artery Bypass Graft (E-CABG) classes. The proportion of patients with different severity categories is shown for each bleeding definition. The risk of death within each category is also shown.

Table 3. Unadjusted Odds Ratios Relating Measured Scores to 28-day Mortality

Universal Definition of Perioperative Bleeding Severity Score Unadjusted Odds Ratios			
Predictor	Odds Ratio	95% CI	P Value
UDPB grade			
Class 0	Reference		
Class 1	5.41	1.46–20.0	0.01
Class 2	6.15	1.81–20.90	0.004
Class 3	41.49	13.06–131.78	< 0.0001
Class 4	158.37	49.30–508.72	< 0.0001
AUC (95% CI): 0.84 (0.81, 0.87)			
E-CABG Bleeding Severity Score Unadjusted Odds Ratios			
Predictor	Odds Ratio	95% CI	P Value
E-CABG grade			
Grade 0	Reference		
Grade 1	3.62	1.95–6.74	< 0.0001
Grade 2	38.77	22.39–67.14	< 0.0001
Grade 3	106.45	52.03–217.80	< 0.0001
AUC (95% CI): 0.85 (0.82, 0.88)			

AUC, area under the curve; E-CABG, European Coronary Artery Bypass Graft; UDPB, Universal Definition of Perioperative Bleeding in Adult Cardiac Surgery.[9]

institutional databases at two hospitals in Italy. Increasing E-CABG severity grades were shown to be independently associated with higher in-hospital mortality and composite adverse events.[11] In a separate study drawn from 3,730 patients in a multicentre prospective registry encompassing 16 centers in six countries (England, Finland, France, Germany, Italy, and Sweden), six different bleeding scores were compared against each other, including E-CABG and the Universal definition of perioperative bleeding.[20] Both E-CABG and the Universal score showed good discriminative and predictive ability, with acceptable area-under-the-curve values for prediction of mortality, stroke, acute kidney injury, and sternal wound infection.[20]

Our study offers strong evidence supporting the use of either score in a clinical trial context. Despite both being useful, we also noted some key differences. Support for the Universal score and E-CABG measuring a similar construct was offered by the higher complex and redo procedures in higher bleeding grades. In terms of content validity, the Universal score captures a wider variety of clinical events associated with bleeding when assigning patients to a given category of bleeding severity. E-CABG

may better capture the adverse impact of higher transfusion needs because it scores almost exclusively transfusion volume. The Universal score also assesses transfusion volume but may better capture coagulopathy related to massive bleeding due to the scoring of recombinant activated factor VII administration, for example.[31] Thus, although the two scores have some overlap, each captures slightly different aspects relevant to major bleeding.

For both scores, it is important to note that patients undergoing surgery with a lower total hemoglobin mass to begin with are more likely to receive red cell transfusions than those with higher hemoglobin mass. Because the amount of red cell transfusions is a major component of both scores, investigators should control for patients' baseline hemoglobin mass if using these scores as endpoints. This also applies to the use of other product transfusions, such as platelets or factor replacement, which may be administered to correct preexisting deficiencies rather than in reaction to bleeding events.[9]

Despite E-CABG including fewer assessed domains than the Universal score, they both have evidence of construct and criterion validity. Interestingly, the scored domain of chest tube output does not appear to contribute significantly to the criterion validity of the Universal score, and any future revision to the Universal score may consider omitting this component. Although chest tube output has been associated with mortality in other studies, this has been in samples where patients receiving transfusion or having other significant clinical events such as reoperation associated with ongoing bleeding were not excluded.[2,32] In our study, chest tube output alone, without the presence of any other items indicative of bleeding, was not associated with increased mortality. Patients with chest tube output and other items indicating bleeding did have increased mortality, which is largely consistent with the existing literature.

The time frame for the scoring of the Universal definition of perioperative bleeding and E-CABG is notably different. E-CABG is scored based on data collected from the initial surgery throughout the entire hospital stay of the patient, whereas the assessment of the Universal score is limited to events that occur from surgery to the first perioperative day. Because E-CABG scores primarily transfusion volume, events during the hospital stay distant or unrelated to the original surgery that result in transfusion are captured and scored as bleeding, which may erroneously be associated with the original surgery. It is important to note this important distinction, which may impact on the construct validity of E-CABG.

Generally, during the conduct of a trial, the more complex the endpoints and the greater the volume of data collected, the higher the risk of incomplete data. Difficulty collecting data to assess either the Universal score or E-CABG was not a problem in the TACS study. Some investigators may prefer to use E-CABG based on the lower number of domains scored and lower burden of data collection. However, any

potential savings in data collection when using E-CABG as an outcome have to be weighed against the reduced number of potential bleeding events captured by E-CABG, particularly more severe bleeding. The probability of more severe bleeding score by the Universal score (class 3 or 4) was nearly double that of the E-CABG (grade 2 or 3) in our sample (23.75% by the Universal score *vs.* 12.39% by E-CABG). A greater proportion of patients are scored as having bleeding events, including more severe bleeding, when the Universal score is used. In addition, the distribution of patients across bleeding categories is more even with the Universal score.

Although we attempted to provide a thorough comparison of these two consensus-based scores, there are limitations to our work. In assessing criterion validity, our outcome was 28-day in-hospital all-cause mortality. This was the data we had available to us, but assessing all-cause mortality not limited to the hospital setting is important. Although limiting mortality to within 28-days allowed us to focus on the immediate perioperative period, certainly mortality beyond this time frame is important. For example, complications of severe bleeding events include acute kidney injury, which may have an impact on patient mortality beyond 28 days and would not have been captured in our data set.[33] Furthermore, in our multivariable logistic regression models examining the association of each bleeding score with mortality, we included as covariates variables that were identified as prognostically important in the literature. Our data set did not include important items scored by EuroSCORE II, a model used worldwide for the prediction of cardiac surgical risk.[34] This precluded us from including it as a covariate in our models.

The adoption of clinically sensible, consistent endpoints in cardiac surgery clinical trials evaluating bleeding has many advantages. In this study, we add to existing evidence supporting the use of these two consensus-based bleeding scores in cardiac surgery. Both the Universal definition of perioperative bleeding and E-CABG demonstrate evidence of criterion, construct, and content validity. However, the Universal score seems to capture more bleeding events and has a more uniform distribution of bleeding categories. This has implications for clinical trial sample size calculations and suggests that fewer patients may be required to demonstrate a difference between groups if the Universal score is used as an endpoint. The Universal score captures a variety of clinically important events related to bleeding beyond transfusion in the time period immediately related to surgery. E-CABG primarily captures transfusion volume over the entire length of hospital stay, which may not always be related to bleeding events associated with the original surgery. On the other hand, the individual components of E-CABG are easily collected from most hospital administrative databases and may represent significantly less burden of work for trial organizers needing to be efficient with their resources. The ongoing growth of clinical trials in cardiac surgery will benefit from the use of either scoring system in future clinical trials measuring bleeding as an outcome of interest.

Acknowledgments

Competing Interests

The authors declare no competing interests.

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References

1. Karkouti K, O'Farrell R, Yau TM, Beattie WS; Reducing Bleeding in Cardiac Surgery Research Group: Prediction of massive blood transfusion in cardiac surgery. Can J Anaesth 2006; 53:781–94

2. Colson PH, Gaudard P, Fellahi JL, Bertet H, Faucanie M, Amour J, Blanloeil Y, Lanquetot H, Ouattara A, Picot MC; ARCOTHOVA group: Active bleeding after cardiac surgery: A prospective observational multicenter study. PLoS One 2016; 11:e0162396

3. Schulman S, Angerås U, Bergqvist D, Eriksson B, Lassen MR, Fisher W; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis: Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. J Thromb Haemost 2010; 8:202–4

4. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, Serebruany V, Valgimigli M, Vranckx P, Taggart D, Sabik JF, Cutlip DE, Krucoff MW, Ohman EM, Steg PG, White H: Standardized bleeding definitions for cardiovascular clinical trials: A consensus report from the Bleeding Academic Research Consortium. Circulation 2011; 123:2736–47

5. Myles PS, Grocott MP, Boney O, Moonesinghe SR; COMPAC-StEP Group: Standardizing end points in perioperative trials: Towards a core and extended outcome set. Br J Anaesth 2016; 116:586–9

6. Prinsen CA, Vohra S, Rose MR, King-Jones S, Ishaque S, Bhaloo Z, Adams D, Terwee CB: Core Outcome Measures in Effectiveness Trials (COMET) initiative: Protocol for an international Delphi study to achieve consensus on how to select outcome measurement instruments for outcomes included in a "core outcome set." Trials 2014; 15:247

7. Koroshetz W: A core set of trial outcomes for every medical discipline? BMJ 2015; 350:h85

8. Williamson PR, Altman DG, Blazeby JM, Clarke M, Devane D, Gargon E, Tugwell P: Developing core outcome sets for clinical trials: Issues to consider. Trials 2012; 13:132

9. Dyke C, Aronson S, Dietrich W, Hofmann A, Karkouti K, Levi M, Murphy GJ, Sellke FW, Shore-Lesserson L, von Heymann C, Ranucci M: Universal definition of perioperative bleeding in adult cardiac surgery. J Thorac Cardiovasc Surg 2014; 147:1458–1463.e1

10. Biancari F, Ruggieri VG, Perrotti A, Svenarud P, Dalén M, Onorati F, Faggian G, Santarpino G, Maselli D, Dominici C, Nardella S, Musumeci F, Gherli R, Mariscalco G, Masala N, Rubino AS, Mignosa C, De Feo M, Della Corte A, Bancone C, Chocron S, Gatti G, Gherli T, Kinnunen EM, Juvonen T: European Multicenter Study on Coronary Artery Bypass Grafting (E-CABG registry): Study protocol for a prospective clinical registry and proposal of classification of postoperative complications. J Cardiothorac Surg 2015; 10:90

11. Mariscalco G, Gherli R, Ahmed AB, Zanobini M, Maselli D, Dalén M, Piffaretti G, Cappabianca G, Beghi C, Biancari F: Validation of the European Multicenter Study on Coronary Artery Bypass Grafting (E-CABG) bleeding severity definition. Ann Thorac Surg 2016; 101:1782–8

12. Higgins PG: Measuring nurses' accuracy of estimating blood loss. J Adv Nurs 1982; 7:157–62

13. Rothermel LD, Lipman JM: Estimation of blood loss is inaccurate and unreliable. Surgery 2016; 160:946–53

14. Vranckx P, Leonardi S, Tebaldi M, Biscaglia S, Parrinello G, Rao SV, Mehran R, Valgimigli M: Prospective validation of the Bleeding Academic Research Consortium classification in the all-comer PRODIGY trial. Eur Heart J 2014; 35:2524–9

15. Fleming TR, DeMets DL: Surrogate end points in clinical trials: Are we being misled? Ann Intern Med 1996; 125:605–13

16. Prentice RL: Surrogate endpoints in clinical trials: Definition and operational criteria. Stat Med 1989; 8:431–40

17. Karkouti K, Callum J, Wijeysundera DN, Rao V, Crowther M, Grocott HP, Pinto R, Scales DC; TACS Investigators: Point-of-care hemostatic testing in cardiac surgery: A stepped-wedge clustered randomized controlled trial. Circulation 2016; 134:1152–62

18. Ricci Z, Cruz DN, Ronco C: Classification and staging of acute kidney injury: Beyond the RIFLE and AKIN criteria. Nat Rev Nephrol 2011; 7:201–8

19. Kinnunen EM, Juvonen T, Airaksinen KE, Heikkinen J, Kettunen U, Mariscalco G, Biancari F: Clinical significance and determinants of the universal definition of perioperative bleeding classification in patients undergoing coronary artery bypass surgery. J Thorac Cardiovasc Surg 2014; 148:1640–1646.e2

20. Brascia D, Reichart D, Onorati F, Perrotti A, Ruggieri VG, Bounader K, Verhoye JP, Santarpino G, Fischlein T, Maselli D, Dominici C, Mariscalco G, Gherli R, Rubino AS, De Feo M, Bancone C, Gatti G, Santini F, Dalén M, Saccocci M, Faggian G, Tauriainen T, Kinnunen EM, Nicolini F, Gherli T, Rosato S, Biancari F: Validation of bleeding classifications in coronary artery bypass grafting. Am J Cardiol 2017; 119:727–33

21. Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, Lockowandt U: EuroSCORE II. Eur J Cardiothorac Surg 2012; 41:734–45

22. Ivanov J, Borger MA, Rao V, David TE: The Toronto Risk Score for adverse events following cardiac surgery. Can J Cardiol 2006; 22:221–7

23. Greiff G, Pleym H, Stenseth R, Berg KS, Wahba A, Videm V: Prediction of bleeding after cardiac surgery: Comparison

of model performances: A prospective observational study. J Cardiothorac Vasc Anesth 2015; 29:311–9

24. Dupuis JY, Wang F, Nathan H, Lam M, Grimes S, Bourke M: The cardiac anesthesia risk evaluation score: A clinically useful predictor of mortality and morbidity after cardiac surgery. ANESTHESIOLOGY 2001; 94:194–204

25. Aktuerk D, McNulty D, Ray D, Begaj I, Howell N, Freemantle N, Pagano D: National administrative data produces an accurate and stable risk prediction model for short-term and 1-year mortality following cardiac surgery. Int J Cardiol 2016; 203:196–203

26. Tran DT, Dupuis JY, Mesana T, Ruel M, Nathan HJ: Comparison of the EuroSCORE and Cardiac Anesthesia Risk Evaluation (CARE) score for risk-adjusted mortality analysis in cardiac surgery. Eur J Cardiothorac Surg 2012; 41:307–13

27. Rankin JS, He X, O'Brien SM, Jacobs JP, Welke KF, Filardo G, Shahian DM: The Society of Thoracic Surgeons risk model for operative mortality after multiple valve surgery. Ann Thorac Surg 2013; 95:1484–90

28. O'Brien SM, Shahian DM, Filardo G, Ferraris VA, Haan CK, Rich JB, Normand SL, DeLong ER, Shewan CM, Dokholyan RS, Peterson ED, Edwards FH, Anderson RP: The Society of Thoracic Surgeons 2008 cardiac surgery risk models: Part 2. Isolated valve surgery. Ann Thorac Surg 2009; 88:S23–42

29. Shahian DM, O'Brien SM, Filardo G, Ferraris VA, Haan CK, Rich JB, Normand SL, DeLong ER, Shewan CM, Dokholyan RS, Peterson ED, Edwards FH, Anderson RP: The Society of Thoracic Surgeons 2008 cardiac surgery risk models: Part 3. Valve plus coronary artery bypass grafting surgery. Ann Thorac Surg 2009; 88:S43–62

30. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16:31–41

31. Karkouti K, Beattie WS, Arellano R, Aye T, Bussieres JS, Callum JL, Cheng D, Heinrich L, Kent B, Lee TW, MacAdams C, Mazer CD, Muirhead B, Rochon AG, Rubens FD, Sawchuk C, Wang S, Waters T, Wong BI, Yau TM: Comprehensive Canadian review of the off-label use of recombinant activated factor VII in cardiac surgery. Circulation 2008; 118:331–8

32. Christensen MC, Dziewior F, Kempel A, von Heymann C: Increased chest tube drainage is independently associated with adverse outcome after cardiac surgery. J Cardiothorac Vasc Anesth 2012; 26:46–51

33. O'Connor ME, Hewson RW, Kirwan CJ, Ackland GL, Pearse RM, Prowle JR: Acute kidney injury and mortality 1 year after major non-cardiac surgery. Br J Surg 2017; 104:868–76

34. Noyez L, Kievit PC, van Swieten HA, de Boer MJ: Cardiac operative risk evaluation: The EuroSCORE II: Does it make a real difference? Neth Heart J 2012; 20:494–8

Appendix

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Early Resumption of β Blockers Is Associated with Decreased Atrial Fibrillation after Noncardiothoracic and Nonvascular Surgery

A Cohort Analysis

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ABSTRACT

Background: Beta (β) blockers reduce the risk of postoperative atrial fibrillation and should be restarted after surgery, but it remains unclear when best to resume β blockers postoperatively. The authors thus evaluated the relationship between timing of resumption of β blockers and atrial fibrillation in patients recovering from noncardiothoracic and nonvascular surgery.

Methods: The authors evaluated 8,201 adult β-blocker users with no previous history of atrial fibrillation who stayed at least two nights after noncardiothoracic and nonvascular surgery as a retrospective observational cohort. After propensity score matching on baseline and intraoperative variables, 1,924 patients who did resume β blockers by the end of postoperative day 1 were compared with 973 patients who had not resumed by that time on postoperative atrial fibrillation using logistic regression. A secondary matched analysis compared 3,198 patients who resumed β blockers on the day of surgery with 3,198 who resumed thereafter.

Results: Of propensity score–matched patients who resumed β blockers by end of postoperative day 1, 4.9% (94 of 1,924) developed atrial fibrillation, compared with 7.0% (68 of 973) of those who resumed thereafter (adjusted odds ratio, 0.69; 95% CI, 0.50–0.95; *P* = 0.026). Patients who resumed β blockers on day of surgery had an atrial fibrillation incidence of 4.9% *versus* 5.8% for those who started thereafter (odds ratio, 0.84; 95% CI, 0.67–1.04; *P* = 0.104).

Conclusions: Resuming β blockers in chronic users by the end of the first postoperative day may be associated with lower odds of in-hospital atrial fibrillation. However, there seems to be little advantage to restarting on the day of surgery itself. (ANESTHESIOLOGY 2018; 129:1101-10)

THE incidence of atrial fibrillation after noncardiac surgery ranges from 3 to 15%.[1–4] Patients who develop this arrhythmia after noncardiac surgery have longer and more costly hospital stays and greater mortality.[1] Furthermore, new clinically detected atrial fibrillation is an independent predictor of stroke in this population.[5] Modifiable factors that influence postoperative atrial fibrillation are thus of considerable interest.

Many patients having noncardiac surgery take long-term beta (β) blockers. A role for these medications as prophylaxis in the population at high risk for coronary artery disease and vascular disease has long been established.[6,7] Many people also take these drugs routinely for management of hypertension and as prophylaxis against arrhythmias. The Perioperative Ischemic Evaluation study showed that perioperative β blockade caused a reduction in new clinically detected atrial

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Editor's Perspective

What We Already Know about This Topic

- Use of beta (β) blockers in the perioperative period is associated with reduced incidence of postoperative atrial fibrillation
- In chronic β-blocker users, optimal timing for β-blocker resumption in the postoperative setting is unclear

What This Article Tells Us That Is New

- Resumption of postoperative β-blocker therapy by the end of postoperative day 1 is associated with reduced incidence of postoperative atrial fibrillation in general surgical patients (noncardiac, nonthoracic, nonvascular surgeries) when compared with patients who resumed β-blocker therapy after postoperative day 1
- There was not a significant difference in incidence of postoperative atrial fibrillation for those patients who postoperatively resumed β-blocker therapy on the day of surgery *versus* anytime thereafter

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fibrillation, myocardial infarctions, and referrals for cardiology care, but there was an increase in bradycardia, hypotension, strokes, and all-cause mortality.[5] The American Heart Association, in its revised guidelines for perioperative β blockade, recommends that β blockers should be continued after noncardiac surgery in patients who take the drugs chronically.[8]

Beta-blocker therapy initiated in the perioperative period reduces the risk of supraventricular arrhythmias in noncardiac surgery patients.[9] However, the benefit of this risk reduction is offset by potential intraoperative hypotension and a consequent increase in cerebrovascular events, acute kidney injury, myocardial injury, and mortality.[5,10] Restarting chronically used β blockers before discharge from the postanesthesia care unit increases cerebrovascular events.[2] In contrast, restart during the first two postoperative days reduces cerebrovascular and cardiovascular events and 30-day mortality.[2] Re-initiating β blockers after surgery may be delayed by potential drug interactions, *nil per os* status, an unstable hemodynamic profile, recent vasopressor use, or inadequate review of patients' home medication profiles. It thus remains unclear when it is best to restart β blockers to maximize benefit and minimize potential risks.

Little is known about the relationship between postoperative atrial fibrillation and when home β blockers should be restarted in patients recovering from noncardiac surgery. We therefore assessed whether resuming β blockers by the end of postoperative day 1 is associated with reduced odds of new-onset and paroxysmal atrial fibrillation in patients recovering from noncardiothoracic and nonvascular surgery. Secondarily, we assessed whether resuming β blockers on the day of surgery is associated with reduced odds of new-onset and paroxysmal atrial fibrillation.

Materials and Methods

With institutional review board approval and waiver of informed consent, data were obtained from the Cleveland Clinic Perioperative Health Documentation System for 8,201 adult β-blocker users who had noncardiac surgery, excluding thoracic and vascular surgery, from June 1, 2008 through January 31, 2016 and stayed at least two postoperative nights at the Cleveland Clinic's Main Campus (Cleveland, Ohio). Patients who had atrial fibrillation at admission or a history of atrial fibrillation were excluded. We further excluded patients in whom key data were missing. When patients had multiple surgeries meeting our inclusion and exclusion criteria, only the first surgery was included in our analysis. New-onset atrial fibrillation was diagnosed when patients were in sinus rhythm preoperatively (as determined by the most recent clinic visit or the day of surgery documentation of vital signs), and subsequently developed atrial fibrillation during their hospitalization. The onset of atrial fibrillation was determined *via* a manual chart review of available documentation of vital signs and physician notes.

Discontinuation of β blockers was defined as the complete cessation of β blockers during the perioperative period (before and day of surgery); *early resumption* was defined as restarting β blockers before the end of the first postoperative day, whereas *late resumption* was defined as restarting β blockers after the end of the first postoperative day including a complete failure to restart β blockers during hospitalization.

Patients categorized by β-blocker resumption day (postoperative day 0, postoperative day 1, postoperative day 2+) were compared on demographic, baseline, and intraoperative variables using Pearson chi-square analysis for categorical variables, one-way ANOVA for normally distributed continuous variables, and Kruskal–Wallis test for ordinal or nonnormal continuous variables.

Primary Analysis

We compared patients who did and did not restart β blockers by the end of the first postoperative day on the incidence of postoperative atrial fibrillation. We excluded 112 patients who experienced new-onset atrial fibrillation before the end of the first postoperative day to avoid immortal time bias; thus, only patients who were still at risk of developing postoperative atrial fibrillation at the end of postoperative day 1 were included.

To control for observed potential confounding variables, we matched each patient who restarted β blockers after the end of postoperative day 1 (late resumption) to a maximum of two patients who restarted by the end of postoperative day 1 (early resumption) using exact and propensity score matching.[11] Specifically, we first estimated the probability of restarting β blockers late (*i.e.*, propensity score) for each patient using logistic regression with late restart (*vs.* early restart) as the outcome and prespecified potential confounding variables listed in the table 1 as independent variables.

Our prespecified list of potential confounding variables includes age, sex, race, body mass index, congestive heart failure, valvular heart disease, hypertension, thyroid disease, coronary artery disease, diabetes, year and duration of surgery, percent of surgery time with mean arterial blood pressure less than 70 mmHg, estimated blood loss, amount of colloids, amount of crystalloids, erythrocyte transfusion, fresh frozen plasma transfusion, platelets transfusion, cryoprecipitate transfusion, and postoperative vasopressor use. Matching was then implemented through a greedy algorithm (SAS macro: gmatch), restricting successful matches to those with the same type of surgery (*i.e.*, first exact matching on type of surgery because it is so related to both exposure and outcome and thus such an important confounder) and those whose estimated propensity score logits (*i.e.*, estimated propensity score) were within 0.2 propensity score logit standard deviations of each other.[12–14] Surgery type was characterized into one of the 244 mutually exclusive clinically appropriate categories using the Agency for Healthcare Research and Quality's single-level Clinical Classifications Software

Table 1. Demographics Baseline and Intraoperative Characteristics (N = 8,201)

Variable	β-Blocker Resumption after Surgery			
	Postoperative Day 0 (N = 4,265)	Postoperative Day 1 (N = 2,932)	Postoperative Day 2+ (N = 1,004)	P Value†
Age, yr	65 ± 14	65 ± 13	64 ± 13	0.019‡
Gender (male)	55%	53%	42%	<0.001
Race				
Caucasian	80%	87%	86%	<0.001
African American	18%	12%	13%	
Others	2%	1%	2%	
Body mass index, kg/m^2	29 [25, 34]	30 [26, 35]	29 [25, 34]	<0.001‡
Congestive heart failure	18%	13%	13%	<0.001
Valvular heart disease	11%	10%	10%	0.413
Hypertension	66%	72%	69%	<0.001
Hypertension with complications	23%	17%	18%	<0.001
Thyroid disease	16%	17%	18%	0.077
Coronary artery disease	41%	35%	33%	<0.001
Diabetes type				
No diabetes	66%	71%	74%	<0.001
Type I diabetes	3%	2%	2%	
Type II diabetes	31%	28%	25%	
Type of surgery*				<0.001
Laminectomy	5%	7%	4%	
Arthroplasty knee	4%	7%	6%	
Hip replacement	4%	7%	6%	
Nephrectomy	4%	6%	5%	
Colorectal resection	4%	5%	7%	
Year of surgery				
2008	11%	15%	12%	<0.001
2009	13%	18%	19%	
2010	12%	14%	14%	
2011	15%	11%	11%	
2012	16%	11%	12%	
2013	12%	10%	9%	
2014	10%	10%	11%	
2015	11%	11%	11%	
2016	1%	1%	<1%	
Duration of surgery, hours	3.7 [2.6, 5.3]	4.1 [3.0, 5.8]	4.5 [3.2, 6.4]	<0.001§
% of surgery with mean arterial pressure <70 mmHg	9 [2, 21]	9 [2, 21]	12 [4, 25]	<0.001§
Estimated blood loss, cc	100 [50, 300]	200 [50, 400]	200 [71, 500]	<0.001§
Amount of colloids, cc	0 [0, 500]	500 [0, 500]	500 [0, 1000]	<0.001§
Amount of crystalloids, L	2.2 [1.3, 3.2]	2.6 [1.8, 3.6]	2.9 [2.0, 4.0]	<0.001§
Erythrocyte transfusion	16%	17%	24%	< 0.001
Fresh frozen plasma transfusion	3%	3%	8%	< 0.001
Platelets transfusion	3%	2%	6%	< 0.001
Cryoprecipitate transfusion	0%	0%	2%	< 0.001
Usage of vasopressor	65%	67%	73%	<0.001

Summary statistics are presented as % of patients, mean ± SD, or median [Q1, Q3], respectively.

*Only most frequent five categories are reported because of limited space.

†Pearson's chi-square test, unless specified.

‡one-way ANOVA.

§Kruskal–Wallis one-way ANOVA by ranks.

for International Classification of Diseases, 9th Revision, Clinical Modification procedure codes. We chose this fairly granular method of adjusting for type of surgery because surgical procedure has been shown to be a strong confounding variable in observational studies in perioperative medicine.[12]

Assessment of balance on the covariables used for the propensity score matching was performed using absolute standardized differences (*i.e.*, the absolute difference in means or proportions divided by the pooled SD). Imbalance was defined as a standardized difference greater than 0.10 in

absolute value; any such covariables were included in the models comparing early and late β-blocker patients on outcomes to reduce potential confounding.[13,14]

The matched groups were compared on postoperative atrial fibrillation using a multivariable logistic regression, adjusting for covariables that were still imbalanced after the matching.

In a sensitivity analysis, instead of using the propensity-matched groups, we included all available patients and used a multivariable model to adjust for confounding. We compared late (restart β blockers after the end of the first postoperative day) and early (restart β blockers by the end of the first postoperative day) restart times using all patients, and included potential confounding variables in the model *via* backward selection, with a significance criterion to leave the model of $P > 0.05$.

Secondary Analysis

In this analysis we changed the early restart period to before end of the day of surgery (instead of end of postoperative day 1 as in primary analysis). We thus compared postoperative atrial fibrillation between patients who did and did not restart β blockers on the day of surgery. In this analysis, 39 patients who experienced postoperative atrial fibrillation right after surgery on the same day were excluded because we wanted to include only the patients who were still at risk of developing postoperative atrial fibrillation at the end of the day of surgery. We one-to-one matched patients who did and did not restart β blockade on the same day of surgery using the same approach as the primary analysis. The matched groups were compared on postoperative atrial fibrillation using a multivariable logistic regression, adjusting for covariables that were still imbalanced after the matching.

We conducted additional sensitivity analyses further varying both the early and late restart periods and comparing groups on atrial fibrillation occurring after the early restart exposure period. For example, when comparing restart by end of postoperative day 0 with restart by end of postoperative day 2, the "outcome period" for both groups would start on postoperative day 1, just after the end of the early restart period. Groups were compared using multivariable logistic regression adjusting for all baseline confounding variables significant at the 0.30 level (0.30 to enter, 0.40 to stay) using stepwise selection. We varied the early restart period from by the end of postoperative day 0 to postoperative day 1, and the late restart period from on or after postoperative day 1 to postoperative day 4.

Sample size for the study was based on the algorithm in figure 1, using all patients during the given time frame of June 1, 2008, to January 31, 2016, who met all predetermined inclusion and exclusion criteria from the protocol. The beginning date for the study was chosen as the earliest data for which the exposure and outcome variables were reliably collected. With the attained data, we were able to estimate CIs for the associations of interest with acceptable precision.

All tests were two-sided, and statistical significance when assessing the associations of interest was claimed when $P < 0.05$. All statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., USA).

Results

From June 1, 2008 to January 1, 2016, a total of 8,201 adult β-blocker users who had noncardiothoracic and nonvascular surgery and stayed at least two nights after surgery at Cleveland Clinic main campus were included in our analysis (fig. 1 and table 1). Our patients were a mean of 65 (SD = 13) years old. The median duration of surgery was 4.0 (Q1, Q3: 2.8, 5.6) hours and median length of hospital stay after surgery was 6 (4, 8) days. Among these patients, 4,265 (52%) restarted β blockers on the day of surgery, 2,932 (36%) on postoperative day 1, 612 (7%) on postoperative day 2, 174 (2%) on postoperative day 3, 92 (1%) on postoperative day 4, and 126 (2%) after postoperative day 4, respectively. Four hundred eighty-four (484) patients experienced postoperative atrial fibrillation (5.9% of 8,201), where 39 (8% of 484) patients had postoperative atrial fibrillation on the same day of surgery, 73 (15%), 105 (22%), 83 (17%), 60 (12%), and 124 (26%) on postoperative day 1 to 4 and after postoperative day 4, respectively.

Among 8,089 patients who were still at risk of developing postoperative atrial fibrillation at the end of postoperative day 1, 7,095 had already restarted β blockers (early group) and 994 patients had not (late group). The incidence of postoperative atrial fibrillation was 4.2% for the early group and 7.1% for the late group. We successfully matched 973 patients (98% of 994) in the late group with 1,924 patients in the early group. Because of the results of matching the two groups were much better balanced on all the prespecified potential confounding variables, only percentage of surgery time with map < 70 mmHg was imbalanced after the matching (table 2, left panel and fig. 2). Within the subset of matched patients, 4.9% (94 of 1,924) retaking β blockers by the end of postoperative day 1 experienced postoperative atrial fibrillation, which was significantly lower than 7.0% (68 of 973) in those retaking after postoperative day 1, giving an odds ratio (early *vs.* Late) of 0.69 (95% CI, 0.50–0.95; $P = 0.026$). Sensitivity analyses provided consistent results (table 3, fig. 3).

Second, we successfully matched 3,198 patients who restarted β blockers on the day of surgery with 3,198 patients who restarted after the day of surgery (table 2, right panel). The incidence of postoperative atrial fibrillation was 4.9% for patients who restarted on the day of surgery and 5.8% for patients who did not, giving a nonsignificant odds ratio of 0.84 (95% CI, 0.67–1.04; $P = 0.107$; table 3, fig. 3).

Finally, when we varied the early and late restart periods in sensitivity analyses using multivariable regression to adjust for confounding (table 4, fig. 4), we found that early restart by the end of postoperative day 0 was not associated with atrial fibrillation, independent of whether the late period was

18,313 unique noncardiac, nonthoracic and nonvascular surgeries performed on 16,328 unique patients who were adult beta blocker users at Cleveland Clinic main campus (June 1, 2008 thru January 31, 2016)

Excluded
474 surgeries on 442 patients to address atrial fibrillation
895 surgeries on 766 patients who had atrial fibrillation prior to surgery
6,815 surgeries on 5,723 patients who stayed less than two postoperative days in the hospital
867 surgeries on 792 patients with beta blocker resumption date/time missing
413 surgeries on 404 patients with race and/or body mass index missing

8,849 surgeries on 8,201 patients met inclusion / exclusion criteria

8,201 patients were kept (first surgery per patient)

Primary analysis
(Early: POD 0 or 1) vs. later

Excluded 112 patients who had atrial fibrillation on same day of surgery (POD0) or on postoperative day one (POD1).

7,095 in the early restart group
994 in the late restart group

2 : 1 matched pairs
1,924 in the early restart group
973 in the late restart group

Secondary analysis
(Early: POD 0) vs. later

Excluded 39 patients who had atrial fibrillation on same day of surgery (POD 0).

4,241 in the early restart group
3,921 in the late restart group

1 : 1 matched pairs
3,198 in the early restart group
3,198 in the late restart group

Fig. 1. Study flow chart. POD, postoperative day.

defined as those restarting on or after postoperative day 1 ($P = 0.793$), postoperative day 2 ($P = 0.060$), postoperative day 3 ($P = 0.074$), or postoperative day 4 ($P = 0.452$). However, early restart by the end of postoperative day 1 was associated with lower odds of atrial fibrillation compared with late restart defined as on or after postoperative day 2 (odds ratio [95% CI] of 0.66 [0.49–0.87], $P = 0.004$) and postoperative day 3 (0.65 [0.43–0.98], $P = 0.039$), but not postoperative day 4 ($P = 0.436$). We note, though, that sample size was smaller at later restart times, which reduced power for detecting associations.

Discussion

The period immediately after surgery is a high-risk period for new-onset or recurrent atrial fibrillation. β blockers are widely used in patients at risk for perioperative myocardial events. They provide heart rate control and reduce sympathetic drive, thus improving myocardial oxygen supply–demand balance. A Cochrane analysis that included nearly 20,000 patients concluded that β blockers prevent supraventricular rhythms after cardiac surgery. However, their role in noncardiac surgery remains unclear because supraventricular arrhythmias are much less common and

Table 2. Demographics Baseline and Intraoperative Characteristics after Propensity Score Matching

Variable	Primary Analysis: Comparing Patients Who Retook β Blockers by the End of Postoperative Day 1 *Versus* After			Secondary Analysis: Comparing Patients Who Retook β Blockers on Day of Surgery *Versus* After		
	Postoperative Day 0, 1 (N = 1,924)	Postoperative Day 2+ (N = 973)	Absolute Standardized Difference†	Postoperative Day 0 (N = 3,198)	Postoperative Day 1+ (N = 3,198)	Absolute Standardized Difference†
Age	64 ± 14	64 ± 13	0.037	65 ± 13	65 ± 13	<0.01
Gender (male)	42%	42%	0.005	52%	52%	< 0.01
Race			0.010			0.030
Caucasian	86%	86%		84%	85%	
African American	12%	12%		15%	14%	
Others	1%	1%		1%	1%	
Body mass index, kg/m²	29 [25, 35]	29 [25, 35]	0.008	29 [25, 35]	29 [25, 35]	0.012
Congestive heart failure	12%	13%	0.026	15%	14%	0.005
Valvular heart disease	9%	10%	0.056	10%	11%	0.023
Hypertension	68%	69%	0.031	70%	69%	0.006
Hypertension with complications	20%	18%	0.046	19%	19%	0.009
Thyroid disease	18%	18%	0.006	17%	17%	0.010
Coronary artery disease	32%	33%	0.020	37%	37%	0.006
Diabetes type			0.055			0.005
No diabetes	74%	73%		70%	70%	
Type I diabetes	3%	2%		2%	2%	
Type II diabetes	24%	25%		28%	28%	
Type of surgery*			0.000			0.000
Laminectomy	5%	5%		7%	7%	
Arthroplasty knee	6%	6%		6%	6%	
Hip replacement	6%	6%		6%	6%	
Nephrectomy	6%	6%		6%	6%	
Colorectal resection	8%	8%		5%	5%	
Year of surgery			0.043			0.053
2008	11%	12%		12%	13%	
2009	17%	19%		14%	18%	
2010	13%	14%		12%	13%	
2011	13%	10%		14%	11%	
2012	14%	12%		15%	11%	
2013	10%	9%		12%	10%	
2014	10%	12%		10%	11%	
2015	11%	11%		10%	12%	
2016	1%	< 1%		1%	1%	
Duration of surgery, hours	4.3 [3.1, 6.1]	4.5 [3.2, 6.2]	0.071	4.0 [2.9, 5.5]	4.1 [3.0, 5.7]	0.063
% of surgery with mean arterial pressure <70 mmHg	9.7 [3.0, 23.4]	11.6 [4.2, 24.5]	0.109	8.1 [2.1, 20.3]	9.4 [2.7, 21.7]	0.076
Estimated blood loss, cc	200 [50, 450]	200 [50, 500]	0.038	150 [50, 350]	150 [50, 400]	0.041
Amount of colloids, mL	500 [0, 1000]	500 [0, 1000]	0.014	0 [0, 500]	0 [0, 500]	0.019
Amount of crystalloids, L	2.8 [1.8, 4.0]	2.85 [1.9, 4.0]	0.036	2.45 [1.6, 3.5]	2.5 [1.7, 3.5]	0.065
Erythrocyte transfusion	22%	22%	0.008	16%	18%	0.053
Fresh frozen plasma transfusion	4%	6%	0.081	3%	4%	0.030
Platelets transfusion	4%	5%	0.068	3%	3%	0.028
Cryoprecipitate transfusion	1%	1%	0.026	0%	< 1%	0.024
Usage of vasopressor	31%	28%	0.059	33%	32%	0.013

Summary statistics are presented as % of patients, mean ± SD, or median [Q1, Q3], respectively.

*Only most frequent five categories are reported because of limited space.

†Absolute standardized difference refers to the absolute difference in means or proportions divided by the pooled SD; any covariables with absolute standard difference ≥0.10 after the propensity score matching would be adjusted for in the analyses.

the presumed benefit is offset by potential hypotension and consequent risk of mortality and strokes.[1,9] Therefore, patients previously on home β blockers are often not restarted on this medication in a timely fashion, presumably because the balance between these competing interests remains unclear. Our results show that resuming chronically used β blockers before the end of postoperative day 1 significantly decreases the odds of postoperative

Absolute Standardized Difference
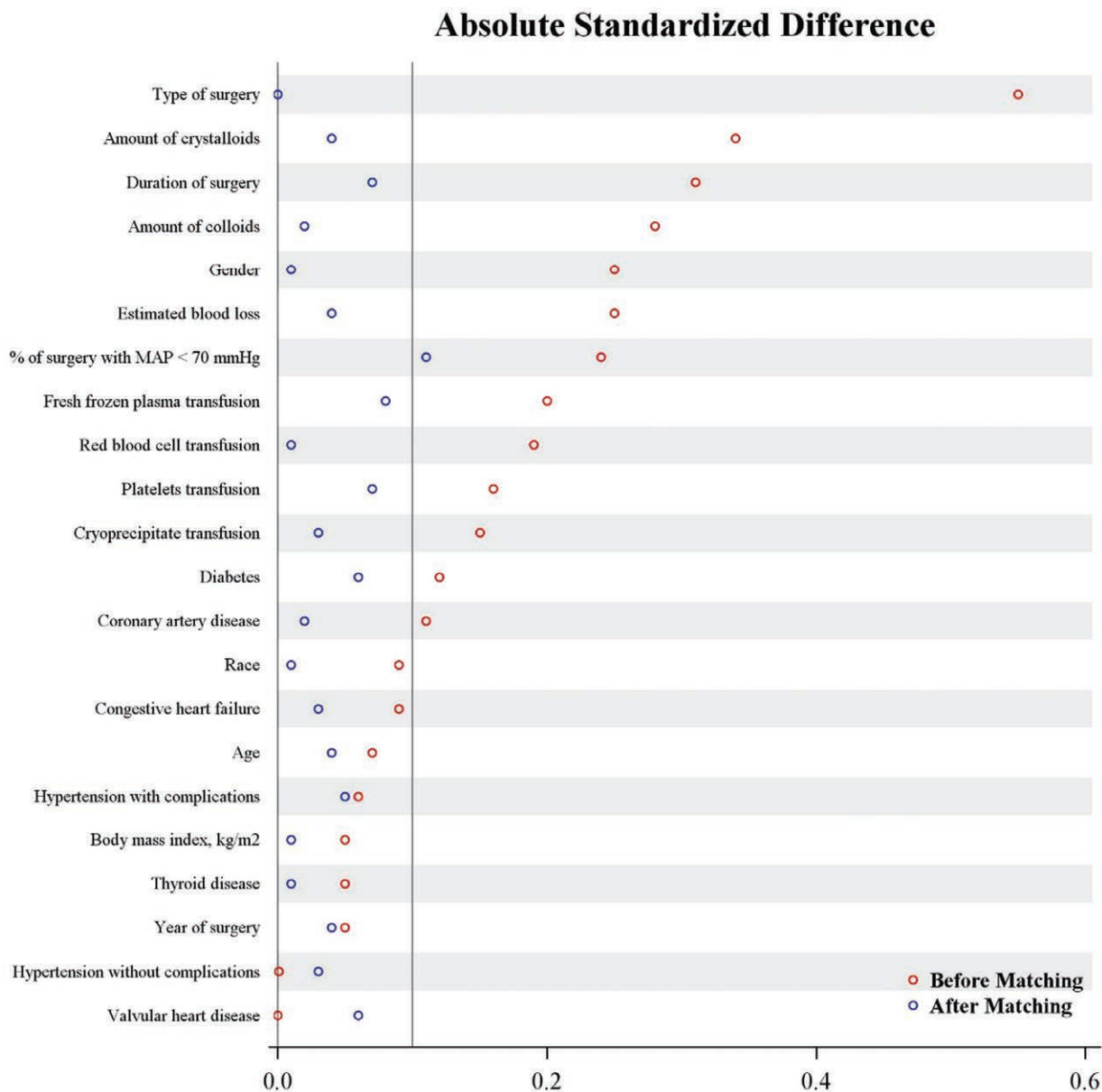
Fig. 2. Plot of absolute standardized difference of covariables used to estimate the propensity score before and after the propensity score matching. MAP, mean arterial pressure.

new-onset and paroxysmal atrial fibrillation after noncardiothoracic and nonvascular surgery.

Bhave *et al.*[1] reported an incidence of postoperative atrial fibrillation of 3% in a large cohort of patients after noncardiac surgery. In the final adjusted analysis, perioperative administration of statins, angiotensin receptor blockers, and angiotensin-converting enzyme inhibitors were associated with a lower risk, whereas β blockers appeared to not make a difference. Their results thus differed from ours, possibly because we clearly separated exposure (timing of β-blocker restart) and outcome (timing of postoperative atrial fibrillation). In contrast, some of the patients Bhave *et al.*[1] considered may have already developed atrial fibrillation before β blockers were restarted. Furthermore, Bhave *et al.*'s analysis

did not differentiate between β blockers that were newly started in the postoperative period or restarted after previous chronic use. Alonso-Coello *et al.*[15] did not find a significant association of metoprolol use in a model to predict atrial fibrillation after noncardiac surgery based on data from the Perioperative Ischemic Evaluation study.[15] However, whereas patients of the Perioperative Ischemic Evaluation study were randomized to receive extended-release metoprolol succinate or placebo starting 2 to 4 h before surgery, our analysis specifically aimed to see the association of postoperative initiation of β blockers and we did not include only a singular class of β blockers (*e.g.*, extended release metoprolol).

Administration of β blockers may reduce long-term mortality in noncardiac patients at a high risk for cardiac events,[16–18]

Table 3. Associations between Timing of β-Blocker Resumption and Postoperative Atrial Fibrillation

Compare Propensity Score–Matched Patients* (Number of Matched: Early *vs.* Late)	Incidence of POAF, Postoperative Atrial Fibrillation (Early *vs.* Late)	Odds Ratio (95% CI) (Early *vs.* Late)	*P* Value
Primary analysis: comparing patients who did and did not restart β blockers by end of POD1			
1-to-2 matching† (N = 1,924 *vs.* N = 973)	94 (4.9%) *vs.* 68 (7.0%)	0.69 (0.50, 0.95)	0.026
Sensitivity analysis			
All patients‡ (N = 7,095 *vs.* N = 994)	301 (4.2%) *vs.* 71 (7.1%)	0.66 (0.50, 0.88)	0.004
Secondary analysis: comparing patients who did and did not restart β blockers by end of POD0			
1-to-1 matching (N = 3,198 *vs.* N = 3,198)	156 (4.9%) *vs.* 185 (5.8%)	0.84 (0.67, 1.04)	0.107

Early indicates restarted β blockers by end of POD1 (primary analysis) or POD0 (secondary analysis). *Late* indicates did not restart β blockers by end of POD1 (primary analysis) or POD0 (secondary analysis).

*Exactly matched on type of surgery and propensity score–matched on all the other potential confounding variables listed in table 1. The matched subsets were compared on postoperative atrial fibrillation using multivariable logistic regression model.

†Adjusted for percent of surgery time with mean arterial pressure < 70 mmHg, which was imbalanced (*i.e.*, absolute standardized difference > 0.10) after the matching.

‡Adjusted for age, congestive heart failure, valvular heart disease, diabetes, coronary artery disease, fresh frozen plasma transfusion, amount of crystalloids, percent of surgery time with mean arterial pressure < 70 mmHg, and year and duration of surgery, which were retained in the multivariable logistic regression model *via* the backward model selection. One hundred twelve patients who had postoperative atrial fibrillation on day of surgery and postoperative day 1 were excluded from this analysis.

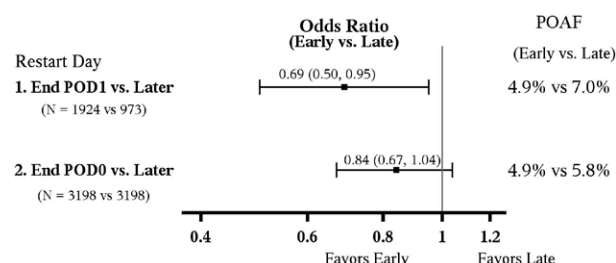POAF, postoperative atrial fibrillation; POD, postoperative day.

Fig. 3. Forest plot depicting the primary and secondary analysis using propensity score matching to compare the two different early restart groups with postoperative atrial fibrillation (POAF). POD, postoperative day.

and withdrawal of β-blocker therapy perioperatively may increase mortality for noncardiac surgery patients at all levels of cardiac risk.[17–19] In addition, noncardiac surgical patients on a chronic β-blocker regimen may be at lower risk for major postoperative cardiac events compared with patients who start taking β blockers within a few days of surgery.[20] Existing evidence thus suggests that although *initiating* perioperative β-blocker therapy harms noncardiac surgical patients, continuing or rapidly resuming β-blocker therapy after surgery is cardioprotective. Our results extend previous understanding by suggesting that resuming β blockers before the end of the first postoperative day is preferable to resuming later.

The Surgical Care Improvement Project originally defined continuation of therapy as extending from 24 h before incision to discharge from the postanesthesia care unit.[21] The 2012 revision extended continuation to include the first two postoperative days.[21] Continuation of β blockers before discharge from the postanesthesia care unit or on the day of surgery was associated with increased cerebrovascular events but not improved cardiovascular event outcomes. However, β-blocker resumption within two postoperative days was associated with reduced cerebrovascular and cardiovascular events, and also

30-day mortality.[2] Our findings are consistent with the reduction of cardiovascular events, however we did not report cerebrovascular events or mortality in our cohort.

In our secondary analysis, we compared patients who restarted β blockers before the end of the day of surgery (about half the patients) with those who started thereafter. It is important to note that the comparison group for this comparison (resumption after the day of surgery) differs from our primary analysis in which the comparison was with patients who restarted β blockers on the second postoperative day or thereafter. We did not find a significant difference in the incidence of postoperative new onset and paroxysmal atrial fibrillation at this comparison time point.

Several factors may explain the apparent lack of benefit from restarting β blockers on postoperative day 0. First, the outcome of interest (atrial fibrillation) is more common on postoperative days 1 and 2 (37% of our patients) *versus* on postoperative day 0 (just 8% of our patients). Second, some patients may have discontinued their β blockers on the day of surgery; it is likely that many used long-acting or sustained-release preparations, which would have provided continued protected on the day of surgery. These findings were further confirmed in our sensitivity analysis, where we varied the early and late restart periods using multivariable regression to adjust for confounding. Our interpretation is that restarting chronically used home β blockers by the end of the first postoperative day is protective compared with restarting thereafter. However, restarting these agents earlier (by the end of the day of surgery) does not seem to provide the same benefit.

The distinction between restarting on the day of surgery *versus* the first postoperative day is important. The immediate postoperative period is often associated with hypotension and bradycardia consequent to insufficient vascular volume, unrecognized bleeding, vasoplegia, residual

Table 4. Sensitivity Analyses Using Multivariable Models for Association between Early or Late Restart and Postoperative Atrial Fibrillation

Model	Early Period Restart	Late Period Restart	Early Restart % (no. events/total)	Late Restart % (no. events/total)	Odds Ratio (CI)	P Value
1	POD0	≥POD1	5.3% (226/4241)	5.6% (219/3921)	1.03 (0.84, 1.3)	0.793
2	POD0	≥POD2	5.3% (226/4241)	7.7% (77/1000)	0.76 (0.57, 1.01)	0.060
3	POD0	≥POD3	5.3% (226/4241)	9.0% (35/390)	0.69 (0.46, 1.04)	0.074
4	POD0	≥POD4	5.3% (226/4241)	7.8% (17/217)	0.81 (0.47, 1.4)	0.452
5*	POD0/1	≥POD2	4.2% (301/7095)	7.1% (71/994)	0.66 (0.49, 0.87)	0.004
6	POD0/1	≥POD3	4.2% (301/7095)	8.0% (31/386)	0.65 (0.43, 0.98)	0.039
7	POD0/1	≥POD4	4.2% (301/7095)	6.5% (14/214)	0.79 (0.44, 1.4)	0.436

Early Period Restart indicates patients restarted β blockers by end of given day (e.g., POD0/1: before end of POD1). *Late Period Restart* indicates patients restarted β blockers on or after the given day.

No. events/total in the Early Restart % and Late Restart % columns indicate the number of patients who developed atrial fibrillation after the restart period divided by number of patients who restarted beta-blockers during the given time period. The given percent is this ratio times 100.

*Model 5 is primary analysis definition of groups; here using multivariable model, not propensity score matching. Multivariable models adjusted for all baseline variables significant at $P < 0.30$ in stepwise regression.

POD, postoperative day.
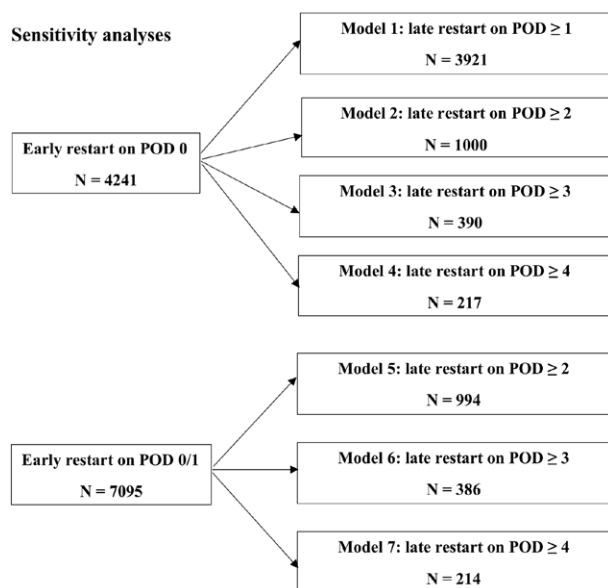
Fig. 4. Detailed flowchart on sample sizes for sensitivity analyses (corresponding to table 4). POD, postoperative day.

neuraxial anesthesia, and anesthetic-induced cardiac depression. Restarting β blockers on the day of surgery is thus more likely to potentially provoke hypotension and bradycardia than starting later. Our results suggest that restarting β blockers by the end of the first postoperative day prevents atrial fibrillation—and may potentially be safer compared with a restart by the end of postoperative day zero, especially in a population with preexisting hypotension and bradycardia.

Despite carefully matching for known potential confounding variables, there is an inherent risk of bias from unknown confounders. For example, it remains likely that patients who were sicker (for example, septic or hemodynamically unstable) were both more likely to develop atrial fibrillation and less likely to be given β blockers because of their unstable condition. Because we selected for patients who stayed at least two nights in the hospital, it could well be

that patients in this study were likely sicker and undergoing larger procedures than the overall surgical population in our cohort. An important trade-off for early β-blocker initiation may be increased cerebrovascular events and mortality with the probable benefit of an improvement in cardiovascular events. Our cohort did not include data for mortality, myocardial injury, or cerebrovascular events and was not powered for these rare outcomes. In addition, we did not see a benefit when β blockers were started before the end of postoperative day zero, and our interpretation of the potential for hypotension or bradycardia remains speculative in the absence of data in this dataset. Furthermore, our results have limits on generalizability because we excluded both thoracic and vascular surgery, two of the highest-risk populations, even though the practice at our institution is to re-initiate β blockers at the earliest in these patients. An additional limitation is that we did not distinguish among types of β blockers used, nor do we know exactly when β blockers were stopped preoperatively. To the extent that patients took extended-release or long-acting preparations and stopped the morning of surgery, they would continue to be β blocked for a day or so. However, knowing that generic metoprolol is the most common β blocker used in our hospital, our results were reliable for this common β blocker. We also could not account for some other drugs (amiodarone, calcium channel blockers, statins, angiotensin-converting enzyme inhibitors) that have been shown to be protective against perioperative atrial fibrillation. Finally, we could not evaluate the duration of chronic β-blocker use, which is of interest in terms of upregulation of β receptors.

In conclusion, resuming administration of chronically used β blockers before the end of postoperative day 1 significantly decreased the odds of postoperative atrial fibrillation in patients recovering from noncardiothoracic and nonvascular surgery. Restarting on the day of surgery appears to offer little advantage and may increase the risk of hypotension and bradycardia, especially in a high-risk population.

Research Support

Competing Interests

Correspondence

Address correspondence to Dr. Khanna: Center for Critical Care, Anesthesiology Institute, Cleveland, Clinic, 9500 Euclid Avenue, G-58, Cleveland, Ohio 44195. ashish@or.org. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

References

1. Bhave PD, Goldman LE, Vittinghoff E, Maselli J, Auerbach A: Incidence, predictors, and outcomes associated with postoperative atrial fibrillation after major noncardiac surgery. Am Heart J 2012; 164:918–24

2. Richman JS, Itani KM, Deierhoi RJ, Henderson WG, Hawn MT: Improved outcomes associated with a revised quality measure for continuing perioperative β-blockade. JAMA Surg 2014; 149:1031–7

3. Kanji S, Williamson DR, Yaghchi BM, Albert M, McIntyre L; Canadian Critical Care Trials Group: Epidemiology and management of atrial fibrillation in medical and noncardiac surgical adult intensive care unit patients. J Crit Care 2012; 27:326. e1–8

4. Makrygiannis SS, Margariti A, Rizikou D, Lampakis M, Vangelis S, Ampartzidou OS, Katsifa K, Tselioti P, Foussas SG, Prekates AA: Incidence and predictors of new-onset atrial fibrillation in noncardiac intensive care unit patients. J Crit Care 2014; 29:697.e1–5

5. Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, Xavier D, Chrolavicius S, Greenspan L, Pogue J, Pais P, Liu L, Xu S, Malaga G, Avezum A, Chan M, Montori VM, Jacka M, Choi P: Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): A randomised controlled trial. Lancet 2008; 371: 1839–47

6. Mangano DT, Layug EL, Wallace A, Tateo I: Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. Multicenter Study of Perioperative Ischemia Research Group. N Engl J Med 1996; 335:1713–20

7. Poldermans D, Boersma E, Bax JJ, Thomson IR, van de Ven LL, Blankensteijn JD, Baars HF, Yo TI, Trocino G, Vigna C, Roelandt JR, van Urk H: The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. N Engl J Med 1999; 341:1789–94

8. Wijeysundera DN, Duncan D, Nkonde-Price C, Virani SS, Washam JB, Fleischmann KE, Fleisher LA; ACC/AHA Task Force Members: Perioperative beta blockade in noncardiac surgery: A systematic review for the 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014; 130:2246–64

9. Blessberger H, Kammler J, Domanovits H, Schlager O, Wildner B, Azar D, Schillinger M, Wiesbauer F, Steinwender C: Perioperative β blockers for preventing surgery-related mortality and morbidity. Cochrane Database Syst Rev 2014: CD004476

10. Mascha EJ, Yang D, Weiss S, Sessler DI: Intraoperative mean arterial pressure variability and 30-day mortality in patients having noncardiac surgery. ANESTHESIOLOGY 2015; 123:79–91

11. Rassen JA, Shelat AA, Myers J, Glynn RJ, Rothman KJ, Schneeweiss S: One-to-many propensity score matching in cohort studies. Pharmacoepidemiol Drug Saf 2012; 21 Suppl 2:69–80

12. Komatsu R, You J, Rajan S, Kasuya Y, Sessler DI, Turan A: Steroid administration after anaesthetic induction with etomidate does not reduce in-hospital mortality or cardiovascular morbidity after non-cardiac surgery. Br J Anaesth 2018; 120:501–8

13. Austin PC: Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med 2009; 28:3083–107

14. Austin PC: An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res 2011; 46:399–424

15. Alonso-Coello P, Cook D, Xu SC, Sigamani A, Berwanger O, Sivakumaran S, Yang H, Xavier D, Martinez LX, Ibarra P, Rao-Melacini P, Pogue J, Zarnke K, Paniagua P, Ostrander J, Yusuf S, Devereaux PJ; POISE Investigators: Predictors, prognosis, and management of new clinically important atrial fibrillation after noncardiac surgery: A prospective cohort study. Anesth Analg 2017; 125:162–9

16. Friedell ML, Van Way CW 3rd, Freyberg RW, Almenoff PL: β-blockade and operative mortality in noncardiac surgery: Harmful or helpful? JAMA Surg 2015; 150:658–63

17. Wallace AW, Au S, Cason BA: Association of the pattern of use of perioperative β-blockade and postoperative mortality. ANESTHESIOLOGY 2010; 113:794–805

18. London MJ, Hur K, Schwartz GG, Henderson WG: Association of perioperative β-blockade with mortality and cardiovascular morbidity following major noncardiac surgery. JAMA 2013; 309:1704–13

19. Hoeks SE, Scholte Op Reimer WJ, van Urk H, Jörning PJ, Boersma E, Simoons ML, Bax JJ, Poldermans D: Increase of 1-year mortality after perioperative β blocker withdrawal in endovascular and vascular surgery patients. Eur J Vasc Endovasc Surg 2007; 33:13–9

20. Ellenberger C, Tait G, Beattie WS: Chronic β blockade is associated with a better outcome after elective noncardiac surgery than acute β blockade: A single-center propensity-matched cohort study. ANESTHESIOLOGY 2011; 114:817–23

21. Doufas AG, Tian L, Davies MF, Warby SC: Nocturnal intermittent hypoxia is independently associated with pain in subjects suffering from sleep-disordered breathing. ANESTHESIOLOGY 2013; 119:1149–62

Prediction Score for Postoperative Neurologic Complications after Brain Tumor Craniotomy

A Multicenter Observational Study

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ABSTRACT

Background: Craniotomy for brain tumor displays significant morbidity and mortality, and no score is available to discriminate high-risk patients. Our objective was to validate a prediction score for postoperative neurosurgical complications in this setting.

Methods: Creation of a score in a learning cohort from a prospective specific database of 1,094 patients undergoing elective brain tumor craniotomy in one center from 2008 to 2012. The validation cohort was validated in a prospective multicenter independent cohort of 830 patients from 2013 to 2015 in six university hospitals in France. The primary outcome variable was postoperative neurologic complications requiring in–intensive care unit management (intracranial hypertension, intracranial bleeding, status epilepticus, respiratory failure, impaired consciousness, unexpected motor deficit). The least absolute shrinkage and selection operator method was used for potential risk factor selection with logistic regression.

Results: Severe complications occurred in 125 (11.4%) and 90 (10.8%) patients in the learning and validation cohorts, respectively. The independent risk factors for severe complications were related to the patient (Glasgow Coma Score before surgery at or below 14, history of brain tumor surgery), tumor characteristics (greatest diameter, cerebral midline shift at least 3 mm), and perioperative management (transfusion of blood products, maximum and minimal systolic arterial pressure, duration of surgery). The positive predictive value of the score at or below 3% was 12.1%, and the negative predictive value was 100% in the learning cohort. In–intensive care unit mortality was observed in eight (0.7%) and six (0.7%) patients in the learning and validation cohorts, respectively.

Conclusions: The validation of prediction scores is the first step toward on-demand intensive care unit admission. Further research is needed to improve the score's performance before routine use. (ANESTHESIOLOGY 2018; 129:1111-20)

NEUROSURGERY remains the cornerstone of curative treatment in brain tumor but is associated with high perioperative morbidity and mortality.[1] The risk of perioperative mortality is more than twofold compared with the average mortality risk when adjusted to a patient's baseline severity.[1] This can be explained by the life-threatening complications that may occur during the perioperative period: intracranial bleeding, intracranial hypertension, and status epilepticus, among others.[2–5] It has therefore been suggested that overnight postoperative monitoring in an intensive care unit (ICU) be mandatory for all patients undergoing elective craniotomy.[2,3,6] However, systematic ICU admission uses medical resources, increases costs, reduces the number

Editor's Perspective

What We Already Know about This Topic

- The authors developed a score for predicting the risk of postoperative complications

What This Article Tells Us That Is New

- The score was developed from 1,094 patients and validated in 830 patients from six French hospitals
- Severe complications occurred in about 11% of each cohort
- The positive predictive value was poor, but the negative prediction value was excellent and might be used to identify patients who do not need critical care

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This article is featured in "This Month in Anesthesiology," page 1A. 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). Part of the work presented in this article has been presented at the National Congress of the French Society of Anesthesiology and Critical Care (SFAR) meeting in Paris, France, September 23 to 24, 2016.

of ICU beds for emergencies, and is not associated with improved postoperative outcome.[7] Although some risk factors have been identified,[8,9] no validated prediction score exists to differentiate patients with high perioperative risk of complications from those who do not require ICU admission. From a medicoeconomic point of view, the use of such scores could help reduce healthcare costs by providing adequate care to high-risk patients only.

Our primary objective was to develop and validate a score that could help physicians decide which patients require overnight ICU admission after elective intracranial neurosurgery to avoid the unnecessary admission of low-risk patients. The secondary objectives of the study were to assess perioperative morbidity and mortality in patients undergoing elective brain tumor craniotomy.

Materials and Methods

This was a multicenter observational study (ClinicalTrials. gov identifier NCT 01801813). The protocol was approved by the Institutional Review Board (Groupe d'Ethique dans le Domaine de la Santé) of the University Hospital of Nantes (Nantes, France). The learning cohort comprised patients undergoing craniotomy for a brain tumor in one center (Nantes) from January 1, 2008, to December 31, 2012. This cohort was developed from a retrospective analysis by screening two prospective databases: Clinicom (Siemens, Germany) for clinical and biologic data (radiologic findings, tumor histology, or other demographic variables) and Pégase (Thélème, France) for perioperative data (such as during surgery, during ICU stay). The data provided in the software enabled us to gather data on primary outcome, baseline demographics, tumor, and perioperative management. We therefore avoided

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*Members of the Société Française d'Anesthésie-Réanimation (SFAR) Research Network are listed in the appendix.

selection bias and included all patients who were operated for brain tumor according to histology. For the validation cohort, a prospective analysis was performed in patients undergoing cerebral craniotomy for brain tumor from January 1, 2013, to December 1, 2015, in six French university hospitals (the University Hospitals of Beaujon, Clichy, Assistance Publique des Hôpitaux de Paris; La Timone, Assistance Publique des Hôpitaux de Marseille; Nantes; Rennes; Strasbourg; and Toulouse). Because our study was purely observational, consent was waived. Oral and written information was provided to patients in the validation cohort. Our Institutional Review Board waived the requirement to provide information for the retrospective analysis. The study was prepared in accordance with transparent reporting of a multivariable prediction model for individual prognosis or diagnosis guidelines.

Inclusion Criteria
Adult patients (older than 18 yr) undergoing elective neurosurgery with craniotomy for a brain tumor confirmed after histologic analysis were eligible for this study.

Noninclusion Criteria
Patients with stereotactic biopsy for brain tumor were not included. Patients undergoing craniotomy for simple biopsy, aneurysm clipping, arteriovenous malformation, cerebral cavernoma, or central nervous system infections and urgent craniotomy were not eligible for this study.

Data Collection
We collected demographic data such as age, sex, American Society of Anesthesiologists class, history of epilepsy, use of preoperative medications such as antiepileptic drugs, β-blockers, previous history of brain tumor surgery,[10] tumor histology, location and intracerebral radiologic severity criteria such as mass effect on median structures, peritumoral edema, size of the tumor,[11] perioperative management such as duration of anesthesia, duration of surgery,[12] surgical position,[13] operative administration of mannitol, fluid administration, blood loss, and highest and lowest arterial blood pressures.[8] Postoperative data such as extubation time, use of mechanical ventilation, intracranial hypertension, intracranial bleeding, urgent neurosurgery, and seizures were recorded. The list of data recorded during the study is provided in Supplemental Digital Content 1 (http://links.lww.com/ALN/B775).

Primary Objective
The primary objective was to develop and validate a score that could predict early severe postoperative neurosurgical complications in the first 24 h in the ICU after elective brain tumor neurosurgery to improve ICU triage and safely discharge patients to wards.

Definition of the Primary Outcome
To define the primary outcome variable, we developed a list of complications that could lead to severe postoperative

neurosurgical complications that require at least 24h of ICU monitoring[14]: moderate to severe intracerebral bleeding confirmed on brain computed tomography scan possibly requiring neurosurgical evacuation, intracranial hypertension confirmed on brain computed tomography scan or with intracranial probe or external ventricular drainage (defined as intracranial pressure at or above 20 mmHg), status epilepticus or seizures (clinical or confirmed by electroencephalogram), need for tracheal intubation and mechanical ventilation after the neurosurgical procedure, impaired consciousness (Glasgow Coma Score at or below 13), unmanageable agitation requiring restraint or sedation, severe swallowing disorders leading to aspiration and respiratory failure (oxygen saturation measured by pulse oximetry at or below 90% or requiring oxygen therapy), unexpected severe motor deficit (motor score at or above 3), and finally death in the perioperative period. In case of minor postoperative intracranial bleeding on brain computed tomography scan but without significant symptoms, a patient could be discharged from the ICU depending on each center's protocol.

The aim of this study was to develop and validate a score specific for neurologic complications. Patients with postoperative complications unrelated to the neurosurgical procedure were therefore not considered for the primary outcome variable (*e.g.*, allergy, iatrogenic complications such as pneumothorax after central venous catheter insertion, pacemaker dysfunction).

Secondary Objectives

The secondary objectives of our study were the description of perioperative management and perioperative morbidity and mortality.

Secondary Outcomes

Perioperative patient morbidity was defined as follows: patient readmission to the ICU during hospitalization and length of hospital stay. We also recorded in-ICU and in-hospital mortality.

Statistical Analysis

Continuous variables were expressed as median (interquartile range) for nonparametric data or mean ± SD for parametric data. Qualitative variables were expressed as N (%).

To construct the risk model for primary outcome, the least absolute shrinkage and selection operator was used for potential risk-factor selection with logistic regression. Conventional selection methods based on P values failed to obtain an adequate multivariable model. Indeed, the number of events in our population was small compared with the number of risk factors tested (125 early postoperative neurosurgical complications and 35 potential risk factors). With the least absolute shrinkage and selection operator method,[15] the usual P < 0.05 is not considered for variable selection. This method penalizes the sum of the absolute values of the regression coefficients leading some coefficients to shrink to 0 and thus simultaneously perform variable selection.[15] The shrinkage

parameter, called λ, is generally selected through the cross-validation method. This method was first performed on the learning cohort and resulted in the selection of 26 potential risk factors. Then, to reduce the number of risk factors, the optimal λ was determined using graphical consideration with an area under the receiver operating characteristic curve of 73% and eight nonzero coefficients in the model.

To validate this predictive model, (1) apparent performance was estimated in the learning cohort and (2) reproducibility was estimated in the validation cohort. Discrimination was evaluated using the area under the receiver operating characteristic curve and its 95% CI, and calibration was assessed using the Hosmer–Lemeshow test. The Brier score was calculated to measure the accuracy of probabilistic predictions. The Brier score provides the probability of a model (*i.e.*, the CranioScore) to predict the occurrence of an outcome (*i.e.*, postoperative complications). The value of the Brier score is between 0 and 1; the closer to 0 the Brier score, the better the model to predict the outcome. Finally, the CranioScore score was constructed with the regression coefficients identified in the multivariable model. We calculated the predicted probabilities of complications based on this score. We classified high-risk or low-risk postoperative complications according to various CranioScore thresholds. The aim of our score is to improve ICU triage and safely discharge patients to wards. This strategy implies favoring a score with the best negative predictive values to avoid false negatives. We therefore tested various CranioScore values in the learning cohort and chose which threshold was the best to discriminate patients with high or low risk of postoperative complications that require overnight ICU monitoring.

The discriminative ability of this dichotomy (sensitivity, specificity, positive predictive value, and negative predictive value) was estimated in both cohorts. We retained the threshold with the best negative predictive value and which could be helpful in the ICU triage process.

An *a priori* sample size calculation was not conducted, and all available data were used to include a minimum of 100 events.[16] We therefore decided to include at least 100 patients with postoperative complications in the learning cohort to obtain an adequate sample size. Regarding the validation cohort, we included a cohort with at least a 40% of the size of the learning cohort to provide robust external validity.[16,17]

All analyses were performed on complete cases. Model selection with the least absolute shrinkage and selection operator method was performed using the penalized package in R, and SAS statistical software version 9.3 (SAS Institute, USA) was used for other analyses.

Results

Description of the Learning Cohort

We included 1,094 patients in the first cohort from January 1, 2008, to December 31, 2012. A flowchart of the learning

cohort is available in Supplemental Digital Content 2 (http://links.lww.com/ALN/B776). Mean age was 57 yr (±15), and the sex ratio of male:female was 521(47.6%):573(52.4%). Demographics and comorbidities for both cohorts are presented in table 1. Brain tumors were meningioma in 355 (32.4%) patients, glioma-glioblastoma in 252 (23%) patients, and metastasis in 238 (21.8%) patients (table 2). Intraoperative data in the learning and validation cohorts are available in table 3. Respectively, 125 (11.4%) patients presented early postoperative neurosurgical complications in the learning cohort, and 114 (16.6%) patients presented complications in the validation cohort, in accordance with the primary outcome variable. Complications are provided in Supplemental Digital Content 3 (http://links.lww.com/ALN/B777).

Multivariable Analysis: Independent Risk Factors for Neurologic Life-threatening Complications

To adequately select the variables associated with early postoperative complications, a least absolute shrinkage and selection operator procedure was performed (Supplemental Digital Content 4, http://links.lww.com/ALN/B778), and eight factors were selected for the multivariable model. The optimal λ (shrinkage parameter) was graphically determined so that the number of risk factors was the lowest (considering the number of events) and the highest area under the receiver operating characteristic curve criterion. These factors were used to develop the score (table 4): Glasgow Coma Score before surgery at or below 14 (odds ratio [OR], 4.55; 95% CI, 1.88 to 11.03; P = 0.0008), history of brain tumor surgery (OR, 2.87; 95% CI, 1.74 to 4.72; P < 0.0001), greatest brain tumor diameter (mm; OR, 1.01; 95% CI, 1.00 to 1.02; P = 0.1), midline shift at or above 3 mm[11] (OR, 1.67; 95% CI, 1.04 to 2.69; P = 0.03), transfusion of packed erythrocytes or plasma or platelets (OR, 1.69; 95% CI, 1.01 to 2.83; P = 0.04), maximum systolic arterial pressure during surgery (mmHg; OR, 1.01; 95% CI, 1.01 to 1.02; P = 0.0002), minimal systolic arterial pressure (mmHg) during surgery (OR, 0.99; 95% CI, 0.97 to 1.00; P = 0.08), and duration of surgery (OR, 1.37; 95% CI, 1.19 to 1.58; P < 0.0001). There were no missing data for all patients included in the learning cohort (N = 1,094). The model showed an area under the receiver operating characteristic curve of 0.73 IC$_{95\%}$ (0.68 to 0.77), Hosmer–Lemeshow test, P = 0.2 (fig. 1).

External Validation of the Score in an Independent Cohort

We tested the robustness of our model in an independent multicenter (six ICUs) prospective cohort of 830 patients undergoing scheduled neurosurgery included from January 1, 2013, to December 31, 2015, in six centers. A flowchart

Table 1. Demographic Data of Patients Undergoing Elective Craniotomy for a Brain Tumor in the Learning and External Validation Cohorts

Parameter	Learning Cohort (N = 1,094)		Validation Cohort (N = 830)		P Value
	N Missing	N (%) or Mean ± SD	N Missing	N (%) or Mean ± SD	
Age, yr	0	57 (±15)	0	56 (±15)	0.7
Male/female	0	521 (47.6)/573 (52.4)	0	395 (47.6)/435 (52.4)	0.9
ASA class	0		1		0.7
I–II		817 (74.7)		624 (75.3)	
III–IV		277 (25.3)		205 (24.7)	
Score NYHA	1		22		0.03
I–II		1,080 (98.7)		787 (97.4)	
III–IV		14 (1.3)		21 (2.6)	
GCS ≤ 14 before procedure	0	25 (2.3)	3	35 (4.2)	0.02
Preoperative motor deficit	0	220 (20.1)	1	193 (23.3)	0.09
Aphasia	0	153 (14)	7	126 (15.3)	0.4
Deglutition disorders	0	15 (1.4)	1	18 (2.2)	0.1
History of craniotomy for brain tumor	0	158 (14.4)	0	133 (16)	0.3
History of epilepsy	0	315 (28.8)	3	244 (29.5)	0.7
Chronic hypertension	0	306 (28)	0	268 (32.3)	0.04
Diabetes mellitus	0	58 (5.3)	5	56 (6.8)	0.1
Preoperative medication					
Antiepileptic drugs	0	472 (43.1)	0	491 (59.2)	< 0.001
Outcome					
In-ICU mortality	0	8 (0.7)	0	6 (0.7)	
Second ICU admission after neurosurgery	0	15 (1.4)	0	27 (3.2)	
In-hospital mortality	0	16 (1.5)	6	9 (1.1)	
Hospital length of stay, days	0	13 (±13)	3	12 (±13)	

Continuous data are expressed as means (± SD) and nominal data as N (%). The parameters regarding outcome were not included in the least absolute shrinkage and selection operator procedure.
ASA, American Society of Anesthesiologists; GCS, Glasgow Coma Score; ICU, intensive care unit; NYHA, New York Heart Association.

Table 2. Histologic and Radiologic Data of Tumors in the Learning and External Validation Cohorts

Parameter	Learning Cohort (N = 1,094)		Validation Cohort (N = 830)		P Value
	N Missing	N (%) or Mean ± SD	N Missing	N (%) or Mean ± SD	
Tumor histology	0		3		
Meningioma		355 (32.4)		260 (31.4)	0.1
Glioma-glioblastoma		252 (23)		229 (27.7)	
Metastasis		238 (21.8)		167 (20.2)	
Other		249 (22.8)		171 (20.7)	
Tumor location					
Frontal lobe	0	492 (45)	3	375 (45.3)	0.8
Parietal lobe	0	202 (18.5)	3	181 (21.9)	0.06
Temporal lobe	0	252 (23)	5	191 (23.1)	0.9
Occipital lobe	0	81 (7.4)	4	68 (8.2)	0.5
Infratentorial	0	202 (18.5)	3	128 (15.5)	0.09
Radiologic severity data (MRI/CT scan)					
Midline shift ≥ 3mm	0	391 (35.7)	11	186 (22.7)	< 0.001
Mass effect	0	816 (74.6)	9	441 (53.7)	< 0.001
Midline location	0	193 (17.6)	12	81 (9.9)	< 0.001
Hydrocephalus	0	82 (7.5)	11	49 (6)	0.1
Peritumoral edema	0	663 (60.6)	9	447 (54.5)	0.01
Compression of the fourth ventricle	0	124 (11.3)	10	46 (5.6)	< 0.001
Greater size, mm	0	40 (±17)	48	40 (±17)	0.8

Continuous data are expressed as means (± SD) and nominal data as N (%).

CT, computed tomography; MRI, magnetic resonance imaging.

of the validation cohort is available in Supplemental Digital Content 2 (http://links.lww.com/ALN/B776). Ninety (10.8%) patients presented early postoperative neurologic complications. Demographics, the type of brain tumor, and perioperative data in this cohort are available in tables 1–3, respectively. The score was applied in 748 patients (82 patients had missing data for at least one of the selected variables). The area under the receiver operating characteristic curve of the score in this cohort was 0.70 $IC_{95\%}$ (0.64 to 0.76), and the Hosmer–Lemeshow test *P* value was 0.1 (fig. 1). The Brier score in this cohort was 0.13.

Definition and Usefulness of a Predictive Score for Complications

The robustness of the multivariable analysis prompted us to validate a score with the selected risk factors. The CranioScore based on these factors (table 4) provides a calculated probability of postoperative neurosurgical complications for each patient and is therefore expressed as a percentage. The CranioScore is only applicable in patients with all available data (no missing data in any of the selected variables). Several probability cutoffs for predicted complications were tested to delineate sensitivity, specificity, and positive and negative predictive values in the learning cohort (table 5). In the learning cohort, a 3% threshold had a sensitivity of 100%, a specificity of 6.2%, a positive predictive value of 12.1%, and a negative predictive value of 100%. With a threshold greater than 3%, 1,034 patients in the learning cohort and 660 patients in the validation cohort presented such values and would have been classified as high-risk patients requiring overnight ICU monitoring. Among these patients, 125 (11.4%) patients with complications would have been accurately classified as "high risk" in the learning cohort. No patients would have been misclassified in the learning cohort. In the validation cohort, 85 (10.2%) patients with complications would have been accurately classified as "high risk." Only one (0.1%) patient would have been misclassified as low risk in the validation cohort. On the other hand, 60 (5.4%) patients in the learning cohort and 88 (10.6%) patients in the validation cohort had a CranioScore at or below 3% and could have been discharged directly to a ward. Table 6 provides the classification of patients according to various values of their CranioScore (1%, 2%, 3%, and others) in the two cohorts. Based on these data (table 6) and using the CranioScore formula (Supplemental Digital Content 5, http://links.lww.com/ALN/B779), a predicted percentage of complications greater than 3% could be proposed to limit the risk of false negatives (patients classified as low risk of complications but who will develop a complication). Two examples of calculations of the CranioScore are provided (Supplemental Digital Content 5, http://links.lww.com/ALN/B779).

Secondary Outcomes

The perioperative management of patients in the validation and learning cohorts is displayed in table 3. In the learning cohort, 8 (0.7%) patients died in the ICU, and 16 (1.5%) died in the hospital. In the validation cohort, 6 (0.7%) patients died in the ICU, and 9 (1.1%) died in the hospital. Secondary outcome data can be found in table 1.

Table 3. Intraoperative Data in the Learning and External Validation Cohorts

Parameter	Learning Cohort (N = 1,094)		Validation Cohort (N = 830)		P Value
	N Missing	N (%) or Mean ± SD	N Missing	N (%) or Mean ± SD	
Age of the neurosurgeon, yr	0		0		
< 40		503 (46)		257 (31)	< 0.001
40–50		427 (39)		323 (38.9)	
≥ 50		164 (15)		250 (30.1)	
Primary agent					
Propofol	0	1,094 (100)	4	566 (68.5)	< 0.001
Halogenated anesthetics	0	0	4	273 (33)	< 0.001
Remifentanyl	0	19 (1.7)	4	245 (29.7)	< 0.001
Sufentanil	0	1,075 (98.3)	2	581 (70.2)	< 0.001
Awake surgery	0	4 (0.4)	1	37 (4.5)	< 0.001
Surgical position	0		2		
Dorsal		888 (81.2)		645 (77.9)	< 0.001
Ventral		128 (11.7)		78 (9.5)	
Lateral		61 (5.6)		94 (11.3)	
Seated position		17 (1.5)		11 (1.3)	
Minimal temperature, °C	195	35.3 (±1)	164	35.7 (±0.6)	< 0.001
Crystalloids, ml	0	1,332 (±592)	20	1,774 (±857)	< 0.001
Colloids , ml	0	412 (±542)	20	222 (±450)	< 0.001
Osmotherapy	0	81 (7.4)	6	93 (11.3)	0.003
Blood loss, ml	35	856 (879)	68	440 (593)	< 0.001
Packed erythrocytes ≥ 2	0	114 (10.4)	8	59 (7.2)	0.01
Transfusion of packed erythrocytes or plasma or platelets	0	133 (12.1)	0	66 (7.9)	0.003
Catecholamine perfusion	0	43 (3.9)	9	70 (8.5)	< 0.001
Maximum SAP, mmHg	0	166 (±27)	18	150 (±26)	< 0.001
Minimal SAP, mmHg	0	80 (±14)	18	83 (±14)	< 0.001
Maximum MAP, mmHg	0	120 (±22)	121	103 (±20)	< 0.001
Minimal MAP, mmHg	0	56 (±10)	119	59 (±12)	< 0.001
Duration of surgery, h	0	2.7 (±1.3)	29	2.8 (±1.6)	0.14
Duration of anesthesia, h	0	4.2 (±1.4)	31	4.4 (±1.9)	0.06

Continuous data are expressed as means (± SD) or median (interquartile range) accordingly and nominal data as N (%). Data suggest that high-volume craniotomy centers[5] report lower rates of complications. Because a selection bias could occur in the validation cohort, which could blunt the center's volume effect, we chose to note the neurosurgeon's age as a surrogate marker of his/her level of expertise. Maximum and minimum blood pressure were retained when the level remained the same during 3 min of monitoring. Blood pressure management was performed according to local protocols.

MAP, mean arterial pressure; SAP, systolic arterial pressure.

Table 4. Multivariable Analysis in the Learning Cohort of Risk Factors of Early Severe Postoperative Neurosurgical Complications (N = 1,094)

	Univariate Analysis		Multivariable Analysis		
	OR$_{unadjusted}$	P Value	β	OR$_{adjusted}$ CI$_{95\%}$	P Value
Intercept			−4.8094		
GCS before procedure (≤ 14 vs. 15)	6.58 (2.92–14.84)	< 0.001	1.5149	4.55 (1.88–11.03)	0.0008
History of brain tumor surgery	2.19 (1.40–3.42)	0.001	1.0534	2.87 (1.74–4.72)	< 0.0001
Greater size of tumor in brain imaging	1.02 (1.01–1.03)	0.001	0.00878	1.01 (1.00–1.02)	0.1
Midline shift in brain imaging ≥ 3 mm	1.99 (1.36–2.89)	0.001	0.5114	1.67 (1.04–2.69)	0.03
Transfusion of a packed erythrocytes or plasma or platelets	3.12 (1.99–4.88)	< 0.001	0.5164	1.68 (1.00–2.80)	0.04
SAP maximum, mmHg	1.01 (1.00–1.02)	0.001	0.0118	1.01 (1.01–1.02)	0.001
SAP minimum, mmHg	0.99 (0.97–1.00)	0.06	−0.0130	0.99 (0.97–1.00)	0.08
Duration of surgery, h	1.38 (1.23–1.56)	< 0.001	0.2981	1.35 (1.17–1.55)	< 0.0001

The least absolute shrinkage and selection operator analysis makes it possible to select variables without being limited by the parsimonious rule in usual logistic regression models by minimizing the sum of the absolute values of the regression coefficients leading some coefficients. This allows the selection of variables to be kept in the final regression model, in spite of the P > 0.05 obtained here with some risk factors (e.g., size of brain tumor).

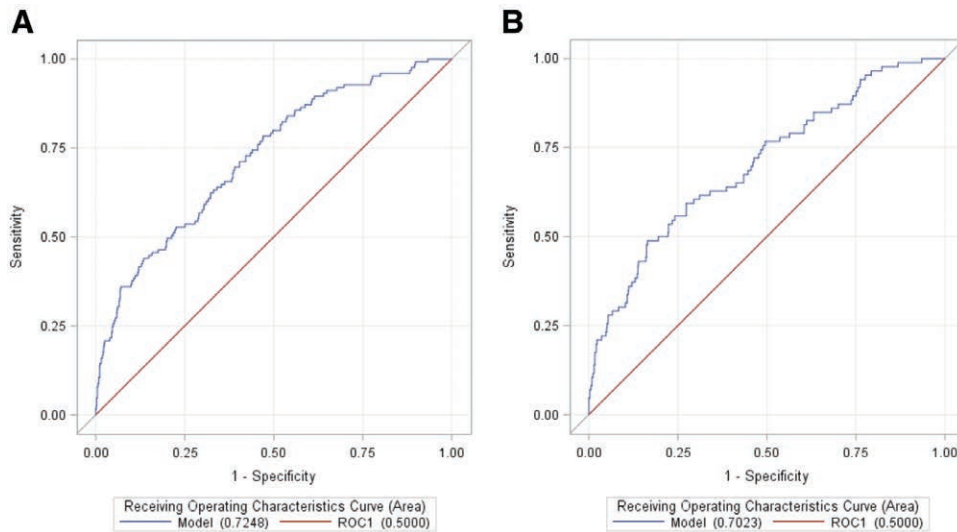GCS, Glasgow Coma Score; OR, odds ratio; SAP, systolic arterial pressure.

Fig. 1. Receiver operating characteristic curves of the CranioScore in the learning (*A*) and validation (*B*) cohorts. (*A*) Receiver operating characteristic curve of the model in the learning cohort with an area under the receiver operating characteristic curve 0.72 $IC_{95\%}$ (0.68 to 0.77), Hosmer–Lemeshow test, *P* = 0.2. (*B*) Receiver operating characteristic curve in the external validation cohort with an area under the receiver operating characteristic curve of 0.70 $IC_{95\%}$ (0.64 to 0.76), Hosmer–Lemeshow test, *P* = 0.1.

Table 5. Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, and Positive and Negative Likelihood Ratio in the Learning Cohort according to the Various Predicted Percentages of Complications of the CranioScore

	Sensitivity, %	Specificity, %	Positive Predictive Value, %	Negative Predictive Value, %	Positive Likelihood Ratio	Negative Likelihood Ratio
> 2%	100 (97.1–100)	0.5 (0.2–1.2)	11.5 (9.6–13.5)	100 (47.8–100)	1.01 (1.00–1.01)	0
> 3%	100 (97.1–100)	6.2 (4.8–7.9)	12.1 (10.2–14.2)	100 (94–100)	1.07 (1.05–1.08)	0
> 4%	96.0 (90.9–98.7)	15.6 (13.4–18.0)	12.8 (10.7–15.1)	96.8 (92.7–99.0)	1.14 (1.09–1.19)	0.26 (0.11–0.61)
> 5%	92.8 (86.8–96.7)	26.1 (23.4–29.0)	13.9 (11.7–16.5)	96.6 (93.6–98.4)	1.26 (1.18–1.34)	0.28 (1.18–1.34)
> 8%	78.4 (70.2–85.3)	51.1 (47.9–54.3)	17.1 (14.1–20.5)	94.8 (92.6–96.6)	1.60 (1.43–1.79)	0.42 (0.30–0.59)
> 10%	65.6 (56.6–73.9)	62.8 (59.7–65.9)	18.6 (15.0–22.5)	93.4 (91.2–95.2)	1.77 (1.52–2.05)	0.55 (0.43–0.70)
> 15%	45.6 (36.7–54.7)	82.7 (80.1–85.0)	25.3 (19.8–31.5)	92.2 (90.2–93.9)	2.63 (2.08–3.33)	0.66 (0.56–0.77)

Table 6. Number of Patients Displaying the Value of Different CranioScore Thresholds and Number of Patients with or without Postoperative Complications in the Learning and Validation Cohorts

CranioScore Thresholds	Cohort	Patients Classified as "High Risk of Complications," N (%)	Patients Classified as "Low Risk of Complications," N (%)	Patients with the Occurrence of Complications Classified as "High Risk," N (%)	Patients with a Wrong Prediction of Complications Classified as "Low Risk," N (%)
> 2%	LC	1,089 (99.5)	5 (0.5)	125 (11.4)	0 (0.0)
	VC	732 (97.9)	16 (2.1)	86 (11.5)	0 (0.0)
> 3%	LC	1,034 (94.5)	60 (5.5)	125 (11.4)	0 (0.0)
	VC	660 (88.2)	88 (11.8)	85 (11.4)	1 (0.1)
> 4%	LC	938 (85.7)	156 (14.3)	120 (11.0)	5 (0.5)
	VC	578 (77.3)	170 (22.7)	78 (10.4)	8 (1.1)
> 5%	LC	832 (76.1)	262 (23.9)	116 (10.6)	9 (0.8)
	VC	488 (65.2)	260 (34.8)	71 (9.5)	15 (2.0)
> 8%	LC	572 (52.3)	522 (47.7)	98 (9.0)	27 (2.5)
	VC	286 (38.2)	462 (61.8)	54 (7.2)	32 (4.3)
> 10%	LC	286 (26.1)	652 (59.6)	82 (7.5)	43 (3.9)
	VC	210 (28.1)	538 (71.9)	48 (6.4)	38 (5.1)
> 15%	LC	225 (20.6)	869 (79.4)	57 (5.2)	68 (6.2)
	VC	116 (15.5)	632 (84.5)	32 (4.3)	54 (7.2)

LC, learning cohort; VC, validation cohort.

Discussion

We validated a score predicting early severe postoperative neurosurgical complications within the setting of elective craniotomy for brain tumor. This score could provide substantial help in discriminating patients requiring mandatory overnight ICU monitoring to screen and treat major complications.

In an international observational study,[18] in-hospital mortality for patients requiring elective noncardiac surgery was higher than expected (up to 4%) with wide variation between countries. Moreover, indirect patient ICU admission after surgery was associated with higher mortality than patients with direct admission, meaning that complications after elective surgery should have been better anticipated.[19] These data favor systematic postoperative ICU admission. However, in a recent multicenter international study, direct ICU admission after surgery did not appear to improve hospital mortality.[7] The benefit of systematic ICU admission is therefore questionable. Up to now, monitoring patients after elective intracranial surgery in an acute care setting has been recommended (ICU, Neuro-ICU) because elective neurosurgery involves substantial morbidity and mortality compared with other types of surgery. An on-demand rather than a routine ICU admission policy could be profitable to high-risk patients and institutions.

In a nationwide multicenter database,[1] patients undergoing neurosurgery had more than a twofold risk of perioperative mortality compared with average mortality. Moreover, mortality after neurosurgery has not decreased over the last few decades.[1,20] This high mortality rate can be explained by life-threatening complications that can occur, such as cerebral hematoma,[9] status epilepticus,[13] and difficulty in weaning the patient from mechanical ventilation.[21] The incidence of complications after a neurosurgical procedure can be as high as 14.3%, especially after craniotomy.[21] These data urgently call for modification of postoperative ICU admission protocols and enhanced screening of patients. These scores could play a role in deciding ICU admission. In neurosurgery after elective craniotomy, selective rather than routine ICU admission could be both safe and cost-effective,[6] but the medical data that could improve this process are currently lacking. With a CranioScore value at or below 3%, patients could be safely discharged from the recovery room to a surgical ward. The percentage of patients with such CranioScore values could seem low. However, given the current policy of systematic ICU admission after neurosurgery, this would be the first step toward safe, medically justified, and cost-effective on-demand ICU admission after intracranial neurosurgery. Such a strategy would be highly innovative because on-demand ICU admission has not been tested in other contexts of high-risk surgery such as cardiac surgery.

Unlike cardiac surgery, there are very few scores to predict outcome in the setting of neurosurgery with craniotomy.[22,23] To the best of our knowledge, only 25 studies on preoperative risk assessment are available in this setting.[24] The scores currently available, such as American Society of Anesthesiologists or Karnofski Performance Status, are not specific for neurosurgery

patients and usually have small samples.[24] The specific preoperative sex, Karnofsky, American Society of Anesthesiology, location, edema grading system associating sex, Karnofski Performance Status, American Society of Anesthesiologists class, location of the brain tumor, and edema was built to predict 1-yr outcome after meningioma surgery in the elderly.[25] The sex, Karnofsky, American Society of Anesthesiology, location, edema score is useful in a selected population of patients undergoing elective craniotomy but is not helpful in the prediction of early postoperative complications with all types of brain tumors. The CranioScore is the first designed nationwide cohort with unselected brain tumor types in patients undergoing neurosurgery. Because we also provide a validation cohort, our results should be applicable to other settings. We have also identified some previously described risk factors such as the duration of surgery,[13] which will strengthen applicability.

Our study has limitations. First, in spite of this large cohort, the sample size of patients with a postoperative complication is rather low, and the selection of the adequate variable to uphold in a traditional regression model could be inadequate, owing to the parsimonious rule. Least absolute shrinkage and selection operator models are not subjected to this limitation even with a high number of variables. Second, our findings suggest associations and not causation, although we provided a large independent validation cohort for external validation of the CranioScore. It is therefore possible that specific therapeutic targets based on the risk factors would improve outcomes. Third, the decision to switch hospital policies from systematic to on-demand ICU admission could involve some major logistics changes. It should enhance ICU bed availability, but it should be accompanied by increased nurse staff training, education, and monitoring in surgical wards. Fourth, a CranioScore cannot be easily calculated. However, this should not be a major drawback with the widespread use of online free calculators and medical apps on smartphones. Fifth, our cohort had a low incidence of awake craniotomy or rare surgical procedures that may have a higher risk of complications such as craniopharyngioma resection. Our score may not apply in such a setting, as well as in patients undergoing craniotomy for other procedures (aneurysm clipping and arteriovenous malformation, among others). In addition, the CranioScore is not applicable in case a patient has missing data in one of the selected variables. However, these variables are routinely monitored. Last, patient ICU admission could rely on the comorbidities for a given patient[18] and not only on the potential occurrence of postoperative complications. In cases of patients with severe comorbidities, other specific scores can be used[26] to evaluate overall perioperative risk.

Conclusions

The CranioScore is a validated score predicting the risk of severe postoperative neurosurgical complications in elective craniotomy for brain neoplasms. It should be of interest to help an attending physician in the on-demand ICU admission process after craniotomy. Given the potential

consequences of misclassification, further research should focus on improving the specificity of prediction scores. The addition of biomarkers could be a promising tool in the prognostication of outcome after neurosurgery[27] and could be tested to enhance the validity of our score.

Acknowledgments

Research Support

Competing Interests

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References

1. Noordzij PG, Poldermans D, Schouten O, Bax JJ, Schreiner FA, Boersma E: Postoperative mortality in The Netherlands: A population-based analysis of surgery-specific risk in adults. ANESTHESIOLOGY 2010; 112:1105–15

2. Magni G, La Rosa I, Gimignani S, Melillo G, Imperiale C, Rosa G: Early postoperative complications after intracranial surgery: Comparison between total intravenous and balanced anesthesia. J Neurosurg Anesthesiol 2007; 19:229–34

3. Manninen PH, Raman SK, Boyle K, el-Beheiry H: Early postoperative complications following neurosurgical procedures. Can J Anaesth 1999; 46:7–14

4. Solheim O, Jakola AS, Gulati S, Johannesen TB: Incidence and causes of perioperative mortality after primary surgery for intracranial tumors: A national, population-based study. J Neurosurg 2012; 116:825–34

5. Trinh VT, Davies JM, Berger MS: Surgery for primary supratentorial brain tumors in the United States, 2000–2009: Effect of provider and hospital caseload on complication rates. J Neurosurg 2015; 122:280–96

6. Beauregard CL, Friedman WA: Routine use of postoperative ICU care for elective craniotomy: A cost-benefit analysis. Surg Neurol 2003; 60:483–9

7. The International Surgical Outcomes Study (ISOS) Group, Kahan BC, Koulenti D, Arvaniti K, Beavis V, Campbell D, Chan M, Moreno R, Pearse RM: Critical care admission following elective surgery was not associated with survival benefit: Prospective analysis of data from 27 countries. Intensive Care Med 2017; 43:971–9

8. Basali A, Mascha EJ, Kalfas I, Schubert A: Relation between perioperative hypertension and intracranial hemorrhage after craniotomy. ANESTHESIOLOGY 2000; 93:48–54

9. Zetterling M, Ronne-Engström E: High intraoperative blood loss may be a risk factor for postoperative hematoma. J Neurosurg Anesthesiol 2004; 16:151–5

10. Cai YH, Zeng HY, Shi ZH, Shen J, Lei YN, Chen BY, Zhou JX: Factors influencing delayed extubation after infratentorial craniotomy for tumour resection: A prospective cohort study of 800 patients in a Chinese neurosurgical centre. J Int Med Res 2013; 41:208–17

11. Ziai WC, Varelas PN, Zeger SL, Mirski MA, Ulatowski JA: Neurologic intensive care resource use after brain tumor surgery: An analysis of indications and alternative strategies. Crit Care Med 2003; 31:2782–7

12. Hanak BW, Walcott BP, Nahed BV, Muzikansky A, Mian MK, Kimberly WT, Curry WT: Postoperative intensive care unit requirements after elective craniotomy. World Neurosurg 2014; 81:165–72

13. Rhondali O, Genty C, Halle C, Gardellin M, Ollinet C, Oddoux M, Carcey J, Francony G, Fauvage B, Gay E, Bosson JL, Payen JF: Do patients still require admission to an intensive care unit after elective craniotomy for brain surgery? J Neurosurg Anesthesiol 2011; 23:118–23

14. French Ministry of Health. Bill of the 19th February 2015, regarding the funding of health-care facilities mentioned in the article L.162-22-6 of the social security code, ensuring activities of medicine, surgery, obstetrics and odontology or ensuring an activity of hospitalization at home. Available at: https://www.legifrance.gouv.fr/affichTexte.do;jsessionid=356F64AEBDB6CCF2F8094717792465E8.tpdila22v_1?cidTexte=JORFTEXT000030280539&dateTexte=20150228. Accessed November 24, 2017

15. Tibshirani R: The lasso method for variable selection in the Cox model. Stat Med 1997; 16:385–95

16. Palazón-Bru A, Folgado-de la Rosa DM, Cortés-Castell E, López-Cascales MT, Gil-Guillén VF: Sample size calculation to externally validate scoring systems based on logistic regression models. PLoS One 2017; 12:e0176726

17. Roquilly A, Feuillet F, Seguin P, Lasocki S, Cinotti R, Launey Y, Thioliere L, Le Floch R, Mahe PJ, Nesseler N, Cazaubiel T, Rozec B, Lepelletier D, Sebille V, Malledant Y, Asehnoune K; ATLANREA Group: Empiric antimicrobial therapy for ventilator-associated pneumonia after brain injury. Eur Respir J 2016; 47:1219–28

18. Pearse RM, Moreno RP, Bauer P, Pelosi P, Metnitz P, Spies C, Vallet B, Vincent JL, Hoeft A, Rhodes A; European Surgical Outcomes Study (EuSOS) Group for the Trials Groups of the European Society of Intensive Care Medicine and the European Society of Anaesthesiology: Mortality after surgery in Europe: A 7 day cohort study. Lancet 2012; 380:1059–65

19. Gillies MA, Harrison EM, Pearse RM, Garrioch S, Haddow C, Smyth L, Parks R, Walsh TS, Lone NI: Intensive care utilization and outcomes after high-risk surgery in Scotland: A population-based cohort study. Br J Anaesth 2017; 118:123–31

20. De la Garza-Ramos R, Kerezoudis P, Tamargo RJ, Brem H, Huang J, Bydon M: Surgical complications following malignant brain tumor surgery: An analysis of 2002–2011 data. Clin Neurol Neurosurg 2016; 140:6–10

21. Rolston JD, Han SJ, Lau CY, Berger MS, Parsa AT: Frequency and predictors of complications in neurological surgery: National trends from 2006 to 2011. J Neurosurg 2014; 120:736–45

22. Bhatti F, Grayson AD, Grotte G, Fabri BM, Au J, Jones M, Bridgewater B; North West Quality Improvement Programme

in Cardiac Interventions: The logistic EuroSCORE in cardiac surgery: How well does it predict operative risk? Heart 2006; 92:1817–20

23. Ad N, Barnett SD, Speir AM: The performance of the EuroSCORE and the Society of Thoracic Surgeons mortality risk score: The gender factor. Interact Cardiovasc Thorac Surg 2006; 6:192–5

24. Reponen E, Tuominen H, Korja M: Evidence for the use of preoperative risk assessment scores in elective cranial neurosurgery. Anesth Analg 2014; 119:420–32

25. Sacko O, Sesay M, Roux FE, Riem T, Grenier B, Liguoro D, Loiseau H: Intracranial meningioma surgery in the ninth decade of life. Neurosurgery 2007; 61:950–4

26. Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, Sugarbaker DJ, Donaldson MC, Poss R, Ho KK, Ludwig LE, Pedan A, Goldman L: Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999; 100:1043–9

27. McDonagh DL, Berger M, Mathew JP, Graffagnino C, Milano CA, Newman MF: Neurological complications of cardiac surgery. Lancet Neurol 2014; 13:490–502

Appendix: Collaborators of the Société Française d'Anesthésie-Réanimation (SFAR) Research Network

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Daily Nitrous Oxide for "Pupblic" Patients of Dr. C. C. Haskell
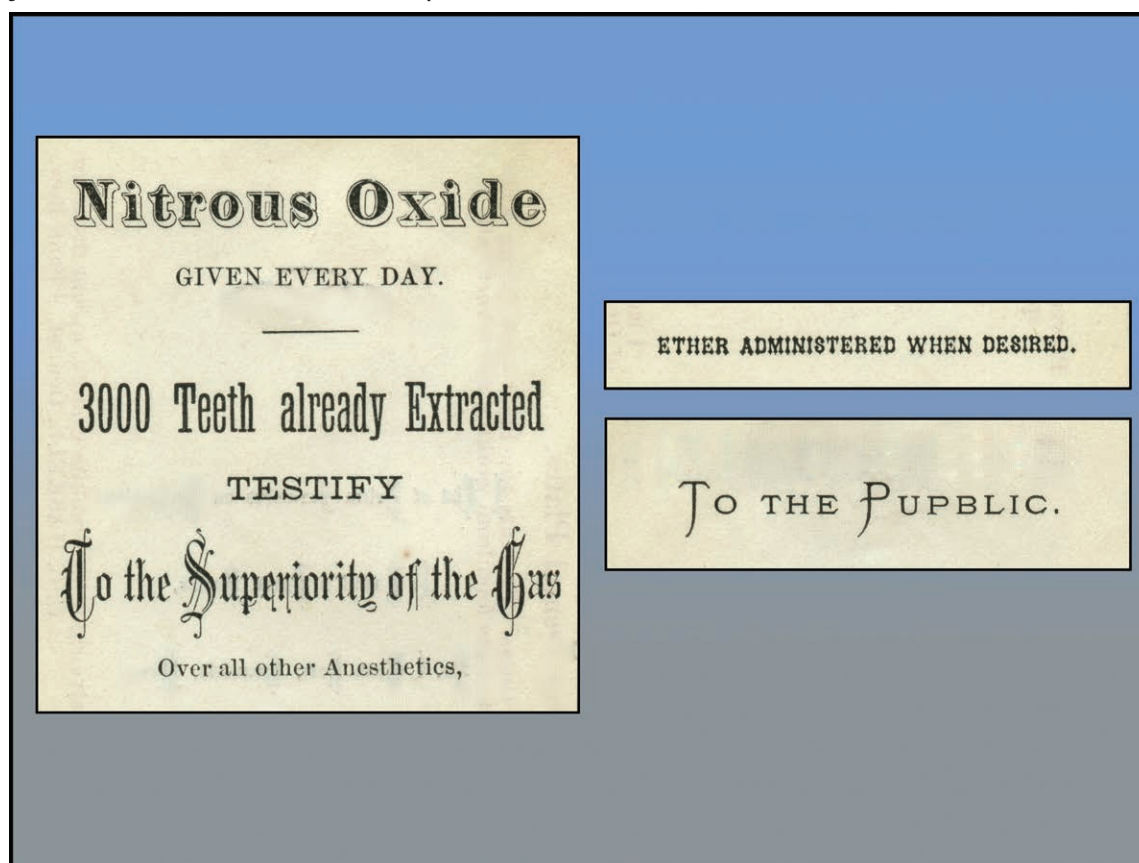
From Springfield, Massachusetts, Dr. Clarence Crowell Haskell (1858 to 1917) published a ca. 1870 pamphlet advertising (*left*) that he administered nitrous oxide "every day." By touting that "3000 teeth already extracted testify to the superiority of the gas over all other anesthetics," Dr. Haskell was mimicking pioneer anesthetist G. Q. Colton, who had advertised his own revival of nitrous-oxide anesthesia. With Haskell's slogan (*upper right*), "Ether administered when desired," he afforded an alternate anesthetic for those not happy to receive laughing gas. "Pupblic" patients (*lower right*) could only pray that Dr. Haskell could administer anesthetics better than he could spell or proofread…. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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Hospital-, Anesthesiologist-, and Patient-level Variation in Primary Anesthesia Type for Hip Fracture Surgery

A Population-based Cross-sectional Analysis

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ABSTRACT

Background: Substantial variation in primary anesthesia type for hip fracture surgery exists. Previous work has demonstrated that patients cared for at hospitals using less than 20 to 25% neuraxial anesthesia have decreased survival. Therefore, the authors aimed to identify sources of variation in anesthesia type, considering patient-, anesthesiologist-, and hospital-level variables.

Methods: Following protocol registration (NCT02787031), the authors conducted a cross-sectional analysis of a population-based cohort using linked administrative data in Ontario, Canada. The authors identified all people greater than 65 yr of age who had emergency hip fracture surgery from April 2002 to March 2014. Generalized linear mixed models were used to account for hierarchal data and measure the adjusted association of hospital-, anesthesiologist-, and patient-level factors with neuraxial anesthesia use. The proportion of variation attributable to each level was estimated using variance partition coefficients and the median odds ratio for receipt of neuraxial anesthesia.

Results: Of 107,317 patients, 57,080 (53.2%) had a neuraxial anesthetic. The median odds ratio for receiving neuraxial anesthesia was 2.36 between randomly selected hospitals and 2.36 between randomly selected anesthesiologists. The majority (60.1%) of variation in neuraxial anesthesia use was explained by patient factors; 19.9% was attributable to the anesthesiologist providing care and 20.0% to the hospital where surgery occurred. The strongest patient-level predictors were absence of preoperative anticoagulant or antiplatelet agents, absence of obesity, and presence of pulmonary disease.

Conclusions: While patient factors explain most of the variation in neuraxial anesthesia use for hip fracture surgery, 40% of variation is attributable to anesthesiologist and hospital-level practice. Efforts to change practice patterns will need to consider hospital-level processes and anesthesiologists' intentions and behaviors. **(ANESTHESIOLOGY 2018; 129:1121-31)**

V ARIATIONS in clinical practice are well documented across different areas of medicine and jurisdictions.[1,2] Some variation in care delivery is warranted and expected. Differences in patient illness and preferences should drive individualization of care in pursuit of better outcomes. However, in some cases, medical practice variation unexplained by patient illness, risk factors, or preferences[2,3] is associated with adverse outcomes.[1,4,5] Identification of reasons for such variation could help inform development of strategies to minimize unexplained variation and improve patient outcomes.

More than 300,000 hip fracture surgeries are performed in the United States annually;[6] more than 20,000 are performed in Canada.[7] Hip fracture surgery is associated with relatively high morbidity and mortality rates (more than 20%[8] and 6%,[9]

Editor's Perspective

What We Already Know about This Topic

- Neuraxial anesthesia use for hip fracture surgery has wide variation in use across hospitals, and hospitals using it for less than 25% of patients may have increased 30-day mortality
- The proportion of the variation in use attributable to patient, provider, and hospital factors remains unknown

What This Manuscript Tells Us That Is New

- Canadian administrative data demonstrate that approximately 60% of the variation in neuraxial use is attributable to patient factors, 20% to provider factors, and 20% to hospital factors
- The specific anesthesiologist or hospital a patient receives care from affects the likelihood of neuraxial use more than most clinical factors

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respectively). Efforts are needed to improve the quality and outcomes of anesthesia care for these high-risk patients. Substantial variation in the use of general anesthesia *versus* neuraxial anesthesia has been documented in the United States,[10] United Kingdom,[11] and Canada.[12] While the current evidence does not convincingly support the role of neuraxial anesthesia in improving postoperative outcomes,[8,10,13–16] neuraxial anesthesia may decrease respiratory and hematologic adverse events,[13] and length of stay.[10] In addition, we have recently shown that patients who have hip fracture surgery in hospitals that use more than 20 to 25% neuraxial anesthesia for hip fracture surgery have significantly higher risk-adjusted survival.[12]

A key step to guiding efforts to decrease unexplained practice variation and improve outcomes is understanding how much variation in anesthesia type is explained by patient-level factors *versus* other factors, such as clinician or hospital practice patterns.[17] We, therefore, conducted a cross-sectional analysis of a population-based cohort to measure the extent of practice variation in choice of anesthesia type attributable to hospital-, anesthesiologist-, and patient-level factors, as well as to identify specific characteristics at each of these levels that significantly influence a patient's likelihood of receiving a neuraxial anesthesia.

Materials and Methods

Setting and Data

Following ethical approval from the Sunnybrook Health Sciences Research Board (Toronto, Canada), we conducted a population-based cross-sectional analysis in Ontario, Canada, where hospital and physician services are provided to all residents through a publicly funded healthcare system and recorded in health administrative datasets that are collected using standardized methods.[18,19] All data were linked deterministically using anonymized, encrypted, patient-specific identifiers at the Institute for Clinical Evaluative Sciences, an independent research institute that houses the health administrative data for the province of Ontario. Datasets used for the study included the Discharge Abstract Database, which captures all hospitalizations; the Ontario Health Insurance Plan database, which captures physician service claims; the National Ambulatory Care Reporting System, which captures details of all emergency and outpatient care; the Continuing Care Reporting System, which records details of long-term and respite care; the Ontario Drug Benefits Database, which captures prescription drug claims for residents 65 yr and older; the Institute for Clinical Evaluative Sciences Physician Database, which houses information on physician specialty, demographics, training, and workload; and the Registered Persons Database, which captures all death dates for residents of Ontario. The analytic dataset was assembled by a trained data analyst independent of the study team. Analysis was performed by the lead author (D.I.M.) and overseen by the senior author (C.v.W). The study protocol was registered at clinicaltrials.gov (NCT02787031, which included two objectives: the outcome study previously

reported[12] and the current variation analysis). The manuscript is reported according to guidelines.[20,21]

Cohort

We identified all Ontario residents who were 66 yr or older on the day of their emergency hip fracture surgery, an age cutoff that allowed us to identify prescription medications in the year before surgery (universal drug coverage is available starting at age 65 yr). These patients were identified using Canadian Classification of Interventions codes to identify hip fracture surgery (diagnostic code S72 for hip fracture; then procedural codes 1VA53, 1VA74, 1VC74, or 1SQ53).[22] Reabstraction studies demonstrate that these codes are accurate and reliable (κ 0.95; positive predictive value, 0.95).[23] We limited our sample to individuals who were admitted to hospital on a nonelective basis to exclude elective hip operations. Participants were identified from April 2002, the date of introduction of the *International Classification of Diseases, Tenth Edition (ICD-10)* to identify diagnoses, and the Canadian Classification of Interventions to identify procedures, to March 2014, the latest time at which all datasets were complete. Patients were excluded if they were treated in a hospital that did fewer than 10 hip fracture surgeries per year or if the anesthesia type was missing from their administrative records.

Exposure

Anesthesia type was captured from the Discharge Abstract Database, where anesthesia type is coded for every operative procedure; reabstraction demonstrates 94% agreement for this field.[24] Anesthesia type was coded in the Discharge Abstract Database as general, spinal, epidural, or combined general and neuraxial. Patients who received an epidural or spinal anesthetic without concurrent general anesthesia were categorized as having received neuraxial anesthesia, while any patient who received general anesthesia (including those who had a combined general anesthesia and neuraxial anesthesia) were categorized as not having received neuraxial anesthesia.

Outcomes

Although adjusted outcome rates have been previously reported,[12] we collected 30-day all-cause mortality (from the Registered Persons Database) and postoperative length of stay (from the Discharge Abstract Database).

Covariates

For each patient, we identified variables available in our data sources that we postulated could influence the receipt of a neuraxial anesthetic. Because our purpose was to explore all possible contributing factors that we could measure, as opposed to creating a parsimonious prediction model, we included factors that could be related, such as diagnosis of pulmonary disease, as well as treatments for pulmonary disease. Demographics were identified from the Registered Persons Database and from the Canadian Census. Standard methods were used to identify all Elixhauser comorbidities based on International

Classification of Diseases, 9th Edition and International Classification of Diseases, 10th Edition, codes from the Discharge Abstract Database in the 3 yr preceding surgery.[25] We also measured the preoperative length of stay. We identified receipt of the following prescription medications in the year before surgery: angiotensin converting enzyme inhibitors or angiotensin receptor blockers, antiarrhythmics, anticoagulants, anticonvulsants, antidepressants, antipsychotics, insulin, oral antihyperglycemics, antiplatelet agents, benzodiazepines, beta blockers, oral corticosteroids, inhaled corticosteroids, inhaled bronchodilators, or dementia drugs (donepezil, rivastigmine, memantine, or galantamine). The Hospital-patient One-year Mortality Risk score was also calculated to measure death risk based on present on admission variables. This score is an externally validated risk adjustment instrument with excellent discrimination (c-statistic, 0.89 to 0.92) and calibration for predicting 1-yr mortality risk in hospitalized patients.[26]

We also identified information about individual anesthesiologists and individual hospitals from which patients received their care. For each physician, we captured their age, sex, years of experience (calculated as year of surgery – [year of graduation + 5 yr for residency training]), and their overall case volume (both hip fractures and non–hip fracture surgery), which reflects each physicians' annual billings compared with that year's average from all physicians in the specialty. We characterized each hospital based on its teaching hospital status (*i.e.*, whether it had a residency training programs in anesthesiology), and volume of hip fracture surgeries performed in the year before the index surgery.

Analysis
SAS (SAS Institute, USA) version 9.4 was used for all analyses. We used standardized differences to compare characteristics between patients who did and did not receive a neuraxial anesthesia for their surgery. Although no universal threshold has been established, differences of 10% or less are considered to indicate balance.[27] All multilevel models were specified and analyzed using PROC GLIMMIX, a part of the SAS software.

Sources of Variation and Predictors of Neuraxial Anesthesia Use
To determine the relative contribution of hospital-, anesthesiologist-, and patient-level factors to variation in neuraxial use, we developed a generalized linear mixed model with a logit link and binary response distribution (*i.e.*, multilevel logistic regression). The multilevel model included two random intercept terms: one for a hospital identifier and one for an anesthesiologist identifier (nested within hospitals). These random intercepts were used to calculate the variance partition coefficient (also known as intraclass correlation coefficient in linear models) and the median odds ratio for receipt of a neuraxial anesthetic.[28] The variance partition coefficient characterizes the proportion of variation attributable to the cluster levels (*i.e.*, hospital and anesthesiologist level). In multilevel logistic models, variance between clusters is measured on the

logistic scale, while individual level variance is on the probability scale. To account for this, we calculated the variance partition coefficient using the linear threshold model method, which normalizes variance measurements to the logistic scale using the formula: variance partition coefficient = variance / (variance + [$\pi^2/3$]).[28] Modified Wald *P* values were used to test if the variance was significantly different from zero.[29] We performed covariance tests to estimate whether model fit was improved with addition of these random intercepts compared to the model with only fixed effects. The median odds ratio is the median value obtained from comparing the adjusted odds of having a neuraxial anesthesia if the same individual underwent surgery at two different randomly selected hospitals, or under the care of two randomly selected anesthesiologists.[28] The median odds ratio always takes a value greater than 1; therefore, a median odds ratio of 1.5 suggests that the median odds of receiving neuraxial anesthesia is 50% higher if the same patient had surgery at one randomly selected hospital *versus* another randomly selected hospital, or under the care of one randomly selected anesthesiologist *versus* another randomly selected anesthesiologist. The median odds ratio was calculated using the formula: median odds ratio = $e^{0.95\sqrt{\text{variance}}}$.[28]

The model also included fixed patient-level effects. Patient-level covariates were chosen based on their postulated role in influencing the choice of anesthesia type: age (classified as 66 to 74 yr, or 75 yr and older as recommended by the National Surgical Quality Improvement Program universal risk calculator[30]); sex (male or female); Hospital-patient One-year Mortality Risk score (as a continuous linear variable, where higher score means higher risk of death); rural residence (binary); neighborhood income quintile (five-level categorical variable); all Elixhauser comorbidities (as binary variables); preoperative length of stay (categorical: 0 to 1 days, 2 days, greater than 2 days); whether surgery was performed on a weekend (binary); acute care hospitalization in the year before admission (binary); emergency department visit in the year before surgery (binary); and each prescription medication described in the Covariates section (as binary variables). We had initially included use of an intraoperative arterial line in our model, but after discussions in the peer-review process, it was agreed that an arterial line may have preceded choice of anesthesia type in some patients (and therefore fit appropriately on the causal pathway), whereas in other cases it may have been placed after (or even due to) effects of the primary anesthesia type (in which case it would be inappropriate to include as a predictor). Therefore, our final analyses did not include an arterial line variable.

We performed a prespecified sensitivity analysis where we excluded patients who had an epidural and patients who had neuraxial anesthesia with concurrent general anesthesia. We also performed a *post hoc* sensitivity analysis where physicians were not assumed to be nested in hospitals, but were specified as a second random intercept at the same level of the data hierarchy as hospitals.

Finally, we created a model that, in addition to the random intercepts and patient-level fixed effects described in

our primary model, also included anesthesiologist-level variables (sex [binary], age quintile, experience quintile, overall case volume quintile), and hospital characteristics (teaching status [binary], annual volume quintile, quintile of average operative time [added after peer-review]). This model was used to determine the adjusted association of patient-, anesthesiologist-, and hospital-level variables with receipt of neuraxial anesthesia. Variables with 95% CIs that did not include 1 (the null value) were considered to be independently associated with the receipt of neuraxial anesthesia.

Missing Data

Outcome data was complete for all participants. Anesthesia type was missing for 96 people (0.08%); these cases were excluded from all analyses. Rural residency status was missing for 0.09% and was imputed with the most common value (not rural). Income quintile was missing and imputed with the group median (3) for 0.5%.

Results

We identified 107,317 hip fracture surgery patients, from 80 different hospitals, greater than 65 yr who had a valid anesthesia type entered in their Discharge Abstract Database record. Neuraxial anesthesia without concurrent general anesthesia was used in 57,080 (53.2%) patients (fig. 1). Hospital-specific

rates of neuraxial anesthesia use varied from 0 to 100%. Of the patients receiving general anesthesia, 3.1% had a concurrent neuraxial anesthesia. A spinal anesthetic was placed in 98.9% of patients having a neuraxial anesthesia without general anesthesia. Characteristics of patients by anesthesia type are provided in table 1. Death within 30 days of surgery occurred in 9,122 (8.5%) individuals. Median postoperative hospital length of stay was 9 days (interquartile range 6 to 18).

From the null model (model 1), which contained only a random intercept term for hospital, but no anesthesiologist clusters or patient-level fixed effects, the hospital-level variance was 1.117 ($P < 0.001$), and the variance partition coefficient was 25.3%. When anesthesiologists were nested within each hospital (model 2), the variance at the hospital level decreased to 0.779 (variance partition coefficient = 19.1%, $P < 0.001$), and the anesthesiologist-level variance was 0.776 (variance partition coefficient = 19.1%, $P < 0.001$). Following addition of patient-level fixed effects (model 3), the variance at the hospital level was 0.821 ($P < 0.001$), and the variance at the anesthesiologist level was 0.816 ($P < 0.001$). Based on these measures of between-cluster variance, 20.0% of variation in neuraxial anesthesia use was attributable to the hospital level, 19.9% to the anesthesiologist, and 60.1% to patient factors. Covariance tests supported improved model fit with addition of hospital-level ($P < 0.001$) and anesthesiologist-level ($P < 0.001$) random intercepts.
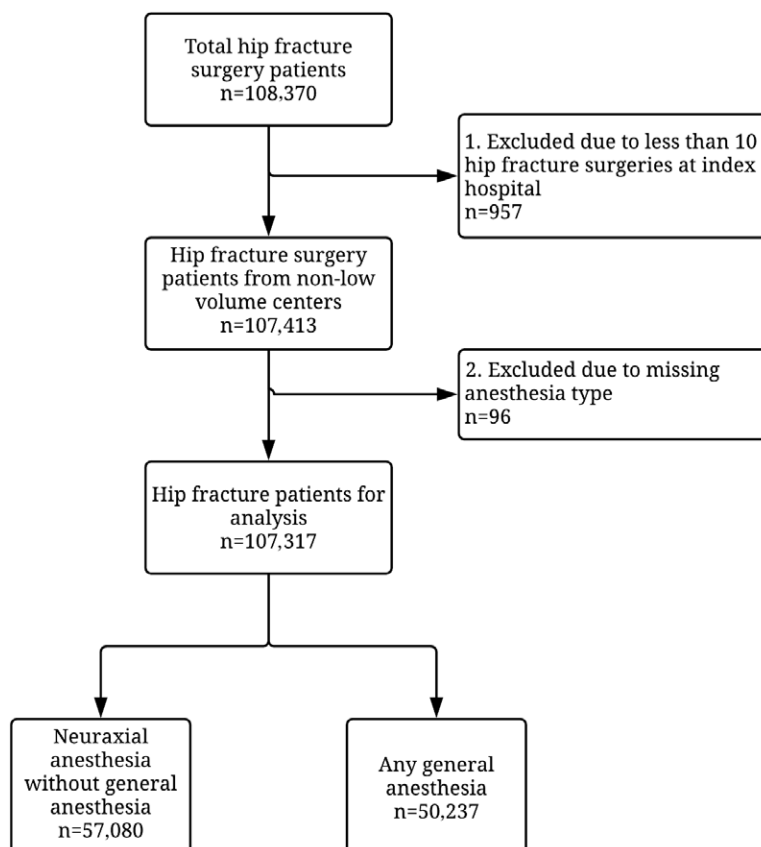
Fig. 1. Study flow diagram.

Table 1. Characteristics of Study Population, by Anesthesia Type

	General Anesthesia (n = 50,237)	Neuraxial Anesthesia (n = 57,080)	Standardized Difference
Demographics			
Age (mean, ±SD)	82 (8)	83 (7)	13.3
Female (%)	73.4	73.5	0.2
Rural (%)	12.2	13.8	4.8
Neighborhood income quintile (median, IQR)	3 (2,4)	3 (2,4)	0
Comorbidities			
Alcohol abuse (%)	2.1	2.1	0.0
ASA Score ≤ 2	16.1	12.8	9.4
ASA Score 3	48	48.2	0.4
ASA Score 4	35	38.4	7.1
ASA Score 5	0.7	0.6	1.2
Atrial arrhythmia (%)	9.4	9.1	1.0
Blood loss anemia (%)	17.1	17.1	0.0
Cardiac valvular disease (%)	4.1	3.1	5.4
Cerebrovascular disease (%)	6.7	6	2.9
Chronic obstructive pulmonary disease (%)	10.9	14.1	9.7
Coagulopathy (%)	3.8	2.7	6.2
Deficiency anemia	—	—	—
Dementia (%)	9.3	10.1	2.7
Depression (%)	4.8	4.6	0.9
Diabetes mellitus without complications (%)	12.8	12	2.4
Diabetes mellitus with complications (%)	9.8	9.9	0.3
Dialysis (%)	1.4	1.2	1.8
Disease of pulmonary circulation (%)	2.3	2.2	0.7
Drug abuse (%)	0.4	0.4	0.0
Heart failure (%)	13.4	13.9	1.5
Hemiplegia (%)	1.2	1.0	1.9
Hypertension without complications (%)	46.3	36.4	20.2
Hypertension with complications (%)	2.6	2.7	0.6
Liver disease (%)	0.8	0.7	1.2
Malignancy (%)	5.8	5.1	3.1
Metastases (%)	1.8	1.4	3.2
Obesity (%)	1.1	0.8	3.1
Peptic ulcer disease (%)	1.4	1.2	1.8
Peripheral vascular disease (%)	2.4	2.5	0.6
Psychoses (%)	1.6	1.3	2.5
Renal disease (%)	4.3	4.4	0.5
Rheumatic disease (%)	1.4	1.2	1.8
Venous thromboembolism (%)	1.1	0.8	3.1
Weight loss (%)	2.5	2.8	1.9
1-yr risk of death	38 (5)	39 (5)	10.4
Healthcare resource use			
Hospitalization in last year	27.5	25.9	3.6
Emergency department visit in last year (%)	60.8	60.8	0.0
Anesthesia care			
Preoperative LOS ≤1 day	79.9	82.9	7.7
2 days	11.4	10.2	3.9
≥3 days	8.7	6.9	6.7
Prescription drugs			
ACE-I/ARB (%)	42.4	42.3	0.2
Antiarrhythmic (%)	3.4	3.0	2.3
Antiplatelet agent (%)	9.9	4.8	19.6
Antipsychotic (%)	13.7	14.2	1.4
Insulin (%)	4.6	4.3	1.5
Anticoagulant (%)	14.1	12.5	4.7

(Continued)

Table 1. (Continued)

	General Anesthesia (n = 50,237)	Neuraxial Anesthesia (n = 57,080)	Standardized Difference
Oral diabetes agent (%)	12.5	12.1	1.2
Beta-blocker (%)	28.2	27.1	2.5
Inhaled bronchodilator (%)	12.6	15.8	9.2
Inhaled corticosteroid (%)	10.3	13	8.4
Oral corticosteroid (%)	6.7	7.1	1.6
Physician characteristics			
Full-time equivalency (mean, ±SD)	1.1 (0.2)	1.1 (0.3)	4.1
Age (mean, ±SD)	48 (10)	47 (9)	15.9
Years in practice (mean, ±SD)	17 (10)	16 (10)	14.1
Female anesthesiologist (%)	23.2	22.5	1.7
Hospital characteristics			
Yearly no. of hip fracture surgeries (mean, ±SD)	228 (130)	212 (94)	14.1
Teaching hospital	35.5	25.2	22.5

— indicates cell sizes less than 6 cannot be reported.
ACE-I/ARB, Angiotensin converting enzyme inhibitor/angiotensin receptor blocker; ASA Score, American Society of Anesthesiologists physical status classification; IQR, interquartile range; LOS, length of stay.
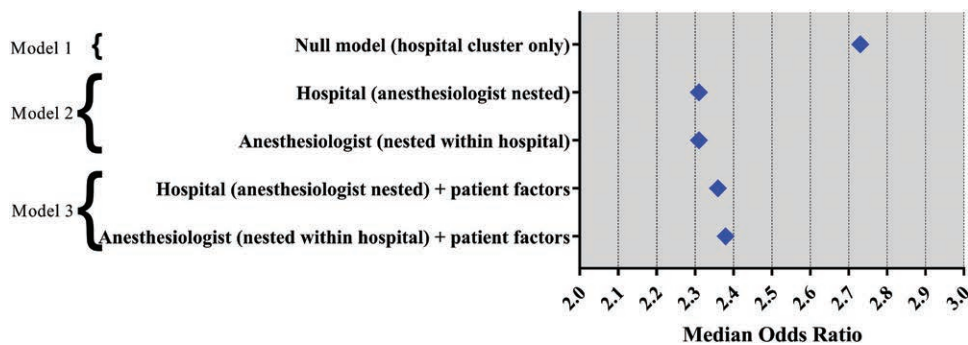
Fig. 2. Median odds ratio for hospital- and anesthesiologist-level clustering in each of the three multilevel models created.

Median odds ratios for model 1 to 3 are compared in figure 2. The model 3 (adjusted) median odds ratio for neuraxial anesthesia use was 2.36 at the physician- and 2.36 at the hospital-level. This means that for a given patient, their median odds of receiving neuraxial anesthesia would differ by more than 2.3-fold, depending on the anesthesiologist or hospital that they received care from. In our sensitivity analysis, in which patients who had an epidural and patients who had neuraxial anesthesia with concurrent general anesthesia were excluded, there was almost no change in the proportion of variation attributable to hospital (20.1%), anesthesiologist (19.9%), or patient (60.0%); the median odds ratio for neuraxial anesthesia use was 2.36 for the hospital and 2.36 for the anesthesiologist. When physicians were not assumed to be nested in hospitals, there was almost no change in the proportion of variation attributable to hospital (19.2%), anesthesiologist (19.4%), or patient (60.4%); the median odds ratio for neuraxial anesthesia use was 2.32 for the hospital and 2.33 for the anesthesiologist.

The adjusted associations of patient, hospital, and physician characteristics with neuraxial anesthesia use are presented as odds ratios in table 2. The c-statistic for this model was 0.83, and a calibration plot suggested that the model was well calibrated (see Supplemental Digital Content, http://links.lww.com/ALN/B789). The strongest patient-level predictors (greater than or equal to 20% change in relative effect size) of neuraxial anesthesia receipt were coagulopathy, dialysis, metastases, obesity, American Society of Anesthesiologists physical status III or IV (*vs.* V), antiplatelet or anticoagulant prescriptions, and having a hemiarthroplasty for surgical fixation. At the hospital level, having surgery at a non–teaching center significantly increased the odds that a patient received an neuraxial anesthesia, while surgical volume was significantly associated with neuraxial anesthesia receipt, but without a clear dose–response relationship. Shorter average case duration was associated with lower odds of neuraxial anesthesia receipt. Anesthesiologists in the highest quintile of overall case volume were the most likely to provide neuraxial anesthesia, however, other measurable anesthesiologist-level variables were not consistently associated with neuraxial anesthesia use.

Discussion

In this population-based cross-sectional study of hip fracture surgery patients, 40% of variation in use of neuraxial anesthesia

Table 2. Predictors of Neuraxial Anesthesia Use

Predictors	Odds Ratio	95% CI
Demographic characteristics		
Age 75 years or older	1.36	1.30–1.42*
Female (*vs.* male)	0.94	0.91–0.97*
Rural (*vs.* not rural)	1.00	0.95–1.05
Neighborhood income quintile (*vs.* highest quintile)		
1 (lowest)	1.03	0.99–1.08
2	1.04	0.99–1.09
3	1.05	0.99–1.10
4	0.99	0.95–1.04
Comorbidities		
Alcohol abuse	1.00	0.90–1.11
Atrial arrhythmia	1.07	1.01–1.13*
Blood loss anemia	1.05	1.01–1.10*
Cardiac valvular disease	0.70	0.65–0.76*
Cerebrovascular disease	1.07	1.01–1.15*
Chronic obstructive pulmonary disease	1.28	1.22–1.35*
Coagulopathy	0.79	0.72–0.85*
Deficiency anemia	1.00	0.87–1.17
Dementia	0.99	0.94–1.05
Depression	0.96	0.89–1.03
Diabetes mellitus without complications	0.99	0.95–1.05
Diabetes mellitus with complications	0.99	0.93–1.05
Dialysis	0.81	0.70–0.93*
Disease of pulmonary circulation	1.00	0.91–1.10
Drug abuse	0.98	0.78–1.24
Heart failure	1.08	1.03–1.13*
Hemiplegia	0.90	0.77–1.04
Hypertension without complications	1.01	0.98–1.05
Hypertension with complications	1.19	1.07–1.31*
Liver disease	0.84	0.71–0.99*
Malignancy	0.93	0.87–1.01
Metastases	0.76	0.67–0.87*
Obesity	0.71	0.62–0.83*
Peptic ulcer disease	0.89	0.78–1.01
Peripheral vascular disease	1.14	1.04–1.25*
Psychoses	0.89	0.79–1.01
Renal disease	1.11	1.02–1.21*
Rheumatic disease	0.87	0.76–0.99*
Venous thromboembolism	0.92	0.79–1.07
Weight loss	1.17	1.07–1.28*
1-yr risk of death (1-point increase in Hospital One-year Mortality Risk score)	1.01	1.01–1.02*
Healthcare resource use		
Hospitalization in last year	0.92	0.89–0.96*
Emergency department visit in last year	1.01	0.98–1.05
ASA Physical Status (*vs.* V)		
II	1.16	0.96–1.49
III	1.42	1.18–1.71*
IV	1.49	1.24–1.79*

(*Continued*)

Table 2. (Continued)

Predictors	Odds Ratio	95% CI
Preoperative length of stay (*vs.* ≥3 days)		
≤1 day	1.14	1.08–1.21*
2 days	1.06	0.99–1.14
Type of hip fixation (*vs.* fixation of femoral shaft)		
Total hip arthroplasty	0.93	0.77–1.13
Hemiarthroplasty	1.27	1.23–1.31*
Fixation of femoral neck	1.17	1.13–1.22*
Weekend surgery (*vs.* weekday)	1.07	1.03–1.10*
Prescription drugs		
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker	1.04	1.01–1.07*
Antiarrhythmic	1.00	0.91–1.09
Anticoagulant	0.69	0.66–0.73*
Antidepressant	0.98	0.94–1.01
Antiplatelet agent	0.28	0.27–0.30*
Benzodiazepine	0.98	0.95–1.01
Dementia medication	1.01	0.97–1.06
Digoxin	1.13	1.06–1.21*
Insulin	0.93	0.86–1.00
Oral diabetes agent	0.97	0.91–1.03
Beta blocker	1.00	0.97–1.04
Inhaled bronchodilator	1.13	1.06–1.20*
Inhaled corticosteroid	1.08	1.01–1.16*
Oral corticosteroid	1.03	0.97–1.09
Antipsychotic	0.93	0.88–0.97*
Hospital characteristics		
Average operating room time quintile (*vs.* highest)		
1 (lowest)	0.76	0.69–0.84*
2	0.84	0.78–0.91*
3	0.94	0.87–1.00
4	1.15	1.06–1.24*
Hospital volume quintile (*vs.* highest)		
1 (lowest)	0.84	0.76–0.92*
2	1.02	0.93–1.12
3	1.25	1.15–1.35*
4	1.16	1.08–1.24*
Teaching hospital (*vs.* nonteaching)	0.80	0.68–0.96*
Physician characteristics		
Full-time equivalency quintile (*vs.* highest)		
1 (lowest)	0.90	0.82–0.97*
2	0.88	0.82–0.95*
3	0.82	0.79–0.85*
4	0.91	0.85–0.97*
Years in practice quintile (*vs.* highest)		
1 (lowest)	0.98	0.82–1.14
2	1.03	0.89–1.19
3	0.98	0.87–1.11
4	0.98	0.87–1.10
Age quintile (*vs.* oldest)		
1 (lowest)	1.08	0.92–1.28
2	1.00	0.87–1.15
3	1.00	0.89–1.13
4	1.00	0.92–1.09
Female anesthesiologist (*vs.* male)	0.98	0.88–1.09

*Significant at the alpha=0.05 level.
ASA, American Society of Anesthesiologists.

was not attributable to patient-level factors. In fact, the median odds of a given patient receiving neuraxial anesthesia varied by more than 2.3-fold between any two randomly selected hospitals or anesthesiologists, independent of baseline patient illness, sociodemographic characteristics, or other factors, such as antiplatelet, anticoagulant, or other medication use that we postulated may influence a patient's probability of receiving neuraxial anesthesia. These findings suggest that interventions targeted at changing anesthesia practice for hip fracture surgery should consider not only patients' risk factors but also hospital-level processes, as well as anesthesiologists' intentions and behaviors.

While practice variation exists across regions, hospitals, and physician practices for many medical conditions,[1] few studies have linked variation to outcomes, and only 10% of studies in a recent systematic review explored causes of variation.[1] While practice variation in anesthesia and perioperative medicine has not been extensively studied, when identified, variation is associated with decreased rates of risk-adjusted survival.[5,12] Therefore, understanding sources of variation is a necessary step toward decreasing unintended variation, and the possibility of associated adverse outcomes. Existing frameworks suggest that variation must be studied in the setting of adequate risk adjustment and should consider geographical and environmental factors (in the case of anesthesiology practice, hospital-level factors), as well as provider-level factors.[2] Our analysis incorporates these recommended best practices, in a cohort of patients where low hospital-level neuraxial anesthesia use is associated with decreased risk-adjusted survival.[12] Through multilevel modeling, we were able to assess hospital- and physician-level contributions to variation, while adjusting for an extensive set of patient-level factors that we postulated would influence choice of anesthesia type, and which did so with good discrimination.

The most important finding to emerge from this analysis is that a substantial proportion of the variation in anesthesia type is not attributable to patient-level characteristics. While neuraxial anesthesia is not consistently associated with decreased mortality,[13] other outcomes such as length of stay may be improved.[10] Combined with the association of decreased survival after surgery in low neuraxial anesthesia–use hospitals, and anticipated results from large patient-centered trials,[31] it is important to recognize that this variation may be unwarranted. That a given patient would be faced with a greater than 2.3-fold difference in their likelihood to receive one anesthesia type *versus* another, simply based on the hospital that he or she presented to, or the anesthesiologists assigned to his or her list, requires attention, especially in jurisdictions that already use low proportions of neuraxial anesthesia for hip fracture surgeries. In fact, this 2.3- to 2.4-fold difference in the probability of receiving a neuraxial anesthetic—attributable to hospitals or anesthesiologists—was more strongly tied to neuraxial anesthesia use than any single patient-level predictor other than receipt of an antiplatelet drug, which guidelines identify as a contraindication to neuraxial anesthesia for 7 days after the last dose.[32] Our findings of a strong influence of physician- and hospital-level factors on variation are also

consistent with other perioperative studies. For example, the median odds of testing and preoperative consultations vary 3-fold between physicians and hospitals before surgery;[5,33] odds of certain operative treatments for cancer may vary more than 2-fold between surgeons and hospitals.[34,35] Estimating variance from these median odds ratios suggests that in other perioperative settings, similar to our study, between 20 to 40% of variation may be explained by non–patient factors.

Reasons for this hospital- and anesthesiologist-level variation are likely multifactorial. First, although many guidelines do recommend the use of neuraxial anesthesia over general anesthesia for hip fracture surgery (including current guidelines in Ontario),[36–39] this is not true of all guidelines.[40] Furthermore, the evidence base supporting the superiority of neuraxial anesthesia *versus* general anesthesia is heterogeneous. This is consistent with existing evidence that demonstrates that variability is highest for therapies where there is limited consensus on what is superior.[41] What the evidence does suggest, however, is that unexplained variation is often associated with adverse patient outcomes. Therefore, strategies to address unexplained variation, including for hip fracture anesthesia care,[17] will need to consider all aspects of the healthcare system.

As we await the results of ongoing trials that may help to build consensus around best anesthesia practice for hip fracture surgery,[31] anesthesiologists should recognize that if future efforts are needed to change practice, we will need to address the local context, using strategies with proven efficacy to promote behavior change in these settings. Our data do provide some insights into areas of focus at the health system level, as teaching and low-volume hospitals were less likely to use neuraxial anesthesia. Hospitals that performed shorter surgeries on average were also less likely to use neuraxial anesthesia, with the effect size for the shortest surgery duration hospitals approximating that of some patient-level contraindications to neuraxial anesthesia, such as coagulopathy and metastatic cancer (odds ratio, 0.76 *vs.* 0.79 and 0.76, respectively). Mechanisms underlying this association will require further study, as the effect of expected case duration was relatively large, would be influenced by a multitude of patient-, physician-, and hospital-level factors, and as the limited data available (which comes from elective hip surgery) suggests an association between use of neuraxial anesthesia and *decreased* time in the operating room.[42] However, health administrative data do not provide a complete and granular description of hospital characteristics. Similarly, while the anesthesiologists with the highest case volumes tended to use more neuraxial anesthesia, we had limited ability to capture anesthesiologist-level variables, and had no data on the beliefs or intentions of anesthesiologists, which may strongly influence practice patterns.[43] Future research will be needed to provide an accurate and in-depth understanding of the specific contributors to hospital- and physician-level anesthesia practice, as this should allow mapping of evidence-based change strategies to identified barriers.

Finally, at the patient level, the significant predictors of neuraxial anesthesia use were not surprising. Older patients

and patients with a higher expected risk of death were more likely to receive a neuraxial anesthesia, while patients with comorbidities associated with abnormal coagulation status (such as liver disease, blood loss anemia, coagulopathy, and dialysis), or who were on medications that interfere with coagulation (such as anticoagulants and antiplatelet agents) were less likely to receive a neuraxial anesthesia. Chronic obstructive pulmonary disease and its associated therapies (inhaled bronchodilators and corticosteroids) were positive predictors of neuraxial anesthesia use, which may reflect a belief and evidence that postoperative pulmonary complications are reduced when neuraxial anesthesia is used.[44] Conditions that may make placement of a neuraxial anesthesia more challenging (obesity, rheumatic disease, metastatic cancer) or that may increase the risk of adverse hemodynamic consequences (cardiac valvular disease) were also negative predictors. Finally, it is important to note that female patients were less likely to receive a neuraxial anesthesia, which suggests that there may be gender inequalities in the provision of perioperative hip fracture care.

Strengths and Limitations

This study features several strengths. Our use of population-based health administrative data allowed us to study practice across a single health system that cares for a population of more than 13 million people. Furthermore, our exposures and outcomes were defined using variables that have been reabstracted to ensure their accuracy and reliability. We were also able to consider hospital- and physician-level predictors of practice variation in addition to simply measuring attributable variation. The limitations of this study should also be considered. Health administrative data are not initially collected for research purposes. Most important, while we were able to account for measured predictors, there are patient-level predictors (such as physiologic, laboratory, cognitive, and functional measures, as well as acute delirium and level of consciousness), hospital-level variables, and specific anesthesiologist variables (such as fellowship training in regional anesthesia or experience with neuraxial techniques) that we could not measure directly. While we did include a variable reflecting the average operating time in each hospital, surgeon-specific variables, (which we could not capture) such as preference for neuraxial anesthesia *versus* general anesthesia and the specific impact of each surgeon on expected duration of surgery, could influence anesthesia decision making and should be considered when available. Patient-preference should contribute to warranted variation, and we had no ability to measure this attribute. While we were unable to identify any existing studies of patient preference for anesthesia type in hip fracture surgery, patients do have varying preferences around other aspects of their hip fracture care.[45–47] The generalizability of our findings to other jurisdictions is uncertain.

Conclusion

Sixty percent of variation in the provision of neuraxial anesthesia for hip fracture surgery may be warranted, as it is attributable to patient factors. However, approximately 20% of variation is attributable to each of the specific hospital and anesthesiologist. Combined with previous research demonstrating that low hospital-level use of neuraxial anesthesia for hip fracture surgery is associated with decreased risk-adjusted survival, our findings suggest that changing patterns of hip fracture anesthesia care will need to address hospital-level processes and anesthesiologists' behaviors and intentions.

References

1. Corallo AN, Croxford R, Goodman DC, Bryan EL, Srivastava D, Stukel TA: A systematic review of medical practice variation in OECD countries. Health Policy 2014; 114:5–14
2. Mercuri M, Gafni A: Medical practice variations: What the literature tells us (or does not) about what are warranted and unwarranted variations. J Eval Clin Pract 2011; 17:671–7
3. McPherson K, Wennberg JE, Hovind OB, Clifford P: Small-area variations in the use of common surgical procedures: An international comparison of New England, England, and Norway. N Engl J Med 1982; 307:1310–4
4. Dalton JE, Zidar DA, Udeh BL, Patel MR, Schold JD, Dawson NV: Practice variation among hospitals in revascularization therapy and its association with procedure-related mortality. Med Care 2016; 54:623–31
5. Wijeysundera DN, Austin PC, Beattie WS, Hux JE, Laupacis A: Variation in the practice of preoperative medical consultation for major elective noncardiac surgery: A population-based study. ANESTHESIOLOGY 2012; 116:25–34
6. Brauer CA, Coca-Perraillon M, Cutler DM, Rosen AB: Incidence and mortality of hip fractures in the United States. JAMA 2009; 302:1573–9

7. Number, percentage and average acute length of stay for top 10 high-volume inpatient surgeries by province/territory, HMDB, 2015–2016. Ottawa, ON, 2017. https://www.cihi.ca/en/quick-stats

8. Radcliff TA: Patient risk factors, operative care, and outcomes among older community-dwelling male veterans with hip fracture. J Bone Jt Surg 2008; 90:34

9. National Hip Fracture Database annual report 2017. London, 2017. http://nhfd.co.uk/files/2017ReportFiles/NHFD-AnnualReport2017.pdf

10. Neuman MD, Rosenbaum PR, Ludwig JM, Zubizarreta JR, Silber JH: Anesthesia technique, mortality, and length of stay after hip fracture surgery. JAMA 2014; 311:2508–17

11. National Hip Fracture Database Anaesthesia Sprint Audit of Practice. London, 2014. https://www.aagbi.org/sites/default/files/NHFD anaesthestic report.pdf.

12. McIsaac DI, Wijeysundera DN, Huang A, Bryson GL, van Walraven C: Association of hospital-level neuraxial anesthesia use for hip fracture surgery with outcomes: A population-based cohort study. ANESTHESIOLOGY 2018; 128:480–91

13. Guay J, Parker MJ, Gajendragadkar PR, Kopp S: Anaesthesia for hip fracture surgery in adults. Cochrane Database of Systematic Reviews Edited by Guay J. Chichester, UK, John Wiley & Sons, Ltd, 2016 doi:10.1002/14651858.CD000521.pub3

14. Neuman MD, Silber JH, Elkassabany NM, Ludwig JM, Fleisher LA: Comparative effectiveness of regional *versus* general anesthesia for hip fracture surgery in adults. ANESTHESIOLOGY 2012; 117:72–92

15. Nordström P, Gustafson Y, Michaëlsson K, Nordström A: Length of hospital stay after hip fracture and short term risk of death after discharge: a total cohort study in Sweden. BMJ 2015; 350:h696

16. Patorno E, Neuman MD, Schneeweiss S, Mogun H, Bateman BT: Comparative safety of anesthetic type for hip fracture surgery in adults: retrospective cohort study. BMJ 2014; 348:g4022

17. White SM, Griffiths R, Moppett IK: Standardising anaesthesia for hip fracture surgery. Anaesthesia 2016; 71:1391–5

18. Vision and Mandate. http://www.cihi.ca/CIHI-ext-portal/internet/EN/SubTheme/about+cihi/vision+and+mandate/cihi010703.

19. About Us. http://www.ices.on.ca/webpage.cfm?site_id=1&org_id=26.

20. Elm E von, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP: Strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. BMJ 2007; 335:806–8

21. Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM; RECORD Working Committee: The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. PLoS Med 2015; 12:e1001885

22. Technical Note: Wait Time for Hip Fracture Surgery Technical Note. Ottawa, ON. https://www.cihi.ca/en/health-system-performance/performance-reporting/indicators/technical-note-wait-time-for-hip-fracture.

23. Juurlink DN, Croxford R, Chong A, Austin P, Tu J, Laupacis A: Canadian Institute for Health Information Discharge Abstract Database : A Validation Study ICES Investigative Report, June 2006. Canadian Institute for Health Information, 2006. https://www.ices.on.ca/Publications/Atlases-and-Reports/2006/Canadian-Institute-for-Health-Information

24. Richards J, Brown A, Homan C: The data quality study of the canadian discharge abstract database. Proc Stat Canada Symp 2001

25. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, Saunders LD, Beck CA, Feasby TE, Ghali WA: Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005; 43:1130–9

26. Walraven C van, McAlister FA, Bakal JA, Hawken S, Donzé J: External validation of the Hospital-patient One-year Mortality Risk (HOMR) model for predicting death within 1 year after hospital admission. CMAJ 2015; 187:725–33

27. Austin PC: Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. Commun Stat - Simul Comput 2009; 38:1228–34

28. Merlo J, Chaix B, Ohlsson H, Beckman A, Johnell K, Hjerpe P, Råstam L, Larsen K: A brief conceptual tutorial of multilevel analysis in social epidemiology: Using measures of clustering in multilevel logistic regression to investigate contextual phenomena. J Epidemiol Community Health 2006; 60:290–7

29. Austin PC, Wagner P, Merlo J: The median hazard ratio: A useful measure of variance and general contextual effects in multilevel survival analysis doi:10.1002/sim.7188

30. Bilimoria KY, Liu Y, Paruch JL, Zhou L, Kmiecik TE, Ko CY, Cohen ME: Development and evaluation of the universal ACS NSQIP surgical risk calculator: A decision aid and informed consent tool for patients and surgeons. J Am Coll Surg 2013; 217:833–42.e1–3

31. Neuman MD, Ellenberg SS, Sieber FE, Magaziner JS, Feng R, Carson JL; REGAIN Investigators: Regional *versus* General Anesthesia for Promoting Independence after Hip Fracture (REGAIN): Protocol for a pragmatic, international multicentre trial. BMJ Open 2016; 6:e013473

32. Horlocker TT, Wedel DJ, Rowlingson JC, Enneking FK, Kopp SL, Benzon HT, Brown DL, Heit JA, Mulroy MF, Rosenquist RW, Tryba M, Yuan CS: Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition). Reg Anesth Pain Med 2010; 35:64–101

33. Chen CL, Lin GA, Bardach NS, Clay TH, Boscardin WJ, Gelb AW, Maze M, Gropper MA, Dudley RA: Preoperative medical testing in Medicare patients undergoing cataract surgery. N Engl J Med 2015; 372:1530–8

34. Rhoads KF, Ackerson LK, Ngo JV, Gray-Hazard FK, Subramanian SV, Dudley RA: Adequacy of lymph node examination in colorectal surgery: Contribution of the hospital *versus* the surgeon. Med Care 2013; 51:1055–62

35. Katz SJ, Hawley ST, Hamilton AS, Ward KC, Morrow M, Jagsi R, Hofer TP: Surgeon influence on variation in receipt of contralateral prophylactic mastectomy for women with breast cancer. JAMA Surg 2018; 153:29–36

36. Quality-Based Procedures Clinical Handbook for Hip Fractures. Toronto, 2013. http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations/clinical-handbooks.

37. Mak JC, Cameron ID, March LM; National Health and Medical Research Council: Evidence-based guidelines for the management of hip fractures in older persons: An update. Med J Aust 2010; 192:37–41

38. Management of hip fracture in older people. National clinical guideline 111. Edinburgh, 2009. http://www.sign.ac.uk/pdf/

39. Griffiths R, Alper J, Beckingsale A, Goldhill D, Heyburn G, Holloway J, Leaper E, Parker M, Ridgway S, White S, Wiese M, Wilson I: Management of proximal femoral fractures 2011. Anaesthesia 2012; 67:85–98

40. Management of hip fractures in the elderly: Evidence-based clinical practice guidelines. Rosemont, Illinois, 2015. https://www.aaos.org/cc_files/aaosorg/research/guidelines/hip-fxguideline.pdf.

41. Wennberg JE: Dealing with medical practice variations: A proposal for action. Health Aff (Millwood) 1984; 3:6–32

42. Basques BA, Toy JO, Bohl DD, Golinvaux NS, Grauer JN: General compared with spinal anesthesia for total hip arthroplasty. J Bone Joint Surg Am 2015; 97:455–61

43. Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PA, Rubin HR: Why don't physicians follow clinical practice guidelines? A framework for improvement. JAMA 1999; 282:1458–65

44. Hausman MS Jr, Jewell ES, Engoren M: Regional *versus* general anesthesia in surgical patients with chronic obstructive pulmonary disease: Does avoiding general anesthesia reduce the risk of postoperative complications? Anesth Analg 2015; 120:1405–12

45. Neuman MD, Ibrahim SA, Barg FA, Osigwe C, Karlawish JH: Race and patient preferences for hip fracture care. J Am Geriatr Soc 2013; 61:468–70

46. Alolabi N, Alolabi B, Mundi R, Karanicolas PJ, Adachi JD, Bhandari M: Surgical preferences of patients at risk of hip fractures: Hemiarthroplasty *versus* total hip arthroplasty. BMC Musculoskelet Disord 2011; 12:289

47. Aggarwal A, Harris IA, Naylor JM: Patient preferences for emergency or planned hip fracture surgery: A cross-sectional study. J Orthop Surg Res 2016; 11:120

ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Warding Off Quacks: Ward's Laudanum in Pittsburgh
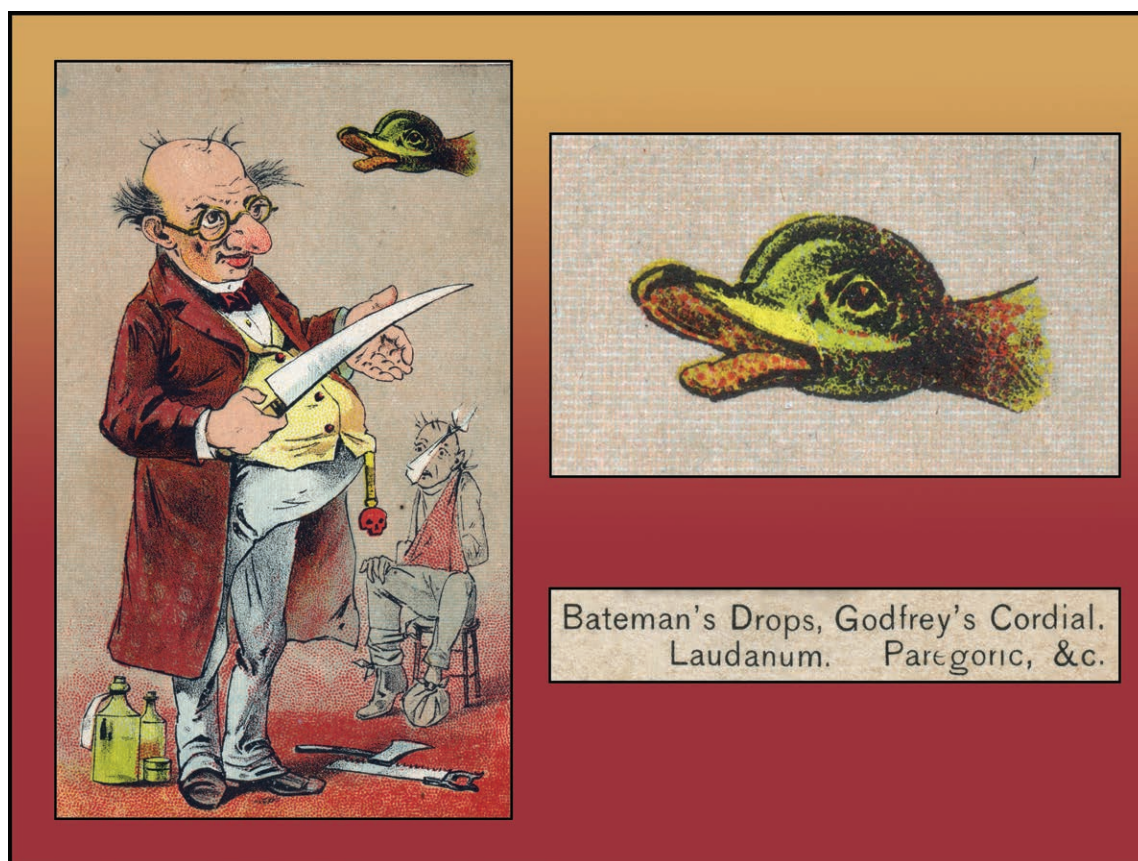
Apprenticing with his pharmacist father in Pittsburgh, Pennsylvania, Robert Egbert Sumner Ward (1857 to 1936) sold laudanum as an antitussive, as an antidiarrheal, and even as an adjuvant to inhaled anesthetics. One of Ward's more popular trade cards (*left*) depicted a charlatan eyeing another quack (*upper right*, the head of a mallard drake) while testing the edge of an amputating knife. At the charlatan's feet are a hatchet, a saw, and scattered bottles. On the reverse of the trade card, druggist Ward advertised alcoholic tincture of opium (Laudanum) as well as variations of that product combined with extra alcohol, camphor, or sweet syrup (Bateman's Drops, Paregoric, or Godfrey's Cordial, respectively). Alongside all of these over-the-counter opiates, Ward advertised his culinary wares, including essences of peppermint, cinnamon, and ginger and "flavoring extracts of vanilla, lemon, &c." By 1887 the druggist was devoting more of his time to selling baker's supplies than to peddling opiates. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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Ultrasound Is Superior to Palpation in Identifying the Cricothyroid Membrane in Subjects with Poorly Defined Neck Landmarks

A Randomized Clinical Trial

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ABSTRACT

Background: Success of a cricothyrotomy is dependent on accurate identification of the cricothyroid membrane. The objective of this study was to compare the accuracy of ultrasonography *versus* external palpation in localizing the cricothyroid membrane.

Methods: In total, 223 subjects with abnormal neck anatomy who were scheduled for neck computed-tomography scan at University Health Network hospitals in Toronto, Canada, were randomized into two groups: external palpation and ultrasound. The localization points of the cricothyroid membrane determined by ultrasonography or external palpation were compared to the reference midpoint (computed-tomography point) of the cricothyroid membrane by a radiologist who was blinded to group allocation. Primary outcome was the accuracy in identification of the cricothyroid membrane, which was measured by digital ruler in millimeters from the computed-tomography point to the ultrasound point or external-palpation point. Success was defined as the proportion of accurate attempts within a 5-mm distance from the computed-tomography point to the ultrasound point or external-palpation point.

Results: The percentage of accurate attempts was 10-fold greater in the ultrasound than external-palpation group (81% *vs.* 8%; 95% CI, 63.6 to 81.3%; $P < 0.0001$). The mean (SD) distance measured from the external-palpation to computed-tomography point was five-fold greater than the ultrasound to the computed-tomography point (16.6 ± 7.5 *vs.* 3.4 ± 3.3 mm; 95% CI, 11.67 to 14.70; $P < 0.0001$). Analysis demonstrated that the risk ratio of inaccurate localization of the cricothyroid membrane was 9.14-fold greater with the external palpation than with the ultrasound ($P < 0.0001$). There were no adverse events observed.

Conclusions: In subjects with poorly defined neck landmarks, ultrasonography is more accurate than external palpation in localizing the cricothyroid membrane. (**ANESTHESIOLOGY 2018; 129:1132–9**)

AIRWAY management is an important skill required for acute care physicians, including intensivists, anesthesiologists, and emergency medicine physicians. Difficult airways remain a major challenge that can lead to serious adverse outcomes and death.[1,2] In rare life-threatening airway crises of "cannot intubate, cannot oxygenate," an emergency cricothyrotomy with the insertion of a breathing tube *via* the cricothyroid membrane is the only option.[3,4] When performing this potentially life-saving procedure, the first critical step is to palpate and correctly identify the cricothyroid membrane because its misidentification is a major cause of tube misplacements, leading to cricothyrotomy failures and serious complications.[2] However, accurate localization of the cricothyroid membrane using the conventional approach of external palpation is more challenging than anticipated where anesthesiologists, emergency medicine physicians, and trauma surgeons poorly localized the cricothyroid membrane.[4–7]

Editor's Perspective

What We Already Know about This Topic

- Accurate identification of the cricothyroid membrane is key for success of emergency cricothyrotomy
- Ultrasound has been reported to identify the cricothyroid membrane more accurately than external palpation in patients with normal neck anatomy

What This Article Tells Us That Is New

- In this randomized clinical trial, 223 adult patients with neck pathologies such as previous neck surgery, irradiation, and/or neck mass who were scheduled for a neck computed-tomography scan were randomly allocated to either the ultrasound group or the external-palpation group
- Accuracy in identification of the cricothyroid membrane, defined as the distance from a point determined by the computed tomography within 5 mm, was 10-fold greater in the ultrasound group (81%, n = 114) than the external-palpation group (8%, n = 109)

Ultrasonography has become increasingly important in the practice of anesthesia, emergency medicine, and critical care.[2] In particular, ultrasonography has been proven to increase success, decrease complications, and enhance patient safety when performing invasive procedures.[2] Increasing evidence has shown a role for ultrasonography of neck landmarks in airway management to accurately identify the cricothyroid membrane.[3–6,8] Conversely, the traditional method of external palpation poorly identified the cricothyroid membrane.[2] Although the majority of the studies comparing ultrasound and external palpation of the cricothyroid membrane were performed on patients with normal neck landmarks, little is known of their performance on patients with poorly defined neck anatomy, particularly in patients with previous neck surgery, neck mass, and/or neck irradiation.

We hypothesized that ultrasound is more accurate than external palpation in identifying the cricothyroid membrane when compared to the accepted standard, computed-tomography scan. The objective of this randomized clinical trial was to compare the accuracy of ultrasound *versus* external palpation in localizing the cricothyroid membrane in patients with poorly defined neck landmarks.

Materials and Methods

This prospective, single-center, single-blinded, randomized clinical trial was reviewed and approved by University Health Network Research Ethics Board (Toronto, Canada; approval No. 12-5327-BE). Written informed consent was obtained from all participants. Our trial is accessible on clinicaltrials.gov with the identifier NCT01725828. The modifications that were made to the protocol are reflected on clinicaltrials.gov.

The study was conducted on 223 American Society of Anesthesiologists physical status I to III patients at least 18 yr of age with neck pathology who were scheduled for a neck computed-tomography scan at University Health Network hospitals (Toronto, Canada) from October 2012 to July 2014. All patients recruited in the study had neck pathologies including previous neck surgery, irradiation, and/or neck mass. We excluded patients who were unable to lie flat, those who were unable to maintain a neutral neck position, and those who refused to participate in the study. The patients' characteristics were recorded, including age, sex, neck circumference, ability to extend the neck, history of previous surgery on the neck, thyromental distance, sternomental distance, and history of difficulty in airway management. Patients were approached by the admitting nurse in the waiting area of the computed-tomography scan suite at the University Health Network and asked about their willingness to participate in a research study. If the patient was willing to participate, detailed information about the study was provided by the research assistant, and informed written consent was obtained. Then the patients

were assessed for eligibility to participate in the study, and eligible patients were assigned to the study groups by the research assistant. The neck anatomy of each patient was assessed by an independent anesthesiologist for the degree of difficulty in identifying the landmarks according to an established grading system[2,6]: easy, visual landmarks; moderate, requires light palpation of landmarks; difficult, requires deep palpation of landmarks; and impossible, landmarks not palpable. Subjects with a score of moderate, difficult, and impossible landmarks were recruited for the study. All patients were randomized by the statistician using a computer-generated random number table for group allocation: external palpation and ultrasound. Randomization assignments were placed in sequentially numbered concealed envelopes. After performing the screening, the envelope was opened by the research assistant, and the patient was assigned to either the ultrasound group or the external-palpation group.

Assessment of the Cricothyroid Membrane
Assessment of the cricothyroid membrane using external palpation or ultrasound was performed by two anesthesia fellows (S.B. and Devdatta Desi, M.D., Research Associate, Department of Anesthesia and Pain Management, Mount Sinai Hospital, University of Toronto, Toronto, Canada) depending on their schedule availability.

External Palpation of the Cricothyroid Membrane. On the day of the computed-tomography scan, an anesthesia fellow (S.B. or D.D.) palpated the neck landmarks of patients in the external-palpation group and marked the anticipated entry point (external-palpation point) of a cricothyrotomy device using a radiopaque computed tomography–compatible sticker marker (ultrasound; SureMark Company, USA). The patients were supine with the neck in the same neutral position as in the computed-tomography scan. Identification of the cricothyroid membrane was performed using the index and third finger of the nondominant hand to palpate the thyroid cartilage in the midline starting from the cephalad and moving caudally to the cricothyroid cartilage.[2] The space between the inferior border of the thyroid cartilage and superior border of the cricoid cartilage is the cricothyroid membrane.

Ultrasonography of the Cricothyroid Membrane. The anesthesia fellows who were involved in the study received a 10-min didactic lecture followed by a 3-min video on the ultrasonographic and palpation techniques to identify the anatomical landmarks and the cricothyroid membrane. They were then given hands-on training at least five times with ultrasound.[2] Furthermore, both fellows had performed a minimum of 20 successful identifications of the cricothyroid membrane using external palpation and ultrasound, which is the required number to achieve competence in ultrasound identification of the cricothyroid membrane.[9] On the day of the computed-tomography scan, one of the anesthesia fellows who was available identified the cricothyroid membrane

of patients in the ultrasound group. The midpoint of the cricothyroid membrane (ultrasound point) was then marked with a SureMark sticker. Ultrasonography of the neck was performed as previously reported using the transverse and longitudinal approach as described by Kristensen[3] and Kristensen *et al.*[10] A portable ultrasound system with a 10- to 5-MHz linear-array transducer (Zonare Medical Systems, Inc., USA) was used for the ultrasound scans. Patients being scanned were positioned supine with the neck in the same neutral position as in the computed-tomography scan.

Computed-tomography Image of the Neck

The neck computed-tomography image of each patient was read by a radiologist staff member who was the only one blinded to the group allocation. The cricothyroid membrane was identified between the inferior border of the thyroid cartilage and superior border of the cricoid cartilage. The digital ruler of the computed-tomography scan was used to measure the horizontal (x-axis) and vertical (y-axis) distance (millimeters) of the cricothyroid membrane. The intersection of the horizontal and vertical axes is referred as the midpoint of the cricothyroid membrane (computed-tomography point).

Our primary outcome was the accuracy in identification of the cricothyroid membrane, which was measured by a digital ruler in millimeters from the computed-tomography point to the ultrasound point or external-palpation point. We defined success as the proportion of accurate attempts within a 5-mm distance from the computed-tomography point to the ultrasound point or external-palpation point.

The study was initially planned with the primary outcome as the absolute distance (millimeters) between the computed-tomography point to the external-palpation point and ultrasound point. Since 2015, there has been an increasing number of studies on ultrasound identification of the cricothyroid membrane, which defined accuracy as a distance of 5 mm or less.[2,4,7,11] Thus, we included the proportion of accurate attempts as a distance of 5 mm or less as a secondary outcome in the clinical trial registration in June 2018. Keeping the same objective and focusing on more clinical relevance, we reported the primary outcome as the proportion of accurate attempts within a 5-mm distance from the computed-tomography point to the ultrasound point or external-palpation point.

The distance of 5 mm or less is based on several studies measuring the dimensions of the cricothyroid membrane.[12,13] This is clinically relevant because a puncture outside this limit is likely to be outside the cricothyroid membrane vertical dimension and may result in cricothyrotomy failure and/or cause unnecessary tissue injuries.[12]

Our pilot data indicated a 50% success rate for accurate identification of the cricothyroid membrane by external palpation. Based on current literature and the data obtained from our previous studies, we hypothesized a 70% success rate for accurate identification of the cricothyroid membrane when using ultrasound. To demonstrate a 20% improvement

in the success rate at 80% power and a 5% significance level, a minimum number of 82 subjects was required in each of the experimental groups (external-palpation group and ultrasound group). To ensure sufficient power for the study, 109 patients were recruited to the external-palpation group, and 114 patients were recruited to the ultrasound group.

Statistical Analysis

The characteristics of each group were presented with frequencies and percentages for categorical variables and compared using the chi-square test. For continuous variables, means and SDs were presented and compared using independent two-sample *t* tests. Normal distribution was checked by examining the histograms. The statistical model was changed from a logistic regression model to a Poisson regression model to examine the rate of successful identification of the cricothyroid membrane and to calculate risk ratios. Possible confounders including body mass index, neck circumference, thyromental distance, sternomental distance ability to extend the neck, previous surgery on the neck, history of difficult intubation, and difficulty of manual identification were adjusted for the model. The distance from the target location was compared between the groups using a *t* test. SAS version 9.3 (SAS Institute, USA) was used for the statistical analysis. All *P* values were two-sided, and a value of *P* < 0.05 was considered statistically significant.

Results

In total, 340 subjects scheduled for a neck computed-tomography scan at University Health Network hospitals were assessed for eligibility. Of those 340, 117 subjects were excluded from the study. None of the participants were excluded from the study after randomization. However, patients who were unable to lie flat, those who were unable to maintain a neutral neck position, and those who refused to participate in the study were excluded at the time of recruitment. A total of 223 patients with poorly defined neck landmarks completed the study, with 109 and 114 patients randomized to the external-palpation and ultrasound groups, respectively (fig. 1). More than half of the patients in each group had previous neck surgery (table 1). The patients' characteristics were similar between groups except for a statistically significant difference in body mass index (table 1). Before the localization of the cricothyroid membrane, the degree of difficulty in palpating the neck landmarks was evaluated for each patient. Table 1 showed that the distribution of patients with various degrees of difficulty was similar between the groups. The localization points of the cricothyroid membrane determined by ultrasonography (ultrasound point) and external palpation (external-palpation point) were compared to the reference midpoint (computed-tomography point) of the cricothyroid membrane identified by computed-tomography scan. Figure 2 shows that the majority of the localization points identified by ultrasound were within 5 mm of the reference computed-tomography
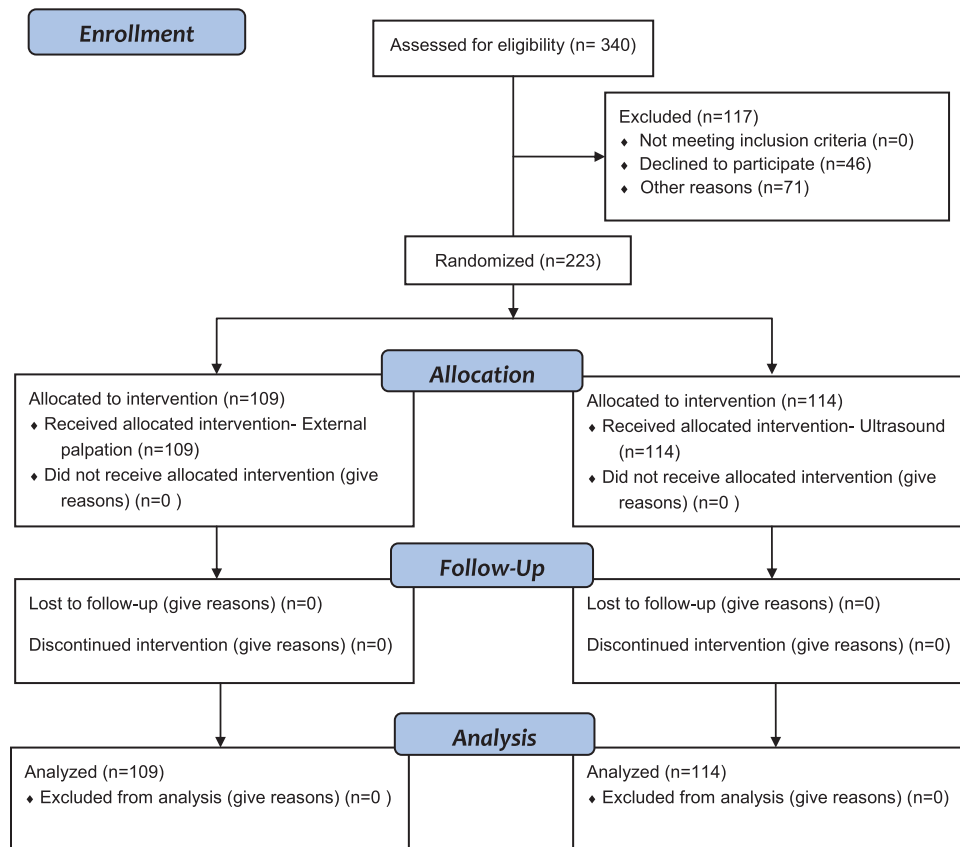
Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram showing participant flow through each stage of the randomized controlled trial (enrollment, intervention allocation, follow-up, and data analysis).

Table 1. Characteristics Comparison between the Two Groups

Variable	External Palpation (N = 109)	Ultrasound (N = 114)	P value
Male, No. (%)	71 (65%)	72 (63%)	0.758
Age, mean ± SD	57.4 (14.9)	57.0 (13.7)	0.800
Weight, mean ± SD, kg	75.2 (16.7)	72.2 (17.2)	0.185
Height, mean ± SD, cm	170 (12)	171 (9)	0.296
Body mass index, mean ± SD	26.1 (4.7)	24.6 (5.2)	0.020
Neck circumference, mean ± SD, cm	38.5 (3.9)	37.6 (5.0)	0.129
Thyromental distance, mean ± SD, cm	8.0 (1.1)	8.0 (1.4)	0.934
Sternomental distance, mean ± SD, cm	14.9 (2.0)	15.0 (1.8)	0.683
Ability to extend neck, No. (%)	101 (93)	100 (88)	0.216
Previous surgery on neck, No. (%)	60 (55)	59 (52)	0.622
History of difficult intubation, No. (%)	7 (6)	5 (4)	0.501
Difficulty of manual cricothyroid membrane identification, No. (%)			0.088
Impossible	15 (14)	6 (5)	
Difficult	29 (17)	36 (32)	
Moderate	65 (60)	72 (63)	

point, contrasting with a more scattered distribution of the localization points identified by external palpation. Our primary outcome was the accuracy in identification of the cricothyroid membrane, which was measured by a digital ruler in millimeters from the computed-tomography point to the ultrasound point or external-palpation point. We defined

success as the proportion of accurate attempts within a 5-mm distance from the computed-tomography point to the ultrasound point or external-palpation point. The percentage of accurate attempts, defined as a distance of 5 mm or less, was 10-fold greater in the ultrasound than external-palpation group (81% *vs.* 8%; 95% CI, 63.6 to 81.3%; $P < 0.0001$).
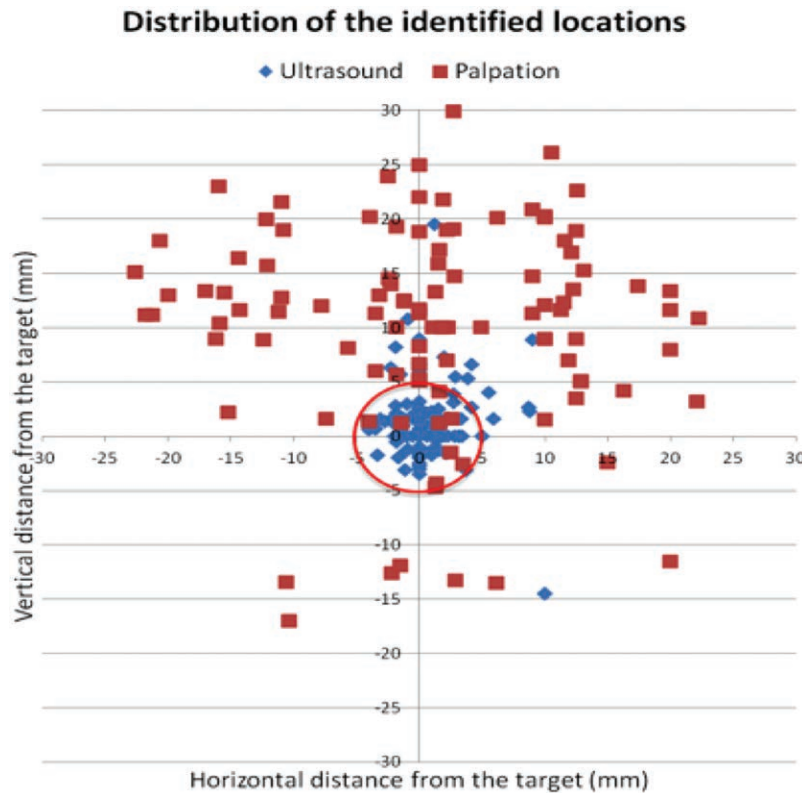
Fig. 2. The distribution of the identified locations in both groups based on vertical and horizontal 5-mm distance from the computer-tomography scan–identified midpoint as the reference.

Table 2. Assessment of the Cricothyroid Membrane between Ultrasound and External-palpation Groups

Assessment	Palpation (N = 109)	Ultrasound (N = 114)	Difference (95% CI)	P value
x-Axis, mean ± SD	1.3 (11.1)	0.8 (2.6)	0.47 (–1.63, 2.57)	0.667
y-Axis, mean ± SD	10.6 (9.8)	1.4 (3.6)	9.19 (7.26, 11.12)	< 0.0001
Distance from the target, mean ± SD	16.6 (7.5)	3.4 (3.3)	13.18 (11.67, 14.70)	< 0.0001
Distance from the target ≤5 mm (%)	9 (8%)	92 (81%)	72.4% (63.6%, 81.3%)	< 0.0001

The mean ± SD distance measured from the external palpation to the computed-tomography point was five-fold greater than the ultrasound to computed-tomography point (16.6 ± 7.5 *vs.* 3.4 ± 3.3 mm; 95% CI, 11.67 to 14.70; *P* < 0.0001; table 2). Poisson regression analysis demonstrated that the risk ratio of inaccurate localization of the cricothyroid membrane was 9.14-fold greater with the external palpation than with the ultrasonography (*P* < 0.0001; table 3). Because both ultrasound and external-palpation techniques are minimally invasive, we did not observe any adverse events in our trial.

Discussion

The primary outcome of this clinical trial was the accuracy in identification of the cricothyroid membrane, which was measured by a digital ruler in millimeters from the computed-tomography point to the ultrasound point or external-palpation point. We defined success as the proportion of accurate attempts within a 5-mm distance from the computed-tomography point to the ultrasound point or external-palpation point.

In this trial, ultrasonography was significantly more accurate than external palpation in localizing the cricothyroid membrane of patients with poorly defined neck landmarks. Furthermore, ultrasonography was highly accurate in localizing the cricothyroid membrane as identified with computed-tomography scan, the accepted standard.

An important finding of our study is the high accuracy of ultrasound (81% *vs.* 8%; 95% CI, 63.6 to 81.3%; *P* < 0.0001; table 3). This is consistent with previous studies looking at ultrasound accuracy with regard to the cricothyroid membrane. Kristensen *et al.*[14] showed an 83% success rate of ultrasound-guided identification of the cricothyroid membrane in morbidly obese females with poorly palpable neck landmarks. Other studies demonstrated a

Table 3. Poisson Regression Model with Successful Identification

Effect	Reference	Risk Ratio	95% CI for Risk Ratio		P value
Ultrasound	Palpation	9.14	4.88	17.13	< 0.0001
Body mass index		1.00	0.98	1.03	0.795
Neck circumference		0.98	0.96	1.00	0.062
Thyromental distance		1.02	0.95	1.10	0.624
Sternomental distance		0.94	0.88	1.02	0.139
Ability to extend neck		0.85	0.62	1.17	0.323
Previous surgery		0.90	0.71	1.15	0.413
History of difficult intubation		0.65	0.39	1.06	0.084
Manual identification					
Difficult	Moderate	1.10	0.85	1.43	0.474
Impossible	Moderate	0.51	0.20	1.28	0.150

Successful identification is defined as within 5 mm of the computer-tomography scan–identified spot.

100% identification of the cricothyroid membrane with ultrasonography in obese nonpregnant[8] and obese pregnant subjects.[4] Although ultrasonography can accurately localize the cricothyroid membrane, there is a paucity of evidence to assess its accuracy against computed-tomography scan as the accepted standard. Furthermore, we observed that the mean ± SD distance measured from the external-palpation point to the computed-tomography point was five-fold greater than from the ultrasound point to the computed-tomography point (16.6 ± 7.5 vs. 3.4 ± 3.3 mm; 95% CI, 11.67 to 14.70; P < 0.0001; table 2; fig. 2). These findings demonstrate that in subjects with neck pathology and poorly defined neck landmarks, ultrasonography is highly accurate in localizing the cricothyroid membrane and is comparable to computed-tomography scan as the accepted standard.

Accurate localization was defined as within less than 5 mm of the midpoint of the cricothyroid membrane as identified by computed-tomography scan. This value was based on the known dimensions of the cricothyroid membrane in human cadavers with a mean width of 8.2 mm with an upper limit of 11.0 mm and a mean height of 10.4 mm with an upper limit of 13.0 mm.[12] Although the 5-mm limit is arbitrary, the value is based on empirical data and is clinically relevant because a puncture within this limit is likely to occur at the recommended site of placement of cricothyrotomy devices to avoid injuries to the vocal cords,[12] whereas a puncture outside this limit may result in cricothyrotomy failure and/or unnecessary complications.

In contrast to ultrasonography, only 8% (9 of 109) of the points made by external palpation were accurate (table 2), with the majority of points located outside the upper limit of both the width and height of the cricothyroid membrane.[12] Moreover, the calculated mean ± SD distance of the points by external palpation was 16.6 ± 7.5 mm (table 2), which is beyond the upper dimensions of the cricothyroid membrane.[12]

Although other studies have demonstrated an accuracy rate of 30 to 71% in patients without neck pathology,[4,6,8,15] we observed a low accurate rate of only 8% in our population with neck pathology. Accurate identification of the cricothyroid membrane using external palpation is often more difficult than anticipated, even under elective conditions.[7,8,11] A study by Lamb et al.[11] showed that anesthesiologist staff and trainees had greater success rates in accurate cricothyroid membrane localization using external palpation in nonobese males (33 of 46, 71.7%) than females (11 of 45, 24.4%) without poor neck landmarks. It is likely that the prominent thyroid cartilage in males allows for the cricothyroid membrane to be more accurately localized.[11] In another study, Aslani et al.[8] reported success rates of 24.4% and 29.3% using external palpation in nonobese women with the neck placed in the neutral and extended positions, respectively. Furthermore, trauma surgeons with experience in surgical airways had a similar success rate of 26% in female volunteers.[7,16] In contrast to external palpation, these studies further demonstrated that ultrasound was successful in accurately localizing the cricothyroid membrane in all the subjects. These findings are concerning and might have important clinical implications in a life-threatening "cannot intubate, cannot oxygenate" situation, in which mislocalization of the cricothyroid membrane by external palpation in patients with neck pathology might lead to failed cricothyrotomies.

Our results may support the high failure rate of operating room emergency needle cricothyrotomies reported in the Fourth National Audit Project study, the largest clinical study on major airway complications of more than 2 million patients during general anesthesia.[17] Although many factors could cause the high failure rate, misidentification of the cricothyroid membrane using external palpation during an emergency cricothyrotomy might be a contributing factor, because 39% of patients in the aforementioned study have neck pathology that may make the cricothyroid membrane more difficult to localize.[17]

The use of ultrasonography in airway management is steadily increasing. Several difficult airway guidelines advocate the use of preprocedure ultrasound to identify the neck landmarks and the cricothyroid membrane before airway management in patients with difficult airways.[4,18] The American Society of Anesthesiologists Difficult Airway Algorithm categorizes a group of patients with "difficult

surgical access."[18] Although the specifics of this patient population are not stated, our findings suggest that neck pathology creates a challenge for identifying neck landmarks by external palpation. Premarking the cricothyroid membrane with ultrasonography in patients with neck pathology could theoretically improve success of a cricothyrotomy and reduce complications when performing this high-stakes procedure.

In a study on human cadavers with poorly defined neck landmarks, Siddiqui *et al.*[2] showed a significantly greater success rate of cricothyrotomy and a three-fold reduction in complications with ultrasound identification compared to external palpation of the cricothyroid membrane. Dinsmore *et al.*[15] demonstrated a significant increase in success rate and a significant decrease in procedure time of cannula tracheotomy using ultrasound-guided compared to non–ultrasound-guided cannula placement in a model with simulated unidentifiable anterior neck anatomy. Furthermore, ultrasound guidance has been shown to facilitate successful puncture between tracheal rings in eight of nine cadavers at the first attempt.[19]

In addition, a limited number of reported clinical cases appear to support the potential value of preprocedural ultrasound. Muhammad *et al.*[20] described four case reports in which ultrasound helped to identify aberrant anatomical variations to safely perform percutaneous tracheostomy or elective open tracheostomy. In a morbidly obese patient with impalpable neck landmarks, tracheostomy was successfully performed under ultrasound guidance.[21] Another case report described that preprocedural ultrasound identification of the cricothyroid membrane resulted in prompt and successful emergency cricothyroidotomy without complications. This was after multiple failed attempts at awake fiberoptic intubation in a patient with airway swelling and impossible neck landmarks secondary to von Recklinghausen disease.[22] Ultrasonography has been proven to increase success, decrease complications, and enhance patient safety when performing invasive procedures.[23] Our study, together with previous reports, suggest the potential role of ultrasound in improving the success and minimizing the complications of performing a cricothyrotomy when the cricothyroid membrane is premarked, particularly in patients with neck pathologies in which the neck landmarks and cricothyroid membrane are poorly defined.

In a study performed on obese laboring patients, increased neck circumference was an independent risk factor for poor accuracy in localizing the cricothyroid membrane using external palpation,[4] which was inconsistent with the finding of our study. Underlying tissue responsible for increasing neck circumference does not appear to affect ultrasound localization of the cricothyroid membrane, and several studies reported accurate cricothyroid membrane localization with ultrasound of obese and morbidly obese volunteers with increased neck circumference.[4,6,8]

Our study has several limitations. The cricothyroid membrane was assessed on patients in the neutral neck position. Location of the cricothyroid membrane is variable depending on the position of the neck,[8] and a less than ideal neutral neck position could have affected the accuracy of the cricothyroid membrane. However, a donut-shaped pillow was used to minimize head movement and maintained the neck in the neutral position during computed-tomography scan. The cricothyroid membrane was identified by two study investigators (D.D., S.B.) using ultrasonography and external palpation. The homogeneity of the assessors could bias the outcomes through learning with repeated assessments. However, this did not appear to be the case because the proportion of accurate points by external palpation was only 8% (9 of 109). Although the two assessors were anesthesia fellows, evidence suggests that clinical experience did not appear to affect the performance in localizing the cricothyroid membrane using external palpation. Such evidence includes a number of studies in which staff anesthesiologists, emergency physicians, surgeons, and anesthesia residents performed equally poorly in localizing the cricothyroid membrane.[5–7]

In conclusion, for patients with neck pathology and poorly defined neck anatomy, ultrasound was significantly more accurate than external palpation in localizing the cricothyroid membrane. In addition, ultrasonography was highly accurate in localizing the cricothyroid membrane identified with computed-tomography scan as the accepted standard. These results support the use of ultrasonography over the conventional approach of external palpation for the prelocalization of the cricothyroid membrane in patients with neck pathology before airway management in anticipation of difficult airways. Our results are widely generalizable to the population who might have history of difficult intubation, surgery on the neck, neck mass, and neck irradiation.

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Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available at: naveed.siddiqui@uhn.ca. Raw data available at: naveed.siddiqui@uhn.ca.

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References

1. Kristensen MS, Teoh WH, Graumann O, Laursen CB: Ultrasonography for clinical decision-making and intervention in airway management: From the mouth to the lungs and pleurae. Insights Imaging 2014; 5:253–79

2. Siddiqui N, Arzola C, Friedman Z, Guerina L, You-Ten KE: Ultrasound improves cricothyrotomy success in cadavers with poorly defined neck anatomy: A randomized control trial. ANESTHESIOLOGY 2015; 123:1033–41

3. Kristensen MS: Ultrasonography in the management of the airway. Acta Anaesthesiol Scand 2011; 55:1155–73

4. You-Ten KE, Desai D, Postonogova T, Siddiqui N: Accuracy of conventional digital palpation and ultrasound of the cricothyroid membrane in obese women in labour. Anaesthesia 2015; 70:1230–4

5. Elliott DS, Baker PA, Scott MR, Birch CW, Thompson JM: Accuracy of surface landmark identification for cannula cricothyroidotomy. Anaesthesia 2010; 65:889–94

6. Nicholls SE, Sweeney TW, Ferre RM, Strout TD: Bedside sonography by emergency physicians for the rapid identification of landmarks relevant to cricothyrotomy. Am J Emerg Med 2008; 26:852–6

7. Hiller KN, Karni RJ, Cai C, Holcomb JB, Hagberg CA: Comparing success rates of anesthesia providers *versus* trauma surgeons in their use of palpation to identify the cricothyroid membrane in female subjects: A prospective observational study. Can J Anaesth 2016; 63:807–17

8. Aslani A, Ng SC, Hurley M, McCarthy KF, McNicholas M, McCaul CL: Accuracy of identification of the cricothyroid membrane in female subjects using palpation: An observational study. Anesth Analg 2012; 114:987–92

9. Oliveira KF, Arzola C, Ye XY, Clivatti J, Siddiqui N, You-Ten KE: Determining the amount of training needed for competency of anesthesia trainees in ultrasonographic identification of the cricothyroid membrane. BMC Anesthesiol 2017; 17:74

10. Kristensen MS, Teoh WH, Rudolph SS, Hesselfeldt R, Børglum J, Tvede MF: A randomised cross-over comparison of the transverse and longitudinal techniques for ultrasound-guided identification of the cricothyroid membrane in morbidly obese subjects. Anaesthesia 2016; 71:675–83

11. Lamb A, Zhang J, Hung O, Flemming B, Mullen T, Bissell MB, Arseneau I: Accuracy of identifying the cricothyroid membrane by anesthesia trainees and staff in a Canadian institution. Can J Anaesth 2015; 62:495–503

12. Dover K, Howdieshell TR, Colborn GL: The dimensions and vascular anatomy of the cricothyroid membrane: Relevance to emergent surgical airway access. Clin Anat 1996; 9:291–5

13. Boon JM, Abrahams PH, Meiring JH, Welch T: Cricothyroidotomy: A clinical anatomy review. Clin Anat 2004; 17:478–86

14. Kristensen MS, Teoh WH, Rudolph SS, Tvede MF, Hesselfeldt R, Børglum J, Lohse T, Hansen LN: Structured approach to ultrasound-guided identification of the cricothyroid membrane: A randomized comparison with the palpation method in the morbidly obese. Br J Anaesth 2015; 114:1003–4

15. Dinsmore J, Heard AM, Green RJ: The use of ultrasound to guide time-critical cannula tracheotomy when anterior neck airway anatomy is unidentifiable. Eur J Anaesthesiol 2011; 28:506–10

16. Law JA: Deficiencies in locating the cricothyroid membrane by palpation: We can't and the surgeons can't, so what now for the emergency surgical airway? Can J Anaesth 2016; 63:791–6

17. Cook TM, Woodall N, Frerk C; Fourth National Audit Project: Major complications of airway management in the UK: Results of the Fourth National Audit Project of the Royal College of Anaesthetists and the Difficult Airway Society: Part 1. Anaesthesia. Br J Anaesth 2011; 106:617–31

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

19. Kleine-Brueggeney M, Greif R, Ross S, Eichenberger U, Moriggl B, Arnold A, Luyet C: Ultrasound-guided percutaneous tracheal puncture: A computer-tomographic controlled study in cadavers. Br J Anaesth 2011; 106:738–42

20. Muhammad JK, Major E, Wood A, Patton DW: Percutaneous dilatational tracheostomy: Haemorrhagic complications and the vascular anatomy of the anterior neck. A review based on 497 cases. Int J Oral Maxillofac Surg 2000; 29:217–22

21. Sustić A, Zupan Z, Antoncić I: Ultrasound-guided percutaneous dilatational tracheostomy with laryngeal mask airway control in a morbidly obese patient. J Clin Anesth 2004; 16:121–3

22. Owada G, Inagawa G, Nakamura K, Kariya T, Goto T: [Usefulness of ultrasound pre-scanning for cricothyroid membrane puncture in a patient with rupture of a pseudoaneurysm]. Masui 2014; 63:77–80

23. Dinh VA, Farshidpanah S, Lu S, Stokes P, Chrissian A, Shah H, Giri P, Hecht D, Nguyen HB: Real-time sonographically guided percutaneous dilatational tracheostomy using a long-axis approach compared to the landmark technique. J Ultrasound Med 2014; 33:1407–15

Oropharyngeal Bacterial Colonization after Chlorhexidine Mouthwash in Mechanically Ventilated Critically Ill Patients

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ABSTRACT

Background: Oropharyngeal care with chlorhexidine to prevent ventilator-associated pneumonia is currently questioned, and exhaustive microbiologic data assessing its efficacy are lacking. The authors therefore aimed to study the effect of chlorhexidine mouthwash on oropharyngeal bacterial growth, to determine chlorhexidine susceptibility of these bacteria, and to measure chlorhexidine salivary concentration after an oropharyngeal care.

Methods: This observational, prospective, single-center study enrolled 30 critically ill patients under mechanical ventilation for over 48 h. Oropharyngeal contamination was assessed by swabbing the gingivobuccal sulcus immediately before applying 0.12% chlorhexidine with soaked swabs, and subsequently at 15, 60, 120, 240, and 360 min after. Bacterial growth and identification were performed, and chlorhexidine minimal inhibitory concentration of recovered pathogens was determined. Saliva was collected in 10 patients, at every timepoint, with an additional timepoint after 30 min, to measure chlorhexidine concentration.

Results: Two hundred fifty bacterial samples were analyzed and identified 48 pathogens including *Streptococci* (27.1%) and Enterobacteriaceae (20.8%). Oropharyngeal contamination before chlorhexidine mouthwash ranged from 10^3 to 10^7 colony-forming units (CFU)/ml in the 30 patients (median contamination level: $2.5 \cdot 10^6$ CFU/ml), and remained between $8 \cdot 10^5$ (lowest) and $3 \cdot 10^6$ CFU/ml (highest count) after chlorhexidine exposure. These bacterial counts did not decrease overtime after chlorhexidine mouthwash (each minute increase in time resulted in a multiplication of bacterial count by a coefficient of 1.001, $P = 0.83$). Viridans group streptococci isolates had the lowest chlorhexidine minimal inhibitory concentration (4 [4 to 8] mg/l); Enterobacteriaceae isolates had the highest ones (32 [16 to 32] mg/l). Chlorhexidine salivary concentration rapidly decreased, reaching 7.6 [1.8 to 31] mg/l as early as 60 min after mouthwash.

Conclusions: Chlorhexidine oropharyngeal care does not seem to reduce bacterial oropharyngeal colonization in critically ill ventilated patients. Variable chlorhexidine minimal inhibitory concentrations along with low chlorhexidine salivary concentrations after mouthwash could explain this ineffectiveness, and thus question the use of chlorhexidine for ventilator-associated pneumonia prevention. (ANESTHESIOLOGY 2018; 129:1140-8)

MILLIONS of patients undergo mechanical ventilation in intensive care units throughout the world yearly. Recent estimates suggest that these numbers will only increase.[1] These patients are exposed, among other risks, to the one of ventilator-associated pneumonia, the most frequent life-threatening nosocomial infection.[2,3] Bacterial oropharyngeal colonization is the first recognized step toward tracheal colonization, which subsequently leads to ventilator-associated pneumonia. This has stemmed from many studies evidencing the temporal and microbiologic relationship between oropharyngeal and tracheal colonization and ventilator-associated pneumonia.[4–6]

Editor's Perspective

What We Already Know about This Topic

- Chlorhexidine is frequently used to reduce oropharyngeal bacterial colonization in mechanically ventilated patients. How effective the drug is remains unclear.

What This Article Tells Us That Is New

- Bacterial colonization was evaluated in 30 mechanically ventilated patients before and after application of 0.12% chlorhexidine.
- Chlorhexidine did not reduce colonization and may, therefore, be less effective than previously assumed.

This universal understanding of the pathophysiology of ventilator-associated pneumonia has formed the basis of oropharyngeal decontamination. Three distinct classes of agents including nonabsorbable antibiotics,[7–10] antiseptics (mainly chlorhexidine),[11–20] and natural antimicrobial peptides[21] have been evaluated in several studies, providing very heterogeneous results. Factors that explain this variability include patient case mix (with a greater efficacy of oropharyngeal decontamination in surgical patients[14,17]), differences in classes of agents, and for each class, parameters such as concentration (for chlorhexidine), frequency and method of administration, and the potential combination with systemic antibiotics (for selective oropharyngeal decontamination). Although oropharyngeal decontamination with antibiotics seems more effective than with antiseptics, the development of antibiotic resistance has limited its widespread use.[8] Hence, in a majority of countries, chlorhexidine is the most commonly used agent,[22,23] and its effect on ventilator-associated pneumonia prevention has been evaluated in many studies.[11–20] Several meta-analyses of these studies have been published with conflicting results. Some recent ones[14,17] indicate that chlorhexidine reduces incidence of nosocomial pneumonia in cardiac surgery patients, but does not in others. This has led some to question the use of chlorhexidine in this patient population.[17] Paradoxically, direct microbiologic assessment of chlorhexidine on oropharyngeal bacterial colonization, at the patient's bedside, is lacking.[24] Thus, we aimed to study chlorhexidine oral care effects on oropharyngeal bacterial microbiota, as well as the susceptibility of oropharyngeal strains to chlorhexidine, and measure residual chlorhexidine salivary concentration in a subset of patients. We hypothesized that oropharyngeal bacterial inoculums might not be affected by chlorhexidine exposure, and that chlorhexidine salivary concentration would rapidly decrease after its administration.

Materials and Methods

Study Design

This observational, single-center study was conducted in a 12-bed university hospital, medicosurgical intensive care unit. Consecutive critically ill patients admitted to the intensive care unit, receiving invasive mechanical ventilation for more than 48 h were included. For technical and organizational reasons, screening was only possible during weekdays. Noninclusion criteria were the following: cervical or mouth surgery in the last 15 days; history of oropharyngeal neoplasm, or of cervical or oropharyngeal radiation therapy; tracheotomy; and age less than 18 yr. In order to be able to detect a significant decrease in bacterial growth, patients whose samples retrieved less than 10^3 CFU/ml bacteria before chlorhexidine care were secondarily excluded, as were those who had two or more missing microbiologic samples. Demographic and clinical data were recorded.

Chlorhexidine Oral Care

All patients under invasive mechanical ventilation had protocol-driven full oral care with 0.12% chlorhexidine solution (Paroex, chlorhexidine digluconate 0.12%; Lichtenheldt GMBH, Germany) every 6 h.[15,25] The procedure included a first oropharyngeal swab (dry swab; DaklaPack, the Netherlands) in the lower gingivobuccal sulcus, to detect and quantify initial bacterial inoculum. This first swab was always performed after the night shift's last oral care and just before the day shift performed its first oral care so as to assess the maximal level of bacterial colonization. Once the swabbing was completed and immediately delivered to the microbiology laboratory for analysis, the oral care consisted of applying 15 ml chlorhexidine with soaked compresses on the teeth, gums, gingival mucosa, palate, and tongue, with a movement from back to front. No rinsing of the mouth was performed after the oral care.

Subsequent swabs were sampled immediately, and at 15, 60, 120, 240, and 360 min after the oral care. For the last 10 patients, 0.5 ml of saliva was collected with a syringe in the lower gingivobuccal sulcus, at 15, 30, 60, 120, 240, and 360 min after the oral care. These samples were then stored at −20°C in conical centrifuge tubes (Nunc; Thermo Scientific, France) for subsequent chlorhexidine-concentration measurement. Every single oral care was reported on the daily patient chart.

Microbiologic Study

Upon reception, swabs were discharged into 0.5 ml of sterile water. Then, samples were diluted to 1/1,000, and 100 μl of this dilution was plated with a rake onto three agar plates: chromogenic agar (UriSelect; Biorad, France), Drigalski agar (Sigma-Aldrich, France), and chocolate agar + PolyViteX (BioMérieux, France). All plates were incubated aerobically at 37°C, with an additional 5% CO_2 for the chocolate agar. After 24h of incubation, the total bacterial count of a sample was counted from the nonselective chocolate agar plate. Quantification of Gram-negative and Gram-positive bacteria was also performed from the three agar plates. Only the two dominant pathogens were stored at −80°C in glycerol media.

Chlorhexidine minimal inhibitory concentrations of dominant pathogens of each patient were determined using the broth microdilution method recommended by the Clinical and Laboratory Standards Institute (Wayne, Pennsylvania).[26] Strains were cultured in 10 ml of brain heart infusion broth (Sigma-Aldrich, France) in conical centrifuge tubes (Nunc;

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Thermo Scientific, France), and incubated for 18 h at 37°C under agitation (200 rotations per min). *Streptococcus* and *Haemophilus* strains were cultured using Haemophilus Test Medium supplement (Oxoid S.A., France) in a carbon dioxide humidified incubator. After 18 h incubation, each culture was diluted to 1/1,000 in blood heart infusion broth (with addition of Haemophilus Test Medium supplement for *Streptococcus* and *Haemophilus* strains). Then, 90 µl of each diluted culture was added to 10 µl of chlorhexidine solution, at different concentrations (0.25 to 256 mg/l), in 96-well microplates (Corning Inc., USA). The microplates were incubated at 37°C aerobically (in a carbon dioxide humidified incubator for *Streptococcus* strains). Minimal inhibitory concentration was read at 24 h. The experiment was repeated three times.

Chlorhexidine Salivary Concentration Study

We determined salivary chlorhexidine concentration for the last 10 patients (February to April 2016). The samples were analyzed by high-pressure liquid chromatography.[27] Sputasol (Oxoid S.A.) was used at the extraction phase to optimize the saliva fluidization: 100 µl of Sputasol was added to 200 µl of saliva. Then, 300 µl of 4.5 M sodium hydroxide and 400 µl of acetonitrile were added. The obtained sample was vortex-mixed and centrifuged for 1 min at 14,000 rpm. Then, 200 µl of the organic phase was transferred into a dry tube and mixed with 370 µl of the mobile phase buffer component. A 20-µl aliquot was injected into the high-pressure liquid chromatography system. A Nova-Pak C18 column (4 µm, 3.9 mm × 150 mm; Waters, France) was used, with a flow rate of 0.8 ml/min. Chlorhexidine was detected at 260 nm. The chromatographic chain was piloted and the peaks determined using the Empower 2 software (Waters). Calibration range and quality controls were prepared in saliva (Saliva, Artificial Oral Fluid, OraFlex; LGC, England). The range was between 0.5 and 50 mg/l (0.5, 1, 2, 5, 10, 20, 30, 50). Any sample concentration greater than the range was diluted in order to allow for chlorhexidine concentration measurement.

Ethics

The Ethics Committee of the French Intensive Care Society (Paris, France) approved the study (n°13-41). Informed consent was not requested due to the purely observational design of our study leading to a waiver of informed consent. Patients and/or family were, however, informed of the study, its purpose and objectives. The study was registered at clinicaltrial.gov (NCT03290105).

Statistical Analysis

The prespecified and *a priori* defined primary outcome was the reduction in total colony-forming units (CFU) over time after chlorhexidine exposure. An *a priori* effect size was difficult to define due to lack of sufficiently precise previous data in the literature on which to base the calculation. We had no same or largely overlapping data sets previously examined for similar outcome measures by our group. Descriptive statistics

were analyzed with GraphPad Prism 7 (GraphPad Software, USA), and the mixed model analysis was carried out using SAS version 9.3 (SAS Institute, USA). Results are presented as the median and range for quantitative variables, or frequency and proportion for categorical variables. We investigated temporal changes in total colony-forming unit per milliliter values, using a linear mixed model to take into account that multiple samples came from individual patients.[28] As colony-forming unit per milliliter data were not normally distributed, they were transformed using the natural logarithmic transformation model. A model with time (baseline, 15, 30, 60, 120, 240, and 360 min), as the repeated-measures factor was constructed. Subjects' identification was included as a random effect to account for the variability due to individual differences between subjects. The interaction of time with (1) mono- or polymicrobial status and (2) isolates' genus was also assessed to test whether time courses of the CFU differed between mono- and polymicrobial samples and between types of isolates, respectively. We selected the unstructured covariance based on the Akaike information criterion. Normality and homoscedasticity of the residuals were examined using graphical methods. Secondary outcomes were the microbiologic analysis of patients' oropharyngeal colonization, minimal inhibitory concentrations of oropharyngeal bacteria to chlorhexidine, and chlorhexidine salivary concentration. Hypothesis testing was two-tailed. There was no *post hoc* testing. A *P* value < 0.05 was considered statistically significant.

Results

Patients

One hundred sixty-eight consecutive patients were admitted to our intensive care unit during the 16-week study period (January to March 2014, and February to April 2016; see patient flow chart, fig. 1 in the Supplemental Digital Content, http://links.lww.com/ALN/B787). Of these, 44 were
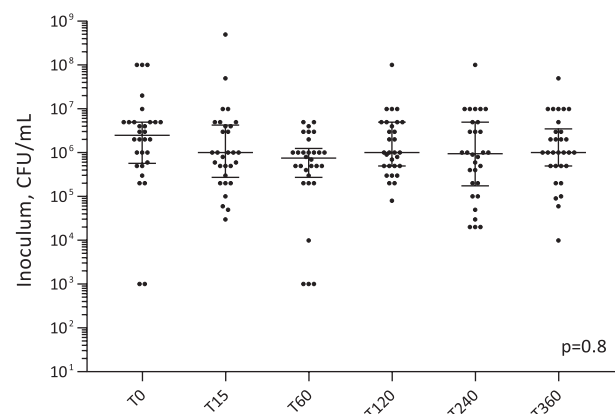
Fig. 1. Evolution of the total inoculum of oropharyngeal isolates, for each patient, at the different timepoints. Results are expressed as means and range. There was no significant change in the total inoculum of oropharyngeal isolates over time. CFU, colony-forming units; T, timepoints, followed by the elapsed minutes since the beginning of the oropharyngeal care.

Table 1. Patient Characteristics

Characteristics	Total, n = 30
Age (yr)	63 [52–71]
Male sex, n (%)	23 (76.7)
Comorbid conditions, n (%)	
Neoplastic disease	4 (13.3)
Cirrhosis	2 (6.7)
Chronic kidney disease	4 (13.3)
Dialysis	1 (3.3)
COPD	6 (20)
HIV	2 (6.7)
Chronic heart failure	7 (23.3)
Chronic alcohol consumption	9 (30)
Reason for ICU admission, n (%)	
Acute respiratory failure	15 (50)
Coma	6 (20)
Septic shock	7 (23.3)
Cardiogenic shock	2 (6.7)
SAPSII	52 [45–73]
Ongoing exposure to antibiotic therapy, n (%)	26 (86.7)
Amoxicillin, n	5
Amoxicillin-clavulanate, n	3
Piperacillin, n	2
Piperacillin-tazobactam, n	2
Third generation cephalosporin, n	9
Azole, n	3
Aminoglycoside, n	6
Carbapenem, n	3
Median time between intubation and inclusion, days	4 [3–7]
Median duration of ventilation, days	11 [8–20]
Median length of ICU stay, days	12 [9–23]
ICU mortality, n (%)	5 (16.7)

Data are presented as n (%) or median [interquartile range], unless otherwise stated.
COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; ICU, intensive care unit; SAPSII, Simplified Acute Physiology Score II.

Table 2. Oropharyngeal Isolates Characteristics

Oropharyngeal Isolates	Isolates, n = 48	CHX MIC (mg/l)
Viridans group streptococci	13 (27.1)	4 [4–8]
Staphylococci	8 (16.7)	24 [14–32]
Staphylococcus haemolyticus	7	32 [12–32]
Staphylococcus aureus	1	16
Enterococci	8 (16.7)	16 [7–20]
Enterococcus faecalis	7	16 [12–24]
Enteroccoccus faecium	1	4
Enterobacteriaceae	10 (20.8)	32 [16–32]
Escherichia coli	4	24 [12–32]
Enterobacter cloacae	2	16 [16–16]
Proteus mirabilis	2	48 [40–56]
Proteus vulgaris	1	32
Hafnia alvei	1	32
Nonfermenting Gram-negative pathogens	7 (14.6)	16 [12–24]
Pseudomonas aeruginosa	6	16 [10–16]
Achromobacter xylosoxidans	1	32
Haemophilus influenzae	1 (2.1)	16
Branhamella catarrhalis	1 (2.1)	16

Data regarding isolates are presented as n (%) and data regarding CHX MIC as median [interquartile range].
CHX, chlorhexidine; MIC, minimal inhibitory concentration.

(six viridans group streptococci, three *P. aeruginosa*, one *Staphylococcus haemolyticus*, one *Escherichia coli*, one *Achromobacter xylosoxidans*), and 18 were polymicrobial.

Changes over Time of Oropharyngeal Bacterial Growth before and after Chlorhexidine Exposure

There were no significant differences in bacterial inoculum per patient over time (fig. 1). Indeed, bacterial counts before chlorhexidine mouthwash did not decrease over time (each minute increase in time resulted in a multiplication of bacterial count by a coefficient of 1.001, $P = 0.83$). Median count before chlorhexidine exposure was $2.5 \cdot 10^6$ CFU/ml and remained between $8 \cdot 10^5$ and $3 \cdot 10^6$ CFU/ml after chlorhexidine exposure (figs. 1 and 2 in the Supplemental Digital Content, http://links.lww.com/ALN/B787). The median inoculum of the 12 monomicrobial samples ($2 \cdot 10^6$ to $5 \cdot 10^5$ CFU/ml, with a nadir of $4 \cdot 10^5$ CFU/ml 240 min after oral care) showed no significant variations *versus* that of the 18 polymicrobial ones ($2 \cdot 10^6$ to $1 \cdot 10^6$ CFU/ml with a nadir of $1 \cdot 10^6$ CFU/ml 60 min after oral care, $P = 0.7$). No significant changes in bacterial growth were observed for any of the different genera of isolated strains (fig. 2). Regarding the species or strains for which oral care led to an initial bacterial count (albeit statistically nonsignificant) decrease, this decrease did not exceed one log, and bacterial regrowth was observed very rapidly afterward.

Minimal Inhibitory Concentrations of Oropharyngeal Bacterial to Chlorhexidine

Enterobacteriaceae had the highest chlorhexidine minimal inhibitory concentration (32 [16 to 32] mg/l, table 2). Of note, even the bacteria exhibiting the lowest minimal

ventilated for more than 48 h, and 34 patients were included. Four patients had at least one exclusion criterion. Characteristics of the remaining 30 patients are displayed in table 1. Median age was 63 yr [52 to 71], with a median Simplified Acute Physiology Score II of 52 [45 to 73]. Twenty-six patients (86.7%) had antibiotics at time of inclusion. These mainly included a third-generation cephalosporin (nine patients), or amoxicillin (either alone [five patients], or in combination with clavulanic acid [three patients]). Eight patients ultimately developed ventilator-associated pneumonia (including five with diverse Enterobacteriaceae and three with *Pseudomonas aeruginosa* pneumonia). For each patient, bacteria responsible for ventilator-associated pneumonia were those documented in the oropharyngeal samples.

Microbiology of Oropharyngeal Colonization

Two hundred fifty samples were collected from the 30 patients. Forty-eight oropharyngeal isolates were identified. These were mainly streptococci (27.1%) and Enterobacteriaceae (20.8%; table 2). Twelve oropharyngeal samples were monomicrobial

Fig. 2. Bacterial growth of the different genus of isolated strains, at the different timepoints. Timepoints are expressed as T, followed by the elapsed minutes since the beginning of the oropharyngeal care. Results are expressed as means and range. There was no significant change in bacterial growth of the different genera of isolated strains over time. CFU, colony-forming units.

inhibitory concentration to chlorhexidine (4 [4 to 8] mg/l) were not affected by chlorhexidine exposure: inoculum of viridans group streptococci isolates varied from $1 \cdot 10^6$ to $5 \cdot 10^5$ CFU/ml at the minimum and again reached $1 \cdot 10^6$ CFU/ml 240 min after the oral care.

Chlorhexidine Salivary Concentration

For the 10 patients whose salivary chlorhexidine concentration were measured, the median salivary chlorhexidine concentration reached a maximum of 47 [19 to 61] mg/l, 15 min after administration, and then dropped to 7.6 [1.8 to 31] mg/l as early as 60 min after the oropharyngeal chlorhexidine care. It gradually decreased thereafter, reaching 2.95 mg/l 360 min after the mouth rinse (fig. 3, $P < 0.0001$). This was associated with the persistence of a strong oropharyngeal bacterial inoculum, between 10^5 and 10^7 CFU/ml.

Discussion

Although a few studies have dealt with chlorhexidine effect on oropharyngeal colonization,[29–34] this study included an
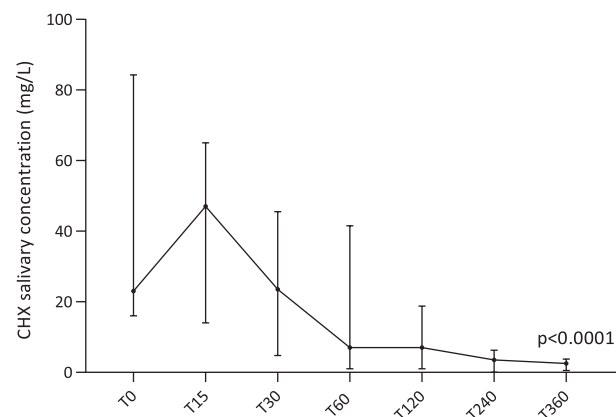
Fig. 3. Chlorhexidine (CHX) salivary concentration at the different timepoints. Timepoints are expressed as T, followed by the elapsed minutes after the oropharyngeal care. Results are expressed as means and range. There was a significant change in chlorhexidine over time.

evaluation of the kinetics of oropharyngeal bacterial colonization minutes and hours following chlorhexidine administration, and measuring chlorhexidine oral concentration in critically ill patients. More precisely, most of the studies dealing with chlorhexidine effect on oropharyngeal colonization did not quantify oropharyngeal inoculums,[30,33,34] or controlled them only once, several hours or days after the oral care.[29,31,32]

Results can be summarized as follows: (1) there was no significant change in median bacterial counts after a standard 0.12% chlorhexidine oropharyngeal care; (2) this result was found irrespective of the bacterial genus involved; (3) even strains with a low minimal inhibitory concentration to chlorhexidine, such as viridans group streptococci, were not affected by 0.12% chlorhexidine; and (4) the chlorhexidine salivary concentration rapidly decreased after its administration during oropharyngeal care. Taken together, these results suggest that 0.12% chlorhexidine may have almost no efficacy *in vivo* on oropharyngeal colonization. These results question the use of chlorhexidine to prevent ventilator-associated pneumonia and provide some explanation for the negative results of chlorhexidine on ventilator-associated pneumonia prevention.[14,17]

Chlorhexidine oral care is widely used to prevent ventilator-associated pneumonia.[22] Yet meta-analyses have yielded discordant results on its effectiveness.[11–20] The major problem of these analyses is that studies included heterogeneous categories of patients and very heterogeneous practices in terms of frequencies of oral care, chlorhexidine concentrations (from 0.12 to 2%), and modes of antiseptic administration (mouthwash, dental paste, swabbing of the mucous membranes), that together question the reliability of the findings. Moreover, chlorhexidine seems to be effective to prevent nosocomial pneumonia only among cardiac surgery patients.[17] In addition, the vast majority of patients included in the three studies after cardiac surgery were intubated less than 48 h. Therefore, one cannot make conclusions about the long-term effect of chlorhexidine in patients ventilated for longer periods. Interestingly, the analysis of

the 13 studies focusing on medical patients only did not find any effect of chlorhexidine on prevention of ventilator-associated pneumonia.[17] This suggests that the positive effect of chlorhexidine reported by some studies is biased by the short duration of ventilation. Importantly, a nonsignificant trend toward an increased mortality in patients randomized to chlorhexidine use was noted (risk ratio, 1.13 [95% CI, 0.99 to 1.28]).[17] Another meta-analysis reported a significant increased mortality in patients randomized to chlorhexidine use (odds ratio, 1.25 [95% CI, 1.05 to 1.50]), possibly related to microaspirations of small amounts of chlorhexidine, leading to acute lung injury.[16] Finally, a very recent study also found that exposure to chlorhexidine oral care was associated with increased risk of death (odds ratio, 2.61 [95% CI, 2.32 to 2.92]).[35] Thus, the use of chlorhexidine remains debated, with some societies having withdrawn chlorhexidine use from their recommendations,[36–38] while others have funded a large international multicenter study to evaluate the benefits of chlorhexidine 2% oral care.[39]

Surprisingly, chlorhexidine has been broadly used for decades in the intensive care unit without prior evaluation of its antibacterial efficacy and its persistence in significant concentrations in the oropharynx of critically ill patients. Most of the only available data can be found for odontological outpatients,[40] who are obviously very different from mechanically ventilated intensive care unit patients.[41] Our results clearly indicate the persistence of a high oropharyngeal bacterial inoculum in intubated patients, despite well-conducted chlorhexidine oral care. This raises the question: Why could chlorhexidine be ineffective? Reported minimal inhibitory concentration levels of chlorhexidine for Enterobacteriaceae and staphylococci were respectively around 4 and 1 to 2 mg/l.[42,43] These figures are considerably lower than those measured in our study (respectively, 32 [16 to 32] and 24 [14 to 32] mg/l). Two non–mutually exclusive explanations may be brought forward for our observations: decreased bacterial susceptibility to chlorhexidine and insufficient concentrations at the site of interest. At the individual level, oropharyngeal isolates, repetitively exposed to chlorhexidine, develop resistance to chlorhexidine. This phenomenon has been suggested to occur at least *in vitro*: Kitagawa *et al.* described an increase of *Enterococcus faecalis* chlorhexidine minimal inhibitory concentration after repeated exposure to chlorhexidine, due to a change in protein expression profiles.[44] After repeated passages in media containing increasing chlorhexidine concentrations, Braoudaki and Hilton observed an increase of *E. coli* O157's minimal inhibitory concentration from 4 to 512 µg/ml.[45] At the population level, one may hypothesize that over the years, *E. coli*'s susceptibility to chlorhexidine has changed, with bacteria becoming more resistant. We indeed have recently described very different chlorhexidine susceptibility patterns in *E. coli* isolates responsible for pneumonia in ventilated patients.[46] Decreasing chlorhexidine susceptibility has also

been described for *Staphylococcus aureus* isolates, after an increase in the use of chlorhexidine in oncology and cardiac surgery pediatric patients between 2001 and 2011.[47,48]

The conflicting results on chlorhexidine efficacy reported in the different meta-analyses obviously question the salivary availability of chlorhexidine. Surprisingly, we found no data reporting values for chlorhexidine salivary concentrations in critically ill ventilated patients. To address this point, we measured salivary chlorhexidine concentration in the last 10 patients. The reason chlorhexidine concentrations were not measured in all patients relates to the delay in establishing the appropriate high-pressure liquid chromatography setup. Our measurements are consistent with those performed in healthy volunteers and nonventilated patients, which reported very low chlorhexidine concentrations early after chlorhexidine oral care.[49,50] Our results indicate a very rapid drop in chlorhexidine salivary concentration as early as 60 min after the oral care (reaching a low of 7.6 mg/l), which is lower than most of the bacteria minimal inhibitory concentration we found. A possible explanation for the rapid decrease could be chlorhexidine absorption to mucin, and partly to albumin in saliva.[51] Hence, a too rapid a drop in chlorhexidine oropharyngeal concentrations may explain its antimicrobial ineffectiveness. Moreover, as previously discussed, subinhibitory chlorhexidine concentrations may contribute to the development of chlorhexidine resistance in oropharyngeal pathogens.

We recognize our study has a few limitations. First, it was not controlled. However, the main objective was to assess chlorhexidine oral care effects on oropharyngeal bacterial microbiota, and to try to unravel its reported ineffectiveness rather than to compare it to another agent. Second, the number of included patients could be regarded as small, in a single-center study. Thus, results might not be generalizable, reflecting the habits and bacterial ecology of this intensive care unit. The results do, however, represent 250 bacterial samples that consistently showed high persistent oropharyngeal bacterial inoculum, despite well-conducted chlorhexidine oral care. It is thus highly unlikely that a larger number of patients would have yielded very different results. We deliberately chose to include only those patients ventilated for more than 48 h because we wished to assess chlorhexidine efficacy in established oropharyngeal colonization. Whether or not oral care with chlorhexidine prevents oropharyngeal colonization from occurring was not directly assessed in the present study. It could be hypothesized that initial bacterial inoculums were much higher than those we measured, and that chlorhexidine just maintained the level of bacteria. However, all our patients received chlorhexidine oral care from the beginning of their intensive care unit admission. The fact that all 30 patients had a very high level of oropharyngeal colonization by day 3 suggests that chlorhexidine was indeed not able to prevent colonization from occurring. Moreover, had chlorhexidine been effective, one

would have expected significant changes in bacterial levels, in parallel with variations in chlorhexidine concentrations. We believe that the stability of bacterial counts suggests that chlorhexidine exposure was ineffective. Third, we used 0.12% chlorhexidine, which is not the highest chlorhexidine concentration available, but the highest in France at the time of the study.[15,17] One might conclude that our results might not be generalizable for other chlorhexidine concentrations. However, stronger solutions of chlorhexidine are not available worldwide, and they are known to be poorly tolerated, causing oral mucosa lesions, because of cytotoxicity.[39,52,53]

Providing exhaustive, longitudinal, fully quantitative (and not semiquantitative as in most studies) bacterial cultures in parallel with assays of chlorhexidine salivary concentration is a definite strength of our study. What alternatives can be proposed to clinicians that would envisage abandoning chlorhexidine? Unfortunately, evidence regarding the efficacy of existing alternatives to chlorhexidine mouth rinse is insufficient.[20] Hence, new approaches need to be developed. We have recently shown that proanthocyanidins extracted from cranberry had the ability to decrease bacterial adhesion to fresh human buccal epithelial cells and that in an animal model, they decreased the virulence of pathogens responsible for ventilator-associated pneumonia.[54] They may be an interesting alternative that obviously requires clinical demonstration of their potential benefit.

Conclusions

To summarize, we showed that, despite its broad use, 0.12% chlorhexidine has almost no effect on oropharyngeal bacterial microbiota in patients requiring invasive mechanical ventilation for more than 48 h, even on strains exhibiting low minimal inhibitory concentrations. High oropharyngeal bacterial inoculums persist, and chlorhexidine salivary concentration rapidly decreases below bacteria minimal inhibitory concentrations to chlorhexidine. These results may partly explain why ventilator-associated pneumonia rates remain above 10 to 15% in intensive care unit patients, despite application of dedicated bundles.[25,55] Given the number of patients that routinely receive oral care with chlorhexidine, our results have major and immediate clinical and economical repercussions since they directly question the pertinence of using chlorhexidine in this indication, and provide some explanations for the divergent results of studies on ventilator-associated pneumonia prevention with chlorhexidine.

Acknowledgments

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Competing Interests

Correspondence

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References

1. Zilberberg MD, Wit M de, Shorr AF: Accuracy of previous estimates for adult prolonged acute mechanical ventilation volume in 2020: Update using 2000–2008 data. Crit Care Med 2012; 40:18–20

2. Hunter JD: Ventilator associated pneumonia. BMJ 2012; 344:e3325

3. Melsen WG, Rovers MM, Groenwold RH, Bergmans DC, Camus C, Bauer TT, Hanisch EW, Klarin B, Koeman M, Krueger WA, Lacherade JC, Lorente L, Memish ZA, Morrow LE, Nardi G, van Nieuwenhoven CA, O'Keefe GE, Nakos G, Scannapieco FA, Seguin P, Staudinger T, Topeli A, Ferrer M, Bonten MJ: Attributable mortality of ventilator-associated pneumonia: A meta-analysis of individual patient data from randomised prevention studies. Lancet Infect Dis 2013; 13:665–71

4. Johanson WG, Pierce AK, Sanford JP: Changing pharyngeal bacterial flora of hospitalized patients. Emergence of gram-negative bacilli. N Engl J Med 1969; 281:1137–40

5. Johanson WG Jr, Pierce AK, Sanford JP, Thomas GD: Nosocomial respiratory infections with gram-negative bacilli. The significance of colonization of the respiratory tract. Ann Intern Med 1972; 77:701–6

6. Dreyfuss D, Djedaïni K, Gros I, Mier L, Le Bourdellés G, Cohen Y, Estagnasié P, Coste F, Boussougant Y: Mechanical ventilation with heated humidifiers or heat and moisture exchangers: Effects on patient colonization and incidence of nosocomial pneumonia. Am J Respir Crit Care Med 1995; 151:986–92

7. Rodríguez-Roldán JM, Altuna-Cuesta A, López A, Carrillo A, Garcia J, León J, Martínez-Pellús AJ: Prevention of nosocomial lung infection in ventilated patients: Use of an antimicrobial pharyngeal nonabsorbable paste. Crit Care Med 1990; 18:1239–42

8. Abele-Horn M, Dauber A, Bauernfeind A, Russwurm W, Seyfarth-Metzger I, Gleich P, Ruckdeschel G: Decrease in nosocomial pneumonia in ventilated patients by selective oropharyngeal decontamination (SOD). Intensive Care Med 1997; 23:187–95

9. Bergmans DC, Bonten MJ, Gaillard CA, Paling JC, van der Geest S, van Tiel FH, Beysens AJ, de Leeuw PW, Stobberingh EE: Prevention of ventilator-associated pneumonia by oral decontamination: A prospective, randomized, double-blind, placebo-controlled study. Am J Respir Crit Care Med 2001; 164:382–8

10. Oostdijk EA, de Smet AM, Blok HE, Thieme Groen ES, van Asselt GJ, Benus RF, Bernards SA, Frénay IH, Jansz AR, de Jongh BM, Kaan JA, Leverstein-van Hall MA, Mascini EM, Pauw W, Sturm PD, Thijsen SF, Kluytmans JA,

Bonten MJ: Ecological effects of selective decontamination on resistant gram-negative bacterial colonization. Am J Respir Crit Care Med 2010; 181:452–7

11. Pineda LA, Saliba RG, El Solh AA: Effect of oral decontamination with chlorhexidine on the incidence of nosocomial pneumonia: A meta-analysis. Crit Care 2006; 10:R35

12. Chan EY, Ruest A, Meade MO, Cook DJ: Oral decontamination for prevention of pneumonia in mechanically ventilated adults: Systematic review and meta-analysis. BMJ 2007; 334:889

13. Chlebicki MP, Safdar N: Topical chlorhexidine for prevention of ventilator-associated pneumonia: A meta-analysis. Crit Care Med 2007; 35:595–602

14. Labeau SO, Van de Vyver K, Brusselaers N, Vogelaers D, Blot SI: Prevention of ventilator-associated pneumonia with oral antiseptics: A systematic review and meta-analysis. Lancet Infect Dis 2011; 11:845–54

15. Li J, Xie D, Li A, Yue J: Oral topical decontamination for preventing ventilator-associated pneumonia: A systematic review and meta-analysis of randomized controlled trials. J Hosp Infect 2013; 84:283–93

16. Price R, MacLennan G, Glen J; SuDDICU Collaboration: Selective digestive or oropharyngeal decontamination and topical oropharyngeal chlorhexidine for prevention of death in general intensive care: Systematic review and network meta-analysis. BMJ 2014; 348:g2197

17. Klompas M, Speck K, Howell MD, Greene LR, Berenholtz SM: Reappraisal of routine oral care with chlorhexidine gluconate for patients receiving mechanical ventilation: Systematic review and meta-analysis. JAMA Intern Med 2014; 174:751–61

18. Zhang TT, Tang SS, Fu LJ: The effectiveness of different concentrations of chlorhexidine for prevention of ventilator-associated pneumonia: A meta-analysis. J Clin Nurs 2014; 23:1461–75

19. Villar CC, Pannuti CM, Nery DM, Morillo CM, Carmona MJ, Romito GA: Effectiveness of intraoral chlorhexidine protocols in the prevention of ventilator-associated pneumonia: Meta-analysis and systematic review. Respir Care 2016; 61:1245–59

20. Hua F, Xie H, Worthington HV, Furness S, Zhang Q, Li C: Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia. Cochrane Database Syst Rev 2016; 10:CD008367

21. Kollef M, Pittet D, Sánchez García M, Chastre J, Fagon JY, Bonten M, Hyzy R, Fleming TR, Fuchs H, Bellm L, Mercat A, Mañez R, Martínez A, Eggimann P, Daguerre M, Luyt CE; Prevention of Pneumonia Study (POPS-1) Trial Group: A randomized double-blind trial of iseganan in prevention of ventilator-associated pneumonia. Am J Respir Crit Care Med 2006; 173:91–7

22. Rello J, Koulenti D, Blot S, Sierra R, Diaz E, De Waele JJ, Macor A, Agbaht K, Rodriguez A: Oral care practices in intensive care units: A survey of 59 European ICUs. Intensive Care Med 2007; 33:1066–70

23. Feider LL, Mitchell P, Bridges E: Oral care practices for orally intubated critically ill adults. Am J Crit Care 2010; 19:175–83

24. Ricard J-D, Lisboa T: Caution for chlorhexidine gluconate use for oral care: Insufficient data. Intensive Care Med 2018; 44:1162–4

25. Bouadma L, Mourvillier B, Deiler V, Le Corre B, Lolom I, Régnier B, Wolff M, Lucet JC: A multifaceted program to prevent ventilator-associated pneumonia: impact on compliance with preventive measures. Crit Care Med 2010; 38:789–96

26. Clinical Laboratory Standards Institute: Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard—Ninth Edition. Wayne, Pennsylvania, 2012, M07–A9

27. Pesonen T, Holmalahti J, Pohjola J: Determination of chlorhexidine in saliva using high-performance liquid chromatography. J Chromatogr B Biomed Appl 1995; 665:222–5

28. Fitzmaurice GM, Laird NM, Ware JH: Applied Longitudinal Analysis, Second Edition. Hoboken, New Jersey, Wiley, 2013

29. Zand F, Zahed L, Mansouri P, Dehghanrad F, Bahrani M, Ghorbani M: The effects of oral rinse with 0.2% and 2% chlorhexidine on oropharyngeal colonization and ventilator associated pneumonia in adults' intensive care units. J Crit Care 2017; 40:318–22

30. Azimi M, Jouybari L, Moghadam S, Ghaemi E, Behnampoor N, Sanagoo A, Hesam M: Antimicrobial effects of chlorhexidine, matrica drop mouthwash (chamomile extract), and normal saline on hospitalized patients with endotracheal tubes. Iran J Nurs Midwifery Res 2016; 21:458–63

31. Rezaei S, Rezaei K, Mahboubi M, Jarahzadeh MH, Momeni E, Bagherinasab M, Targhi MG, Memarzadeh MR: Comparison the efficacy of herbal mouthwash with chlorhexidine on gingival index of intubated patients in intensive care unit. J Indian Soc Periodontol 2016; 20:404–8

32. Safarabadi M, Ghaznavi-Rad E, Pakniyat A, Rezaie K, Jadidi A: Comparing the effect of echinacea and chlorhexidine mouthwash on the microbial flora of intubated patients admitted to the intensive care unit. Iran J Nurs Midwifery Res 2017; 22:481–5

33. Kusahara DM, Friedlander LT, Peterlini MA, Pedreira ML: Oral care and oropharyngeal and tracheal colonization by Gram-negative pathogens in children. Nurs Crit Care 2012; 17:115–22

34. Grap MJ, Munro CL, Elswick RK Jr, Sessler CN, Ward KR: Duration of action of a single, early oral application of chlorhexidine on oral microbial flora in mechanically ventilated patients: A pilot study. Heart Lung 2004; 33:83–91

35. Deschepper M, Waegeman W, Eeckloo K, Vogelaers D, Blot S: Effects of chlorhexidine gluconate oral care on hospital mortality: a hospital-wide, observational cohort study. Intensive Care Med 2018; 44:1017–26

36. Hellyer TP, Ewan V, Wilson P, Simpson AJ: The Intensive Care Society recommended bundle of interventions for the prevention of ventilator-associated pneumonia. J Intensive Care Soc 2016; 17:238–43

37. Torres A, Niederman MS, Chastre J, Ewig S, Fernandez-Vandellos P, Hanberger H, Kollef M, Li Bassi G, Luna CM, Martin-Loeches I, Paiva JA, Read RC, Rigau D, Timsit JF, Welte T, Wunderink R: International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia: Guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociación Latinoamericana del Tórax (ALAT). Eur Respir J 2017; 50:1–26

38. Klompas M, Branson R, Eichenwald EC, Greene LR, Howell MD, Lee G, Magill SS, Maragakis LL, Priebe GP, Speck K, Yokoe DS, Berenholtz SM; Society for Healthcare Epidemiology of America (SHEA): Strategies to prevent ventilator-associated pneumonia in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol 2014; 35:915–36

39. Plantinga NL, Wittekamp BHJ, Leleu K, Depuydt P, Van den Abeele AM, Brun-Buisson C, Bonten MJM: Oral mucosal adverse events with chlorhexidine 2% mouthwash in ICU. Intensive Care Med 2016; 42:620–1

40. Veksler AE, Kayrouz GA, Newman MG: Reduction of salivary bacteria by pre-procedural rinses with chlorhexidine 0.12%. J Periodontol 1991; 62:649–51

41. Dennesen P, van der Ven A, Vlasveld M, Lokker L, Ramsay G, Kessels A, van den Keijbus P, van Nieuw Amerongen A, Veerman E: Inadequate salivary flow and poor oral mucosal status in intubated intensive care unit patients. Crit Care Med 2003; 31:781–6

42. Kõljalg S, Naaber P, Mikelsaar M: Antibiotic resistance as an indicator of bacterial chlorhexidine susceptibility. J Hosp Infect 2002; 51:106–13

43. Grare M, Dibama HM, Lafosse S, Ribon A, Mourer M, Regnouf-de-Vains JB, Finance C, Duval RE: Cationic compounds with activity against multidrug-resistant bacteria: Interest of a new compound compared with two older antiseptics, hexamidine and chlorhexidine. Clin Microbiol Infect 2010; 16:432–8

44. Kitagawa H, Izutani N, Kitagawa R, Maezono H, Yamaguchi M, Imazato S: Evolution of resistance to cationic biocides in Streptococcus mutans and Enterococcus faecalis. J Dent 2016; 47:18–22

45. Braoudaki M, Hilton AC: Adaptive resistance to biocides in Salmonella enterica and Escherichia coli O157 and cross-resistance to antimicrobial agents. J Clin Microbiol 2004; 42:73–8

46. La Combe B, Bleibtreu A, Messika J, Fernandes R, Clermont O, Branger C, Billard-Pomares T, Barnaud G, Magdoud F, Eveillard M, Kouatchet A, Lasocki S, Asfar P, Corvec S, Lakhal K, Armand-Lefevre L, Wolff M, Timsit JF, Bourdon S, Reignier J, Martin S, Fihman V, de Prost N, Bador J, Charles PE, Goret J, Boyer A, Wallet F, Jaillette E, Nseir S, Landraud L, Ruimy R, Danin PE, Dellamonica J, Cremniter J, Frat JP, Jauréguy F, Clec'h C, Decré D, Maury E, Dreyfuss D, Denamur E, Ricard JD: Decreased susceptibility to chlorhexidine affects a quarter of Escherichia coli isolates responsible for pneumonia in ICU patients. Intensive Care Med 2018; 44:531–3

47. McNeil JC, Hulten KG, Kaplan SL, Mahoney DH, Mason EO: Staphylococcus aureus infections in pediatric oncology patients: High rates of antimicrobial resistance, antiseptic tolerance and complications. Pediatr Infect Dis J 2013; 32:124–8

48. McNeil JC, Ligon JA, Hulten KG, Dreyer WJ, Heinle JS, Mason EO, Kaplan SL: Staphylococcus aureus infections in children with congenital heart disease. J Pediatric Infect Dis Soc 2013; 2:337–44

49. Musteata FM, Pawliszyn J: Assay of stability, free and total concentration of chlorhexidine in saliva by solid phase microextraction. J Pharm Biomed Anal 2005; 37:1015–24

50. Below H, Assadian O, Baguhl R, Hildebrandt U, Jäger B, Meissner K, Leaper DJ, Kramer A: Measurements of chlorhexidine, p-chloroaniline, and p-chloronitrobenzene in saliva after mouth wash before and after operation with 0.2% chlorhexidine digluconate in maxillofacial surgery: A randomised controlled trial. Br J Oral Maxillofac Surg 2017; 55:150–5

51. Tsuchiya H, Miyazaki T, Ohmoto S: High-performance liquid chromatographic analysis of chlorhexidine in saliva after mouthrinsing. Caries Res 1999; 33:156–63

52. Balloni S, Locci P, Lumare A, Marinucci L: Cytotoxicity of three commercial mouthrinses on extracellular matrix metabolism and human gingival cell behaviour. Toxicol In Vitro 2016; 34:88–96

53. Tantipong H, Morkchareonpong C, Jaiyindee S, Thamlikitkul V: Randomized controlled trial and meta-analysis of oral decontamination with 2% chlorhexidine solution for the prevention of ventilator-associated pneumonia. Infect Control Hosp Epidemiol 2008; 29:131–6

54. Margetis D, Roux D, Gaudry S, Messika J, Bouvet O, Branger C, Ponnuswamy P, Oufella HA, Dreyfuss D, Denamur E, Ricard JD: Effects of proanthocyanidins on adhesion, growth, and virulence of highly virulent extraintestinal pathogenic escherichia coli argue for its use to treat oropharyngeal colonization and prevent ventilator-associated pneumonia. Crit Care Med 2015; 43:e170–8

55. Bouadma L, Mourvillier B, Deiler V, Derennes N, Le Corre B, Lolom I, Régnier B, Wolff M, Lucet JC: Changes in knowledge, beliefs, and perceptions throughout a multifaceted behavioral program aimed at preventing ventilator-associated pneumonia. Intensive Care Med 2010; 36:1341–7

Morbidity and Mortality of Crystalloids Compared to Colloids in Critically Ill Surgical Patients

A Subgroup Analysis of a Randomized Trial

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ABSTRACT

Background: The multicenter randomized Colloids *versus* Crystalloids for the Resuscitation of the Critically Ill (CRISTAL) trial was designed to test whether colloids altered mortality compared to crystalloids in the resuscitation of intensive care unit patients with hypovolemic shock. This preplanned analysis tested the same hypothesis in the subgroup of surgical patients.

Methods: The CRISTAL trial prospectively defined patients as critically ill surgical patients whenever they underwent emergency or scheduled surgery immediately before or within 24 h of intensive care unit admission and had hypovolemic shock. The primary outcome measure was death by day 28. Secondary outcome measures included death by day 90, the need for renal replacement therapy, or the need for fresh frozen plasma transfusion.

Results: There were 741 critically ill surgical patients, 356 and 385 in the crystalloid and colloid arm, respectively. Median (interquartile range) age was 66 (52 to 76) yr, and 484 (65.3%) patients were male. Surgery was unscheduled in 543 (73.3%) cases. Mortality by day 28 did not significantly differ for crystalloids 84 (23.6%) *versus* colloids 100 (26%; adjusted odds ratio, 0.86; 95% CI, 0.61 to 1.21; P = 0.768). Death by day 90 (111 [31.2%] *vs.* 122 [31.7%]; adjusted odds ratio, 0.97; 95% CI, 0.70 to 1.33; P = 0.919) did not significantly differ between groups. Renal replacement therapy was required for 42 (11.8%) patients in the crystalloids arm *versus* 49 (12.7%) in the colloids arm (P = 0.871).

Conclusions: The authors found no survival benefit when comparing crystalloids to colloids in critically ill surgical patients.
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PERIOPERATIVE hemodynamic instability may lead to cardiovascular morbidity and requires prompt recognition and correction. Possible causes include blood loss, fluid deficit, or sepsis. Fluid therapy is therefore a key component of the perioperative management of surgical patients. Resuscitation fluids are divided into two categories: colloid and crystalloid solutions. The ideal fluid to be used in the surgical setting remains uncertain.[1,2] Colloids are composed of heavy molecular weight molecules, which are retained in the plasma compartment. Hemodynamic goals are reached by administrating smaller volumes of colloids than crystalloids.[3–5] Among colloids, starches are the most commonly administered fluid. The use of starches has been restricted by the European Medicines Agency in sepsis, burns, or critically ill patients[6] because of the risk of acute kidney injury and of death.[5,7] The U.S. Food and Drug Administration also issued a warning about the increased risk of renal failure or death,

Editor's Perspective

What We Already Know about This Topic

- Whether crystalloid or colloids are preferable for treatment of hypovolemic shock in surgical patients remains unclear

What This Article Tells Us That Is New

- In a preplanned subgroup analysis of a previous trial, the authors compared 28-day mortality in 741 surgical patients with hypovolemic shock who were randomized to crystalloids or colloids
- Mortality at 30 and 90 days was similar in the two groups, and colloid administration did not increase the need for dialysis
- Colloid administration did not improve mortality but also did not cause renal injury

as well as a risk of bleeding after cardiopulmonary bypass associated with starches.[6] However, because these data do not derive exclusively from surgical patients, extrapolation

of these findings to the perioperative period is questionable. Indeed, crystalloids are not devoid of side effects such as hyperchloremic metabolic acidosis, reduced renal blood flow, or impaired renal cortical perfusion.[8,9]

The Colloids *versus* Crystalloids for the Resuscitation of the Critically Ill (CRISTAL) trial was designed to test the hypothesis that colloids altered 28-day mortality compared with crystalloids for fluid resuscitation in a general population of critically ill patients.[4] This *a priori* defined secondary analysis tested the same hypothesis in the subgroup of surgical critically ill patients. Patients were identified as surgical whenever they underwent emergency or scheduled surgery immediately before or within 24 h of intensive care unit admission. Our primary outcome was 28-day mortality. Secondary outcomes included the occurrence of organ dysfunction over a 28-day period, as well as the need for renal replacement therapy, secondary surgical intervention, blood product administration, intensive care unit and hospital length of stay, and 90-day mortality.

Materials and Methods

Study Setting and Patients
The CRISTAL trial (ClinicalTrials.gov NCT00318942) randomly assigned 2,857 acutely hypovolemic patients from 57 participating centers in Europe, North Africa, and North America to receive either crystalloids or colloids.[4] The study protocol was approved by local institutional review boards. Deferred written informed consent was obtained from participants or legally authorized surrogates. Included participants had not previously received any fluid in the intensive care unit and required fluid resuscitation for acute hypovolemia. Acute hypovolemia was defined by the combination of (1) hypotension: systolic arterial pressure of less than 90 mmHg, mean arterial pressure of less than 60 mmHg, orthostatic hypotension (*i.e.*, decrease in systolic arterial pressure of at least 20 mmHg, from the supine to the semirecumbent position), or a delta pulse pressure of 13% or higher; (2) evidence for low filling pressures and low cardiac index, assessed either invasively or noninvasively; and (3) signs of tissue hypoperfusion or hypoxia, including at least two of the following clinical symptoms: Glasgow Coma Scale score of less than 12, mottled skin, urinary output of less than 25 ml/h, or capillary refilling time of 3 s or longer; and arterial lactate levels higher than 2 mM, blood urea nitrogen higher than 56 mg/dl, or a fractional excretion of sodium of less than 1%.[4]

A computer-generated list with fixed-block permutation (n = 4) was used to randomize patients on a 1 to 1 ratio. Randomization was stratified by center and by three admission diagnoses: sepsis, multiple trauma, and other causes of hypovolemic shock. Allocation concealment used sealed envelopes at the bedside to allow randomization of eligible patients without any delay. Investigators were blinded to block size.

Eligible patients were randomly allocated to fluid resuscitation with crystalloids or with colloids. In the crystalloids group, allowed treatments included isotonic or hypertonic saline and any buffered solutions. In the colloids group, hypooncotic (*e.g.*, gelatins, and 4 or 5% of albumin) and hyperoncotic (*e.g.*, dextrans, hydroxyethyl starches, and 20 or 25% of albumin) solutions were permitted. Within each treatment group, investigators could use whichever fluids were available at their institution. The amount of fluid and duration of treatment was left at the discretion of the investigators with the following restrictions: (1) the daily total dose of hydroxyethyl starch could not exceed 30 ml/kg of body weight and (2) investigators were required to follow any local regulatory agency recommendations governing use. Patients had to be managed according to their randomization arm except for (1) maintenance fluids, which were isotonic crystalloids, regardless of treatment group, and (2) in instances in which physicians wished to administer albumin in response to demonstrated hypoalbuminemia (serum albumin concentration less than 20 g/dl).

The blinding of the clinicians to the fluid interventions was considered by the study advisors to be inappropriate or infeasible because study treatments had to be available immediately for resuscitation to ensure avoidance of nonstudy fluids in emergent situations. In addition, because the intervention would be continued until intensive care unit discharge and could thus be highly variable, there was no practical way to stock sites with adequate supplies of masked fluid solutions. However, the mortality endpoints were collected and assessed by study members blinded to treatment assignment. Similarly, the principal investigator, study sponsor, and the members of the data and safety monitoring board remained blinded to the study interventions until all patients were followed up and the final analysis was executed.

For this analysis, we included all surgical patients included in the original trial. Surgical patients were *a priori* defined as patients requiring elective or unscheduled surgery, either before or up to 24 h after intensive care unit admission.

Data Collection
At the time of randomization, age, sex, cause of intensive care unit admission, type of admission (medical, elective surgery, unscheduled surgery, trauma), McCabe class,[10] disability scale score,[11] cause of hypovolemia (divided into three separate strata: sepsis, trauma, and other), Simplified Acute Physiology Score II,[12] Sequential Organ Failure Assessment score,[13] Injury Severity Score,[14] signs of hypovolemia, and amount of fluids administered before randomization were collected. The global Sequential Organ Failure Assessment score was recorded daily over a 7-day period and thereafter on days 14 and 28. Any occurrence of renal replacement therapy was recorded. We assessed the need for secondary surgical intervention and for blood product administration (including platelets, fresh frozen plasma, and packed erythrocytes) over a 7-day period. Outcomes included intensive

care unit and hospital length of stay, as well as death by days 28 and 90.

Statistical Analysis

Quantitative variables were expressed as median (interquartile range) and categorical variables as number (percentage). When designing the CRISTAL trial, we anticipated that responses to colloids *versus* crystalloids may vary across different groups of patients, namely sepsis, trauma, and other categories of acute hypovolemia. Thus, randomization was stratified according to these three groups of patients. In addition, we anticipated potential qualitative interaction between treatment responses within each of these strata and the type of admission, namely surgical *versus* medical. Thus, we planned to report the estimation of treatment effects in the surgical and medical groups of patients separately. We undertook an intention-to-treat analysis for the primary outcome, death by day 28, where patients, once selected in one treatment group according to randomization, were analyzed in the group assigned by the randomization, insuring the absence of any selection or attrition bias. No imputation was used. Nevertheless, in response to peer review, per-protocol analyses were added as a secondary analysis including all participants who adhered adequately to the assigned treatment. Categorical variables were compared with the Fisher exact test, and continuous variables were compared with the Wilcoxon rank sum test. To assess differences over time of the Sequential Organ Failure Assessment score across both arms, we built a linear mixed-effects model. This allowed us to model observational heterogeneity incurred by repeat measurements of the score in the same patient (with fixed effects of Sequential Organ Failure Assessment and time) and accounted for the fact that some individuals may have higher values than others (by using a random intercept).

All patients were followed until day 90 unless death occurred before day 90, so that analysis of mortality data across randomized groups used the chi-square test; estimate of odds ratio of death according to fluid used a logistic model, adjusted to the nature of surgery. To display the cumulative incidence of death, we used nonparametric estimator and then compared between randomized groups by the Gray test.

All analyses were preplanned, except for those factors selected for adjustment and additional analyses requested by the reviewers or editors. Statistical analyses were performed with SAS 9.3 (SAS Inc., USA) and R 2.13.0 (http://www.R-project.org/; accessed August 10, 2017) software. Tests were two-sided. The results were adjusted for multiple comparisons.[15] P levels less than 0.05 were considered statistically significant.

Results

Baseline Characteristics

Of 2,857 patients in the initial trial, there were 741 critically ill surgical patients (fig. 1). Of those 741 surgical patients, 484 (65.3%) were male, 369 (49.8%) suffered from sepsis, and the median age was 66 (52 to 76) yr. In total, 356 patients (48%) were allocated to the crystalloids arm, and 385 (52%) were allocated to the colloids arm. Surgery was elective for 198 (26.7%) patients and unscheduled for 543
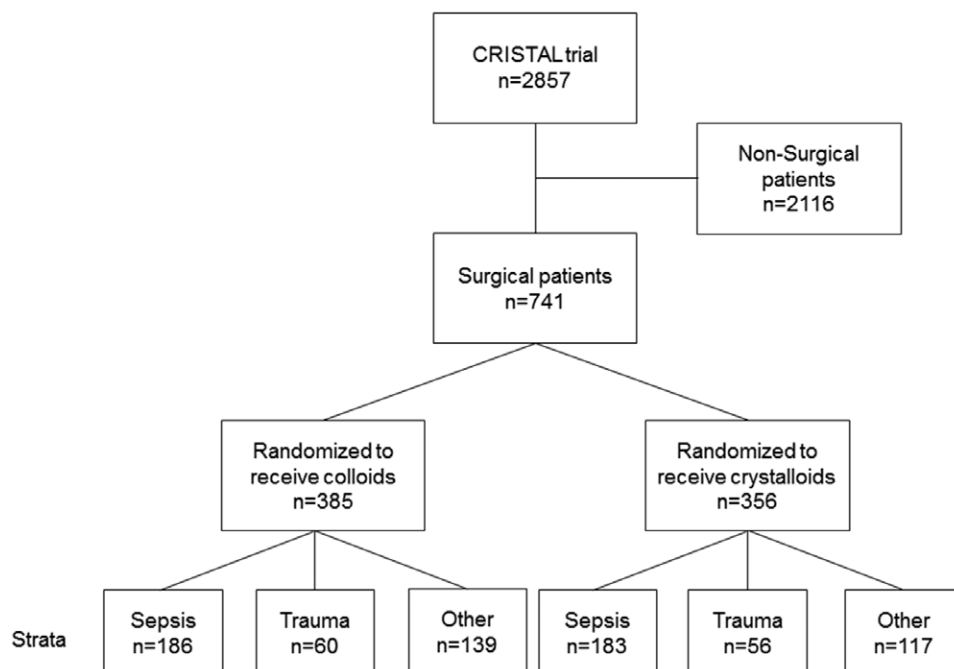
Fig. 1. Enrollment, randomization, and predetermined strata.

(73.3%) patients; 395 patients (53.3%) underwent general or abdominal surgery, 198 patients (26.7%) underwent orthopedic surgery, 127 patients (17.1%) underwent cardiac surgery, and 21 patients (2.9%) underwent neurosurgery. In both arms, some patients received crystalloids and/or colloids in the operating theater before intensive care unit admission and before randomization (table 1). Nevertheless, severe acute hypovolemia was present upon randomization as highlighted by tachycardia, low systolic blood pressure and high diastolic blood pressure, low cardiac index, and high arterial lactate levels (Supplemental Digital Content, supplemental table 1, http://links.lww.com/ALN/B772).

Outcomes

Patients in the crystalloids arm received a median 7-day cumulative dose of fluids of 4,275 (2,000 to 7,500) ml *versus* 2,750 (1,500 to 4,500) ml for patients in the colloids arm (table 2). By day 1, the amount of fluids was markedly ($P < 0.0008$) higher in the crystalloids than in the colloids-treated patients (fig. 2). Over time, 14.8% (n = 57) of patients in the colloids arm received crystalloids, whereas 5.6% (n = 20) of patients in the crystalloids arm received colloids.

There was no difference in the occurrence of death by day 28 between groups: 84 (23.6%) in the crystalloids arm compared to 100 (26%) patients in the colloids arm (adjusted

Table 1. Main Characteristics at Baseline According to Randomization Arm

	Colloids Arm (n = 385)	Crystalloids Arm (n = 356)
Age, median (IQR), yr	65 (52–76)	67 (52–76)
Male sex, n (%)	249/385 (64.7)	235/356 (66.0)
Reason for ICU admission, n (%)		
Scheduled surgery	109/385 (28.3)	89/356 (25.0)
Emergency surgery	276/385 (71.7)	267/356 (75.0)
Source of admission to ICU, n (%)		
Community	158/385 (41.0)	156/356 (43.8)
Hospital ward	199/385 (51.7)	175/356 (49.2)
Other ICU	15/385 (3.9)	18/356 (5.0)
Long-term care facility	13/385 (3.4)	7/356 (2.0)
Type of surgery		
General surgery	200/385 (51.9)	195/356 (54.8)
Orthopedic surgery	102/385 (26.5)	96/356 (27.0)
Cardiac surgery	72/385 (18.7)	55/356 (15.4)
Neurosurgery	11/385 (2.9)	10/356 (2.8)
McCabe class, n (%)		
No underlying disease or no fatal disease	215/383 (56.1)	210/356 (59.0)
Underlying ultimately fatal disease (> 5 yr)	23/383 (6.0)	13/356 (3.6)
Underlying rapidly fatal disease (< 1 yr)	145/383 (37.9)	133/356 (37.4)
Knaus disability scale, n (%)		
A	94/383 (24.5)	89/356 (25.0)
B	139/383 (36.3)	133/356 (37.4)
C	91/383 (23.8)	83/356 (23.3)
D	59/383 (15.4)	51/356 (14.3)
Glasgow Coma Scale score, median (IQR)	13 (4–15)	13 (5–15)
Simplified Acute Physiology Score II, median (IQR)	45 (30–62)	47 (33–66)
Sequential Organ Failure Assessment score, median (IQR)	7 (4–11)	7 (5–11)
Injury Severity Score, median (IQR)	22 (16–29)	24 (17–34)
Cause of hypovolemia, n (%)		
Sepsis	186/385 (48.3)	183/356 (51.4)
Trauma	60/385 (15.6)	56/356 (15.7)
Other	139/385 (36.1)	117/356 (32.9)
Fluid administration before ICU admission (within the past 12 h)		
Crystalloids, n (%)	269/385 (70.0)	231/356 (64.9)
Dose, median (IQR), ml	1,000 (500–2,500)	1,500 (500–2,500)
Colloids, n (%)	266/385 (69.1)	235/356 (66.0)
Dose, median (IQR), ml	500 (0–1,000)	500 (0–1,000)

The Knaus scale is defined as follows: A, prior good health, no functional limitations; B, mild to moderate limitation of activity because of chronic medical problem; C, chronic disease producing serious but not incapacitating restriction of activity; and D, severe restriction of activity caused by disease; includes persons bedridden or institutionalized because of illness.
ICU, intensive care unit; IQR, interquartile range.

Table 2. Type of Fluid Administered by Randomization Arm (Cumulative Dose Administered over a 7-day Period)

	Colloids Arm (n = 385)	Crystalloids Arm (n = 356)	P
Isotonic saline, n (%) Volume, median (IQR), ml	70/385 (18.2) 2,000 (1,000–4,900)	313/356 (87.9) 3,000 (1,500–5,500)	0.0001 0.050
Ringer's lactate, n (%) Volume, median (IQR), ml	36/385 (9.4) 3,500 (1,000–6,125)	120/356 (33.7) 2,500 (1,000–5,000)	0.001 0.815
Hypertonic saline, n (%) Volume, median (IQR), ml	9/385 (2.3) 750 (350–2,500)	16/356 (4.5) 1,250 (620–2,625)	0.462 0.893
Gelatins, n (%) Volume, median (IQR), ml	171/385 (44.4) 1,500 (1,000–3,500)	7/356 (2.0) 500 (500–750)	0.002 0.098
Hydroxyethyl starch, n (%) Volume, median (IQR), ml	299/385 (77.7) 1,500 (1,000–2,275)	24/356 (6.7) 500 (500–1,125)	0.004 0.002
Albumin 20%, n (%)* Volume, median (IQR), ml	5/385 (1.3) 200 (200–300)	11/356 (3.1) 330 (200–400)	0.166 0.832
Albumin 4%, n (%)* Volume, median (IQR), ml	5/385 (1.3) 500 (500–500)	6/356 (1.7) 725 (500–1,362)	0.867 0.754

*Administration of albumin to correct hypoalbuminemia (albumin < 20 g/l) was not taken into account.
IQR, interquartile range.

odds ratio, 0.86; 95% CI, 0.61 to 1.21; P = 0.768; fig. 3). No interaction of the intervention with any of the randomization strata (sepsis, trauma, and other) was found (fig. 4). No interaction of the intervention with the type of surgery was found (fig. 5). There was no difference in the occurrence of death by day 90 between groups: 111 (31.2%) in the crystalloids arm compared to 122 (31.7%) patients in the colloids arm (adjusted odds ratio, 0.97; 95% CI, 0.70 to 1.33;

P = 0.919; fig. 6). The time course of the global Sequential Organ Failure Assessment score was similar in both groups (P = 0.915; fig. 7). The median number of days alive within the first 7 days with a Sequential Organ Failure Assessment score less than 6 did not significantly differ between arms: 2 (0 to 4.25) days in the crystalloids arm *versus* 2 (0 to 4) days in the colloids arm (P = 0.786). Renal replacement therapy was required for 42 patients (11.8%) in the crystalloids
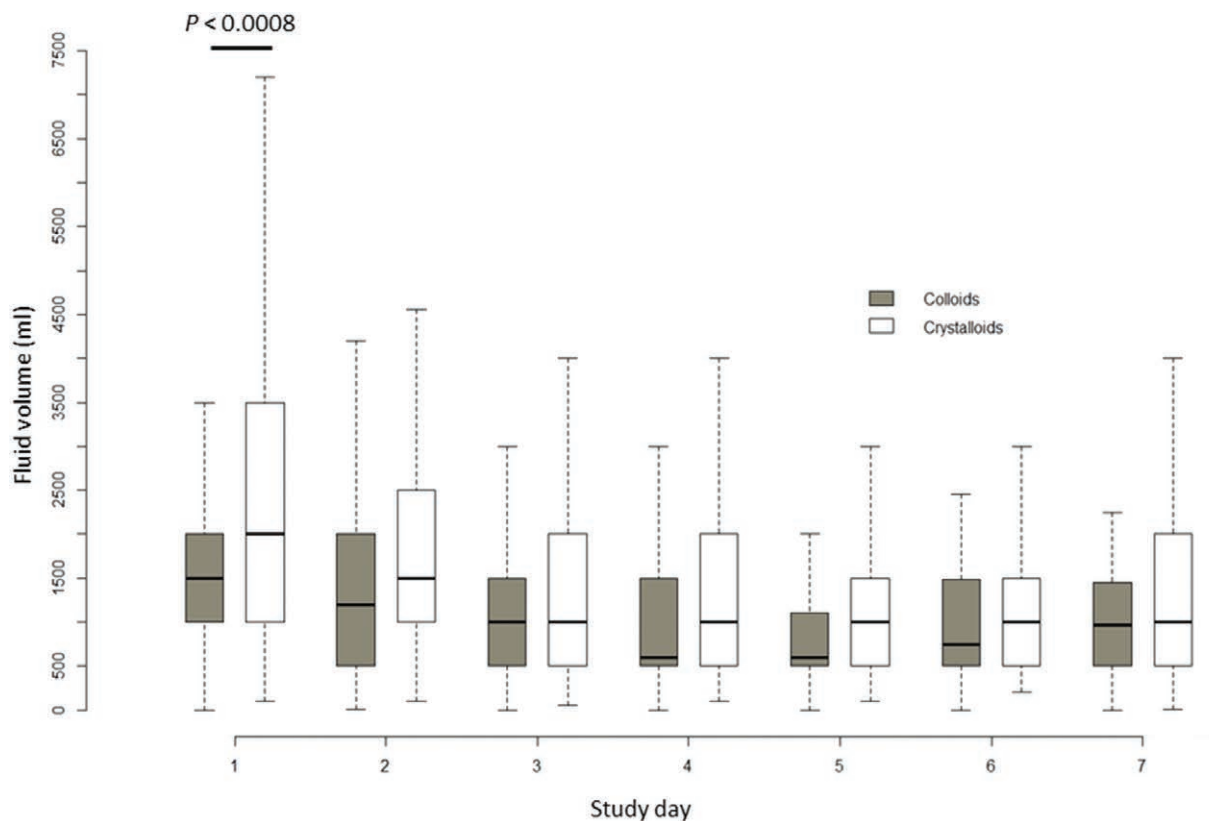
Fig. 2. Total fluid administered over a 7-day period. The amount of colloids administered to achieve hemodynamic stability over the first 24 h was markedly lower than the amount of crystalloids (P < 0.0008).

arm *versus* 49 patients (12.7%) in the colloids arm, over a 7-day period (*P* = 0.897). The median length of stay in the intensive care unit did not significantly differ: 7 (3 to 17) days in the crystalloids arm compared to 7 (3 to 15) days in the colloids arm (*P* = 0.855). The median length of stay in the hospital was 22 (11 to 40) days in the crystalloids arm compared to 21 (10.5 to 38) days in the colloids arm (*P* = 0.815). We also performed a per-protocol comparison of the 340 patients who effectively received colloids and the 259 patients who effectively received crystalloids. Of note, we excluded from the per-protocol analysis all patients in the crystalloid arm who had been treated by albumin even though the protocol provided for albumin supplementation in case of hypoalbuminemia. The per-protocol analysis did not find any difference in the rate of death by day 28 (87 [25.6%] *vs.* 54 [20.8%]; adjusted odds ratio, 0.75; 95% CI, 0.51 to 1.12; *P* = 0.429). The results of the per-protocol analysis are in table 3.

Secondary Surgical Interventions and Blood Transfusion

Secondary surgery was required in 278 (37.5%) patients, of which 131 (36.8%) were in the crystalloids group and 147 (38.2%) in the colloids group (*P* = 0.875). A median number of 2.7 (2.2 to 3.4) units of packed erythrocytes were administered to patients in the crystalloids arm compared to 2.7 (2.3 to 3.5) units in the colloids arm (*P* = 0.890). A median number of 2 (1 to 5) units of platelets was administered to patients in the crystalloids arm compared to 2 (1 to 3) units in the colloids arm (*P* = 0.533). A median volume of 450 (175 to 800) ml of fresh frozen plasma was administered in the crystalloids arm compared to 600 (400 to 1,200)

Fig. 3. Mortality over a 28-day period after randomization in the colloid group, compared with the crystalloid group.
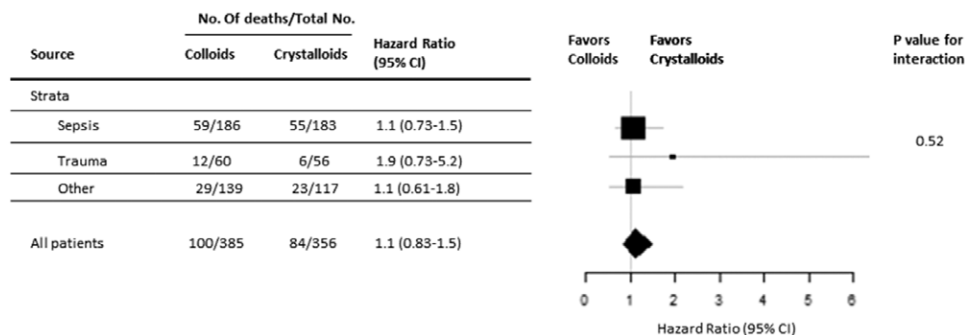
Fig. 4. Hazard ratio for 28-day mortality in the colloid group, compared with the crystalloid group, overall and in predefined subgroups. Size of data markers correspond to the relative size of each subgroup. *Error bars* indicate 95% CIs.
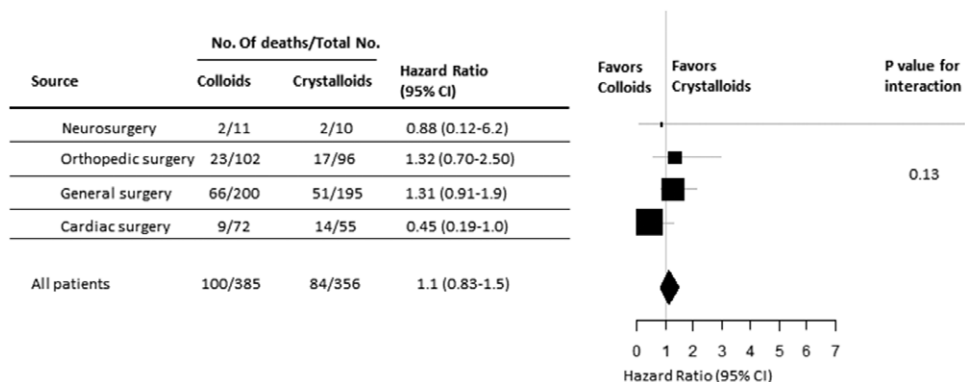
Fig. 5. Hazard ratio for 28-day mortality in the colloid group, compared with the crystalloid group, overall and by type of surgery. Size of data markers correspond to the relative size of each subgroup. *Error bars* indicate 95% CIs.
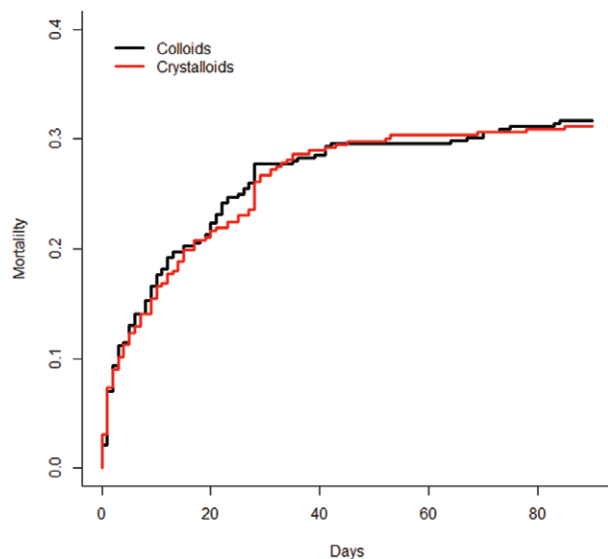
Fig. 6. Mortality over a 90-day period after randomization in the colloid group, compared with the crystalloid group.
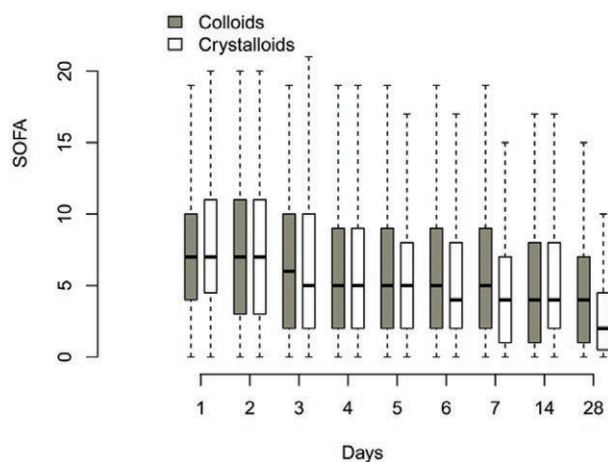
Fig. 7. Global Sequential Organ Failure Assessment score over a 28-day period after randomization in the colloid group, compared with the crystalloid group. *Error bars* indicate 95% CIs. SOFA, Sepsis-related Organ Failure Assessment.

ml in the colloids arm ($P = 0.108$). Additional information regarding the requirement for blood products are found in Supplemental Digital Content, supplemental tables 2 to 7 (http://links.lww.com/ALN/B772). The results of the per-protocol analysis regarding surgical interventions and blood transfusions are found in table 3.

Discussion

In this subgroup analysis of a large pragmatic trial comparing the administration of crystalloids to colloids in surgical patients, we found that colloids did not exhibit a significantly different safety profile from crystalloids. The current analysis encompasses both elective and unscheduled surgery associated with clinically significant hypovolemia. Our main

finding was that 28-day mortality did not differ between treatment arms, both in the intention-to-treat and the per-protocol analyses. Additionally, mortality by day 28 did not differ in any of the three prespecified strata. Mortality by day 90 did not differ between treatment arms, neither in the intention-to-treat nor in the per-protocol analysis. In-hospital and in–intensive care unit length of stay did not differ between treatment arms. The need for secondary surgical interventions did not significantly differ between groups. The amounts of packed erythrocytes, of platelets, and of fresh frozen plasma did not differ between patients treated by crystalloids and those receiving colloids. Importantly, the global Sequential Organ Failure Assessment score and the need for renal replacement therapy did not differ between groups. Because patients were randomized in CRISTAL to receive products belonging to a broad family of fluids, extrapolating our findings to a particular type of solution, such as balanced solutions, is hazardous.[16] We did not record enough data to provide information regarding the development of acute kidney injury in this cohort. However, in similar trials, the occurrence of acute kidney injury was found to be inconsistent with other markers of kidney failure, such as the requirements for renal replacement therapy.[5,7]

The whole population of the CRISTAL trial mainly encompassed patients admitted to the intensive care unit for medical reasons (71%).[4] In the primary analysis of the CRISTAL trial, death by day 28 did not differ significantly between the colloids and crystalloids groups (relative risk, 0.96; 95% CI, 0.88 to 1.04; $P = 0.26$), and mortality by day 90 was significantly lower in the colloids arm (relative risk, 0.92; 95% CI, 0.86 to 0.99; $P = 0.03$). In this exploratory analysis of the surgical population, mortality rates by days 28 and 90 are broadly similar to that of the global CRISTAL population, as well as the risk for renal replacement therapy requirement (relative risk, 0.93; 95% CI, 0.83 to 1.03; $P = 0.19$). Data pertaining more specifically to the surgical subpopulation (*e.g.*, bleeding risk and need for secondary surgery) were not analyzed in the whole population of the CRISTAL trial.

Colloids for the Surgical and the Trauma Patient

The most thoroughly studied subtype of colloid in the surgical context is starch. Retrospective studies hint at the possibility of acute kidney injury after the administration of starches in the surgical setting.[17] However, several small randomized controlled trials in elective surgery reported no renal side effect related to hydroxyethyl starch administration.[18,19] In the Crystalloid *versus* Hydorxyethyl Starch Trial, the number of surgical patients undergoing renal replacement therapy did not differ between both groups: 61 of 1,425 assigned to hydroxyethyl starch (4.3%) *versus* 45 of 1,447 assigned to saline (3.0%) (relative risk, 1.38; 95% CI, 0.94 to 2.01).[20] The Fluids in Resuscitation of Severe Trauma trial, comparing the administration of starches to that of crystalloids in both blunt and penetrating trauma, found no difference in mortality,

Table 3. Main Outcomes, Per-protocol Analysis

	Colloids Arm (n = 340)	Crystalloids Arm (n = 259)	P
Death by day 28, n (%)	87/340 (25.6)	54/259 (20.9)	0.494
Death by day 90, n (%)	109/340 (32.1)	74/259 (28.6)	0.745
Renal replacement therapy, n (%)	48/340 (14.1)	27/259 (10.4)	0.525
Length of stay in the ICU, median (IQR), days	7 (3–14)	6 (3–15)	0.891
Length of stay in the hospital, median (IQR), days	21 (10–38)	20 (11–38)	0.905
Secondary surgery requirement, n (%)	132/340 (38.8)	98/259 (37.8)	0.870
Packed erythrocyte transfusion, median (IQR), units	2 (2–4)	2 (2–4)	0.467
Platelet transfusion, median (IQR), units	2 (1–3)	2.5 (1.25–3)	0.533
Fresh frozen plasma administration, median (IQR), ml	600 (400–1,088)	400 (108–600)	0.034

ICU, intensive care unit; IQR, interquartile range.

whereas acute kidney injury occurred more frequently in the saline group.[21] A recent trial found that the use of colloids was associated with fewer complications than use of crystalloids in elective abdominal surgery.[22] Several meta-analyses of surgical patients concluded that starches do not induce additional renal injury.[23–25] Although these analyses have been criticized,[26,27] our findings, namely no increased need for renal replacement therapy associated with the administration of colloids, are in keeping with previous reports. Such a difference in the occurrence of acute kidney injury between subjects affected by sepsis and those affected by surgery or trauma may be related to different pathophysiology of acute kidney injury. If blood loss from trauma or during surgery leads to hypotension and renal ischemia, prompt restoration of renal hemodynamic may reduce the incidence of acute kidney injury.[28] The pathophysiology of sepsis-associated acute kidney injury is wholly different, because acute kidney injury may occur despite normal renal blood flow.[29] Pathophysiologic mechanisms of sepsis-associated acute kidney injury include inflammation, microcirculatory dysfunction, and endothelial cell injury.[30] Starches may also affect bleeding in surgical patients. Several trials comparing starches to crystalloids found that starches reduced the clot strength and increased bleeding during both major surgery and cardiac surgery.[31–33] In the Fluids in Resuscitation of Severe Trauma trial, patients suffering from blunt trauma randomized to the hydroxyethyl starch group required significantly more blood products than those randomized to receive saline.[21] We did not observe any difference in the required amount of packed erythrocytes, platelets, or fresh frozen plasma. Little is known of the effect of colloid *versus* crystalloid solutions on mortality in the surgical setting, because surgical-related mortality in most circumstances is extremely low. In the subgroup of patients undergoing surgery before randomization into the 6S trial, death by day 90 occurred in 61 of 131 patients in the hydroxyethyl starch subgroup *versus* 53 of 146 patients in the Ringer's acetate subgroup (relative risk, 1.28; 95% CI, 0.97 to 1.70; *P* = 0.42).[34] A last point to be mentioned when comparing crystalloids to colloids is the cost of each product. CRISTAL was not designed to analyze the cost of both interventions.

No power computation was performed when this secondary analysis of the trial was undertaken. Nevertheless, given the sample size of 741 patients broadly divided into two equal-sized groups, the statistical power to detect an effect size of at least 0.2 was above 80%. Strengths of the current study include the fact that our data set stems from a pragmatic, randomized clinical trial, depicting the use of resuscitation fluids in real-world conditions. Additionally, our analyses were preplanned, and we report on a small number of outcomes, reducing the risk of false-positive results.[35] Our study has several limitations. First, we did not have access to perioperative blood loss; we therefore had to use a surrogate marker of blood loss, the number of packed erythrocytes administered. Second, because our population consists of patients who were transferred from the operating theater to the intensive care unit, extrapolation of our findings to all patients managed in the operating theater requires careful consideration.

Conclusions

In surgical patients included in the CRISTAL trial, we found no difference between colloids and crystalloids regarding safety, namely the risk of death or of organ failure, including acute kidney injury. The safety of colloids was comparable to that of crystalloids in our population of surgical patients treated for hypovolemic shock.

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Competing Interests

The authors declare no competing interests.

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References

1. Bellomo R, Bion J, Finfer S, Myburgh J, Perner A, Reinhart K; all co-signatories: Open letter to the Executive Director of the European Medicines Agency concerning the licensing of hydroxyethyl starch solutions for fluid resuscitation. Br J Anaesth 2014; 112:595–600

2. Coriat P, Guidet B, de Hert S, Kochs E, Kozek S, Van Aken H; all co-signatories listed online: Counter statement to open letter to the Executive Director of the European Medicines Agency concerning the licensing of hydroxyethyl starch solutions for fluid resuscitation. Br J Anaesth 2014; 113:194–5

3. Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, Moerer O, Gruendling M, Oppert M, Grond S, Olthoff D, Jaschinski U, John S, Rossaint R, Welte T, Schaefer M, Kern P, Kuhnt E, Kiehntopf M, Hartog C, Natanson C, Loeffler M, Reinhart K; German Competence Network Sepsis (SepNet): Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 2008; 358:125–39

4. Annane D, Siami S, Jaber S, Martin C, Elatrous S, Declère AD, Preiser JC, Outin H, Troché G, Charpentier C, Trouillet JL, Kimmoun A, Forceville X, Darmon M, Lesur O, Reignier J, Régnier J, Abroug F, Berger P, Clec'h C, Cle'h C, Cousson J, Thibault L, Chevret S; CRISTAL Investigators: Effects of fluid resuscitation with colloids *vs.* crystalloids on mortality in critically ill patients presenting with hypovolemic shock: The CRISTAL randomized trial. JAMA 2013; 310:1809–17

5. Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, Glass P, Lipman J, Liu B, McArthur C, McGuinness S, Rajbhandari D, Taylor CB, Webb SA; CHEST Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group: HydroxyCethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med 2012; 367:1901–11

6. European Medicines Agency: PRAC confirms that hydroxy-ethyl-starch solutions (HES) should no longer be used in patients with sepsis or burn injuries or in critically ill patients. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/10/WC500151964.pdf. Accessed May 7, 2018

7. Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Åneman A, Madsen KR, Møller MH, Elkjær JM, Poulsen LM, Bendtsen A, Winding R, Steensen M, Berezowicz P, Søe-Jensen P, Bestle M, Strand K, Wiis J, White JO, Thornberg KJ, Quist L, Nielsen J, Andersen LH, Holst LB, Thormar K, Kjældgaard AL, Fabritius ML, Mondrup F, Pott FC, Møller TP, Winkel P, Wetterslev J; 6S Trial Group; Scandinavian Critical Care Trials Group: Hydroxyethyl starch 130/0.42 *versus* Ringer's acetate in severe sepsis. N Engl J Med 2012; 367:124–34

8. Scheingraber S, Rehm M, Sehmisch C, Finsterer U: Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. ANESTHESIOLOGY 1999; 90:1265–70

9. Chowdhury AH, Cox EF, Francis ST, Lobo DN: A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte® 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. Ann Surg 2012; 256:18–24

10. McCabe WR, Jackson GG: Gram-negative bacteremia: I. Etiology and ecology. Arch Intern Med 1962; 110:847–55

11. Knaus WA, Zimmerman JE, Wagner DP, Draper EA, Lawrence DE: APACHE-acute physiology and chronic health evaluation: A physiologically based classification system. Crit Care Med 1981; 9:591–7

12. Le Gall JR, Lemeshow S, Saulnier F: A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 1993; 270:2957–63

13. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, Reinhart CK, Suter PM, Thijs LG: The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure: On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996; 22:707–10

14. Baker SP, O'Neill B, Haddon W Jr, Long WB: The Injury Severity Score: A method for describing patients with multiple injuries and evaluating emergency care. J Trauma 1974; 14:187–96

15. Benjamini Y, Hochberg Y: Controlling the false discovery rate: A practical and powerful approach to multiple testing. J R Stat Soc Ser B Methodol 1995; 57:289–300

16. Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M: Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA 2012; 308:1566–72

17. Kashy BK, Podolyak A, Makarova N, Dalton JE, Sessler DI, Kurz A: Effect of hydroxyethyl starch on postoperative kidney function in patients having noncardiac surgery. ANESTHESIOLOGY 2014; 121:730–9

18. Kancir AS, Pleckaitiene L, Hansen TB, Ekeløf NP, Pedersen EB: Lack of nephrotoxicity by 6% hydroxyethyl starch 130/0.4 during hip arthroplasty: A randomized controlled trial. ANESTHESIOLOGY 2014; 121:948–58

19. Kancir AS, Johansen JK, Ekeloef NP, Pedersen EB: The effect of 6% hydroxyethyl starch 130/0.4 on renal function, arterial blood pressure, and vasoactive hormones during radical prostatectomy: A randomized controlled trial. Anesth Analg 2015; 120:608–18

20. Wilkes M, Navickis, RJ: Postoperative renal replacement therapy after hydroxyethyl starch infusion: A meta-analysis of randomised trials. Neth J Crit Care 2014:4–9

21. James MF, Michell WL, Joubert IA, Nicol AJ, Navsaria PH, Gillespie RS: Resuscitation with hydroxyethyl starch improves renal function and lactate clearance in penetrating trauma in a randomized controlled study: The FIRST trial (Fluids in Resuscitation of Severe Trauma). Br J Anaesth 2011; 107:693–702

22. Joosten A, Delaporte A, Ickx B, Touihri K, Stany I, Barvais L, Van Obbergh L, Loi P, Rinehart J, Cannesson M, Van der Linden P: Crystalloid *versus* colloid for intraoperative goal-directed fluid therapy using a closed-loop system: A randomized, double-blinded, controlled trial in major abdominal surgery. ANESTHESIOLOGY 2018; 128:55–66

23. Martin C, Jacob M, Vicaut E, Guidet B, Van Aken H, Kurz A: Effect of waxy maize-derived hydroxyethyl starch 130/0.4 on renal function in surgical patients. ANESTHESIOLOGY 2013; 118:387–94

24. Van Der Linden P, James M, Mythen M, Weiskopf RB: Safety of modern starches used during surgery. Anesth Analg 2013; 116:35–48

25. Jacob M, Fellahi JL, Chappell D, Kurz A: The impact of hydroxyethyl starches in cardiac surgery: A meta-analysis. Crit Care 2014; 18:656

26. Groeneveld AB, Navickis RJ, Wilkes MM: Hydroxyethyl starch 130/0.4 and postoperative acute kidney injury. ANESTHESIOLOGY 2013; 119:733–5

27. Takala J, Hartog C, Reinhart K: Safety of modern starches used during surgery: Misleading conclusions. Anesth Analg 2013; 117:527–8

28. Goren O, Matot I: Perioperative acute kidney injury. Br J Anaesth 2015; 115:ii3–14

29. Zarbock A, Gomez H, Kellum JA: Sepsis-induced acute kidney injury revisited: Pathophysiology, prevention and future therapies. Curr Opin Crit Care 2014; 20:588–95

30. Ergin B, Kapucu A, Demirci-Tansel C, Ince C: The renal microcirculation in sepsis. Nephrol Dial Transplant 2015; 30:169–77

31. Rasmussen KC, Johansson PI, Højskov M, Kridina I, Kistorp T, Thind P, Nielsen HB, Ruhnau B, Pedersen T, Secher NH: Hydroxyethyl starch reduces coagulation competence and increases blood loss during major surgery: Results from a randomized controlled trial. Ann Surg 2014; 259:249–54

32. Skhirtladze K, Base EM, Lassnigg A, Kaider A, Linke S, Dworschak M, Hiesmayr MJ: Comparison of the effects of albumin 5%, hydroxyethyl starch 130/0.4 6%, and Ringer's lactate on blood loss and coagulation after cardiac surgery. Br J Anaesth 2014; 112:255–64

33. Schramko A, Suojaranta-Ylinen R, Kuitunen A, Raivio P, Kukkonen S, Niemi T: Hydroxyethylstarch and gelatin solutions impair blood coagulation after cardiac surgery: A prospective randomized trial. Br J Anaesth 2010; 104:691–7

34. Müller RG, Haase N, Wetterslev J, Perner A: Effects of hydroxyethyl starch in subgroups of patients with severe sepsis: Exploratory post-hoc analyses of a randomised trial. Intensive Care Med 2013; 39:1963–71

35. Sun X, Ioannidis JP, Agoritsas T, Alba AC, Guyatt G: How to use a subgroup analysis: Users' guide to the medical literature. JAMA 2014; 311:405–11

ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

York Dentist Kurwin Eisenhart Provided "Any Anesthetic Desired"

From the Ben Z. Swanson Collection of the Wood Library-Museum of Anesthesiology, this "floral spray" type of trade card (*high*) was distributed around 1886 by a dental surgeon headquartered above the post office on Center Square in York, Pennsylvania. Born the year that Simpson pioneered chloroform anesthesia, Kurwin L. Eisenhart, D.D.S. (1847 to 1925) was one of the few dentists in York who could administer not only chloroform, but also ether, nitrous oxide, or "vitalized air," which was laughing gas supplemented with alcohol and chloroform. Indeed, he advertised (*low*) that he could extract teeth "by any anesthetic desired." (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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David S. Warner, M.D., Editor

Succinylcholine and Intracranial Pressure

James E. Cottrell, M.D.

Intracranial and Hemodynamic Changes after Succinylcholine Administration in Cats. By Cottrell JE, Hartung J, Giffin JP, and Shwiry B. *Anesthesia & Analgesia* 1983; 62:1006–9. Reprinted with permission.

Abstract: Bolus injections of succinylcholine (1.5 mg/kg) significantly increased intracranial pressure (ICP) in cats under normal conditions from control levels of 8 +/- 1 mmHg to 16 +/- 3 mmHg (+/- SEM, P less than 0.01), and in the presence of artificially increased ICP from control levels of 27 +/- 1 mmHg to 47 +/- 4 mmHg (*P* less than 0.01). These approximately 100% increases in ICP were accompanied by a transitory decrease in mean arterial pressure (approximately 10 s), followed by a 15 to 20% increase (*P* less than 0.05). Pulmonary arterial pressure increased 20 to 30% (*P* less than 0.05). These results, when considered in conjunction with results previously obtained in humans, suggest that succinylcholine may be contraindicated in neurosurgical patients.

AS residents, most of us are intimidated by the mountain of knowledge that we need to climb. As fellows, falsely confident that we have scaled at least halfway to the peak, an impish notion begins to insinuate itself—the possibility that we might be able to make the mountain a little higher. That was a stimulating aspiration for anyone lucky enough to work with the likes of Ephraim S. [Rick] Siker, M.D. (deceased, previously of University of Pittsburgh Medical Center Mercy Hospital, Pittsburgh, Pennsylvania), and Bernard [Bernie] Wolfson, M.D. (retired, previously of University of Pittsburgh Medical Center Mercy Hospital, Pittsburgh, Pennsylvania), in the early 1970s.

Our first article tested the hypothesis that preoperative intermittent positive pressure breathing therapy would improve postoperative pulmonary function in patients with chronic obstructive lung disease.[1] We were not able to reject the null hypothesis, but according to the custom of *Anesthesia & Analgesia* in 1973, as first author, I got my picture in the article (fig. 1)—and yes, I sent a reprint to my mother!

We had better luck with the null hypothesis in our 1976 paper on airway resistance during sedation of my fellow residents![2] So I got off to a lucky start with pulmonary studies before being drafted by the U.S. Navy, where my lucky streak continued. I was packed for Vietnam when a last-minute change of deployment landed me in the Naval Health Facility at Keflavik, Iceland, and I applied for a faculty appointment at Borgaspitalin in Reykjavik, Iceland, where I did some clinical work and taught medical students, residents, and anesthesia nurses.

James E. Cottrell, M.D.

Fig. 1. From Cottrell JE, Siker ES: Preoperative intermittent positive pressure breathing therapy in patients with chronic obstructive lung disease: Effect on postoperative pulmonary complications. Anesth Analg 1973; 52:258–62. Reprinted with permission from Cottrell and Siker.[1]
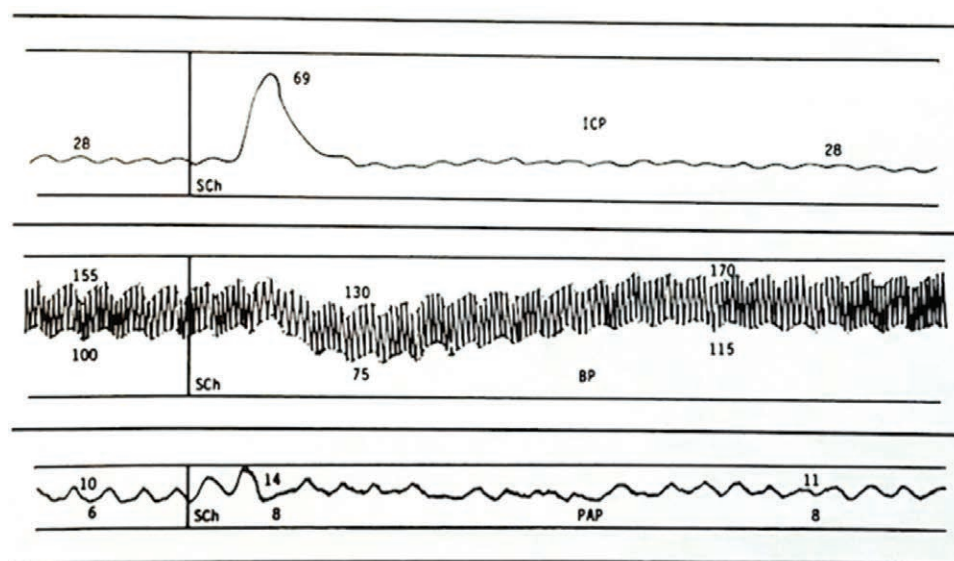
Fig. 2. Tracing of intracranial pressure (ICP), blood pressure (BP), and pulmonary arterial pressure (PAP) for approximately 100 s. *Vertical line*, injection of succinylcholine (Sch; 1.5 mg/kg; from cat No. 10, initial ICP increased). Reprinted with permission from Cottrell *et al.*[10]

After a year in Iceland, I was assigned to coordinate the neuroanesthesia section of the Philadelphia Naval Hospital, Philadelphia, Pennsylvania, which served as sufficient experience to land essentially the same job back in civilian life, as an assistant professor at New York University, New York, New York. As a level 1 trauma center, Bellevue Hospital, New York, New York, had an amazing team of neurosurgeons, neurologists, and vascular neuroradiologists, and a sophisticated brain and spinal cord monitoring facility. But I had mixed feelings. On one hand, with so many experts and so much high-end monitoring, I felt like a kid in a candy store; on the other hand, at times I felt like a first-year resident—if not a first-year medical student!

One of those amazing surgeons was always asking us about intracranial pressure (ICP) and commenting on brain swelling during open cranium procedures. After closure, he would leave a ventricular drain or place a Becker Bolt so we could directly monitor ICP in the neurointensive care unit. Meanwhile, our vascular surgeon loved to use vasoactive drugs to demonstrate how he could relax spastic vessels around an aneurysm with topical papaverine and an intravenous infusion of aminophylline. So, the time was right to

formally investigate the effect of commonly used drugs on ICP and cerebral perfusion pressure.

Our first investigation measured changes in ICP, osmolality, and electrolytes after administration of mannitol and furosemide in craniotomy patients. The data warranted our recommendation "that furosemide be used instead of mannitol when diuresis is desired in patients with increased ICP, and in those who have pre-existing cardiac and electrolyte abnormalities."[3,4] Over the ensuing decades, we investigated these and other variables, *in vitro* and *in vivo*, after administration of nitroprusside,[5,6] nitrous oxide,[7] nitroglycerin,[8] naloxone,[9] succinylcholine,[10] nifedipine,[11] midazolam,[12] thiopental,[13] tetrodotoxin,[14] diltiazem,[15] atracurium,[16] trimethaphan,[17] lidocaine,[18] sevoflurane,[19] desflurane,[20] and protein kinase Mzeta,[21] among others.

From the above list, I chose the publication "Intracranial and Hemodynamic Changes after Succinylcholine Administration in Cats"[10] to serve as a Classic Paper Revisited—an article that addressed the concern that a commonly used muscle relaxant could cause ischemic damage from decreased cerebral perfusion pressure when given to a patient with low intracranial compliance, or even irreparable damage from

brainstem herniation through the foramen magnum consequent to a large, sudden increase in ICP.

The backstory on our succinylcholine investigation is that we were in the laboratory to determine whether we could measure ICP in cats *via* cisterna magna puncture with a double-lumen 18-gauge needle in preparation for testing the effect of nifidepine-induced hypotension on normal and elevated ICP. We were pleased to find that our double-lumen technique gave a breath-to-breath sensitive measure of ICP through one lumen with that sensitivity maintained while increasing ICP through the other lumen. We were about to inject a final test dose of nifedipine when pancuronium-induced paralysis appeared to be wearing off. We decided to give an injection of succinylcholine to buy the small amount of time needed give one last dose of nifedipine. To our surprise, the ICP tracing spiked immediately upon injection of succinylcholine (fig. 2). After establishing this effect of succinylcholine with repeated injections, we decided to delay the nifedipine study[11] and design a protocol for testing the effect of succinylcholine on ICP.[10]

Subsequent to our finding in cats, Lanier *et al.*[22,23] found convincing evidence that succinylcholine induces sufficient muscle afferent activity to generate immediate electroencephalographic arousal accompanied by rapidly elevated cerebral blood flow and increased ICP in dogs. To date, seven investigations have found that succinylcholine increases ICP in patients,[24–30] suggesting that our observations in cats warranted clinical concern. Two of those investigations also found that succinylcholine-induced increases in ICP can be ameliorated by previous administration of alternative muscle relaxants.[29,30]

Although reports relating succinylcholine administration to brain herniation have not been published, absence of evidence is not evidence of absence,[31] especially when dealing with rare and life-threatening events.[32] Brain herniation aside, empirical evidence supporting the physiologic basis for succinylcholine-induced cerebral ischemia has recently been published in a thoughtfully designed and analyzed retrospective study entitled "Succinylcholine Is Associated with Increased Mortality When Used for Rapid Sequence Intubation of Severely Brain Injured Patients in the Emergency Department."[33]

Competing Interests

The author declares no competing interests.

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Address correspondence to Dr. Cottrell: State University of New York, Downstate Medical Center, Department of Anesthesiology – Box 6, 450 Clarkson Avenue, Brooklyn, New York 11203. James.Cottrell@downstate.edu. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

References

1. Cottrell JE, Siker ES: Preoperative intermittent positive pressure breathing therapy in patients with chronic obstructive lung disease: Effect on postoperative pulmonary complications. Anesth Analg 1973; 52:258–62

2. Cottrell JE, Wolfson B, Siker ES: Changes in airway resistance following droperidol, hydroxyzine, and diazepam in normal volunteers. Anesth Analg 1976; 55:18–21

3. Cottrell JE, Robustelli A, Post K, Turndorf H: Furosemide- and mannitol-induced changes in intracranial pressure and serum osmolality and electrolytes. ANESTHESIOLOGY 1977; 47:28–30

4. Cottrell JE, Marlin AE: Furosemide and human head injury. J Trauma 1981; 21:805–6

5. Cottrell JE, Patel K, Turndorf H, Ransohoff J: Intracranial pressure changes induced by sodium nitroprusside in patients with intracranial mass lesions. J Neurosurg 1978; 48:329–31

6. Cottrell JE, Casthely P, Brodie JD, Patel K, Klein A, Turndorf H: Prevention of nitroprusside-induced cyanide toxicity with hydroxocobalamin. N Engl J Med 1978; 298:809–11

7. Hartung J, Cottrell JE: Nitrous oxide reduces thiopental-induced prolongation of survival in hypoxic and anoxic mice. Anesth Analg 1987; 66:47–52

8. Cottrell JE, Gupta B, Rappaport H, Turndorf H, Ransohoff J, Flamm ES: Intracranial pressure during nitroglycerin-induced hypotension. J Neurosurg 1980; 53:309–11

9. Estilo AE, Cottrell JE: Hemodynamic and catecholamine changes after administration of naloxone. Anesth Analg 1982; 61:349–53

10. Cottrell JE, Hartung J, Giffin JP, Shwiry B: Intracranial and hemodynamic changes after succinylcholine administration in cats. Anesth Analg 1983; 62:1006–9

11. Griffin JP, Cottrell JE, Hartung J, Shwiry B: Intracranial pressure during nifedipine-induced hypotension. Anesth Analg 1983; 62:1078–80

12. Giffin JP, Cottrell JE, Shwiry B, Hartung J, Epstein J, Lim K: Intracranial pressure, mean arterial pressure, and heart rate following midazolam or thiopental in humans with brain tumors. ANESTHESIOLOGY 1984; 60:491–4

13. Bendo AA, Kass IS, Cottrell JE: Anesthetic protection against anoxic damage in the rat hippocampal slice. Brain Res 1987; 403:136–41

14. Cottrell JE, Hartung J, Giffin JP, Shwiry B: Intracranial pressure during tetrodotoxin-induced hypotension. Anesth Analg 1984; 63:1005–8

15. Mazzoni P, Giffin JP, Cottrell JE, Hartung J, Capuano C, Epstein JM: Intracranial pressure during diltiazem-induced hypotension in anesthetized dogs. Anesth Analg 1985; 64:1001–4

16. Giffin JP, Litwak B, Cottrell JE, Hartung J, Capuano C: Intracranial pressure mean arterial pressure and heart rate after rapid paralysis with atracurium in cats. Can Anaesth Soc J 1985; 32:618–21

17. Karlin A, Hartung J, Cottrell JE: Rate of induction of hypotension with trimetaphan modifies the intracranial pressure response in cats. Br J Anaesth 1988; 60:161–6

18. Lei B, Popp S, Capuano-Waters C, Cottrell JE, Kass IS: Lidocaine attenuates apoptosis in the ischemic penumbra and reduces infarct size after transient focal cerebral ischemia in rats. Neuroscience 2004; 125:691–701

19. Liu J, Yang L, Lin D, Cottrell JE, Kass IS: Sevoflurane blocks the induction of long-term potentiation when present during, but not when present only before, the high-frequency stimulation. ANESTHESIOLOGY 2018; 128:555–63

20. Dimaculangan D, Bendo AA, Sims R, Cottrell JE, Kass IS: Desflurane improves the recovery of the evoked postsynaptic population spike from CA1 pyramidal cells after hypoxia in rat hippocampal slices. J Neurosurg Anesthesiol 2006; 18:78–82

21. Hsieh C, Tsokas P, Serrano P, Hernández AI, Tian D, Cottrell JE, Shouval HZ, Fenton AA, Sacktor TC: Persistent increased PKMζ in long-term and remote spatial memory. Neurobiol Learn Mem 2017; 138:135–44

22. Lanier WL, Milde JH, Michenfelder JD: Cerebral stimulation following succinylcholine in dogs. ANESTHESIOLOGY 1986; 64:551–9

23. Lanier WL, Iaizzo PA, Milde JH: Cerebral function and muscle afferent activity following intravenous succinylcholine in dogs anesthetized with halothane: The effects of pretreatment with a defasciculating dose of pancuronium. ANESTHESIOLOGY 1989; 71:87–95

24. Halldin M, Wahlin A: Effect of succinylcholine on the intraspinal fluid pressure. Acta Anaesthesiol Scand 1959; 3:155–61

25. Sondergard W: Intracranial pressure during general anaesthesia. Dan Med Bul 1961;8:18–25

26. Lewelt W, Moszynski K, Kozniewska H: Effects of depolarizing, nondepolarizing muscle relaxants and intubation on the ventricular fluid pressure. In: Beks JwF, Bosch DA, Brock M, eds. Intracranial Pressure III. Berlin, Springer-Verlag, 1976, pp 215–8

27. Moszyński K: Dynamic changes in cerebrospinal fluid pressure during neurosurgical operations. Acta Neurochir (Wien) 1976; 34:295–6

28. Marsh ML, Dunlop BJ, Shapiro HM, Gagnon RL, Rockoff MA: Succinylcholine-intracranial pressure effects in neurosurgical patients. Anes Analg 1980; 59:550–1

29. Minton MD, Grosslight K, Stirt JA, Bedford RF: Increases in intracranial pressure from succinylcholine: Prevention by prior nondepolarizing blockade. ANESTHESIOLOGY 1986; 65:165–9

30. Stirt JA, Grosslight KR, Bedford RF, Vollmer D: "Defasciculation" with metocurine prevents succinylcholine-induced increases in intracranial pressure. ANESTHESIOLOGY 1987; 67:50–3

31. Hartung J, Cottrell JE, Giffin JP: Absence of evidence is not evidence of absence. ANESTHESIOLOGY 1983; 58:298–300

32. Hartung J, Cottrell JE: Negative inferences about rare events require large samples. ANESTHESIOLOGY 1993; 79:1155–6

33. Patanwala AE, Erstad BL, Roe DJ, Sakles JC: Succinylcholine is associated with increased mortality when used for rapid sequence intubation of severely brain injured patients in the emergency department. Pharmacotherapy 2016; 36:57–63

ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Chloroforming a Hoosier Holiday Turkey

On Christmas day in 1930, *The Indianapolis Star* featured the culinary adventures of a bride-to-be from Richmond, Indiana. In attempting to dispatch her plucky-but-unplucked holiday turkey in a humane manner, the young woman had chloroformed the feisty fowl before defeathering and then refrigerating it overnight. As the *Star* recorded, when "she opened the refrigerator the next morning, the turkey had recovered from the chloroform and although weak from the plucking and cold" …was still alive. The naked bird was chloroformed again until "thoroughly dead" and roasted in the oven. Not surprisingly, the fowl tasted foul. Indeed, the "turkey had been so thoroughly chloroformed that neither hostess nor guests could partake of it." (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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Brian P. Kavanagh, M.B., F.R.C.P.C., Editor

Images in Anesthesiology: Diagnosis of Atrial Tachycardia with Transesophageal Echocardiography

Damien Contou, M.D., Jean-Pierre Laforêt, M.D., Jo-Anna Tirolien, M.D., Hervé Mentec, M.D.
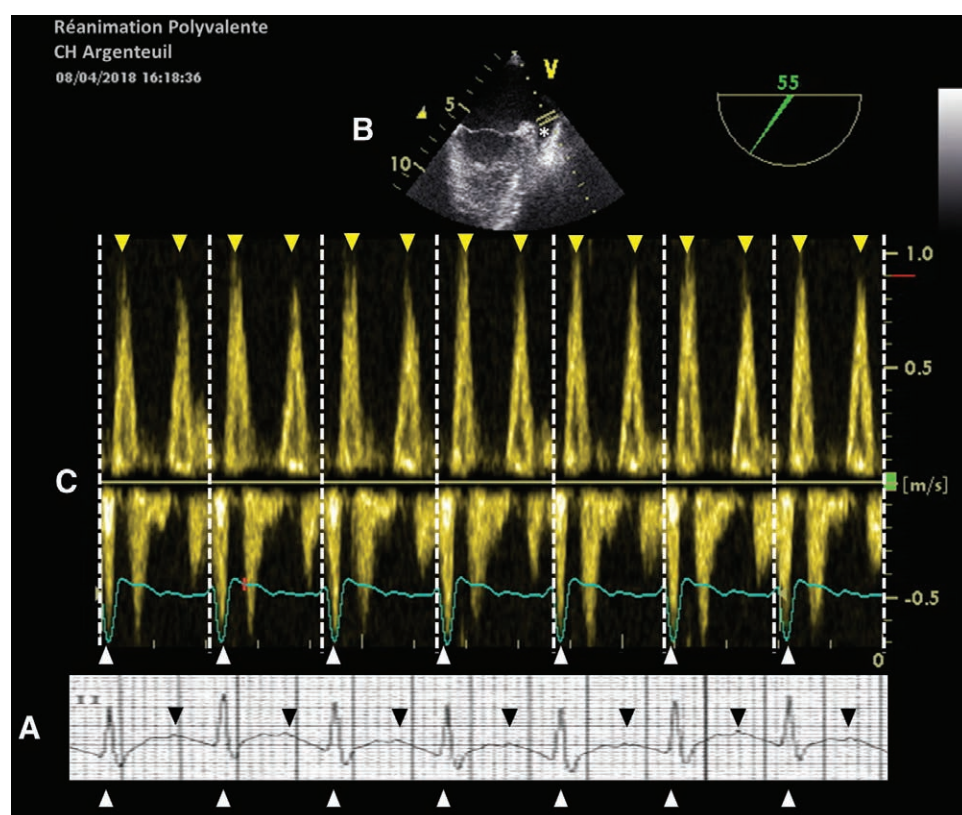
A PREVIOUSLY healthy 52-yr-old man was admitted to the intensive care unit for septic shock and diffuse alveolar hemorrhage caused by leptospirosis. He received high-dose norepinephrine (2.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$); the heart rate was 155 beats/min, and the electrocardiogram revealed regular tachycardia with narrow QRS complexes (image *A, white arrows*). A P wave (image *A, black arrows*) was observed in the middle of each RR interval, and it was unclear if the rhythm was sinus tachycardia, atrial tachycardia, or atrial flutter. Transesophageal echocardiography, performed for evaluation of shock, included pulsed-wave Doppler ultrasound directed to the left atrial appendage (image *B,* *).

This demonstrated two atrial contractions (image *C, yellow arrows*) between each QRS complex (image *C, white arrows*), suggesting atrial tachycardia with a 2:1 atrioventricular block. Because there was no atrial thrombus, electrical cardioversion (150 J) was performed; the rhythm converted to sinus rhythm and the requirement for norepinephrine significantly decreased. The patient ultimately recovered and was discharged home. New-onset supraventricular arrhythmias are common (up to 42%) in patients with septic shock.[1] When interpretation of the electrocardiogram is difficult, transesophageal echocardiography Doppler can distinguish among supraventricular arrhythmias.[2] The presence of two left atrial appendage contractions between two QRS complexes suggests atrial tachycardia or flutter with a 2:1 atrioventricular block. Electrical cardioversion is a first-line therapy if hemodynamically unstable,[3] but it can cause systemic embolization in the presence of a left atrial thrombus.

Competing Interests

The authors declare no competing interests.

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References

1. Seemann A, Boissier F, Razazi K, Carteaux G, de Prost N, Brun-Buisson C, Mekontso Dessap A: New-onset supraventricular arrhythmia during septic shock: Prevalence, risk factors and prognosis. Ann Intensive Care 2015; 5:27

2. Agmon Y, Khandheria BK, Gentile F, Seward JB: Echocardiographic assessment of the left atrial appendage. J Am Coll Cardiol 1999; 34:1867–77

3. Amar D: Perioperative atrial tachyarrhythmias. Anesthesiology 2002; 97:1618–23

Profound Vasoconstriction

Implications for Percutaneous Arterial Access

Daniel G. Taylor, M.B.Ch.B., F.F.I.C.M., Luigi Camporota, M.D., Ph.D.
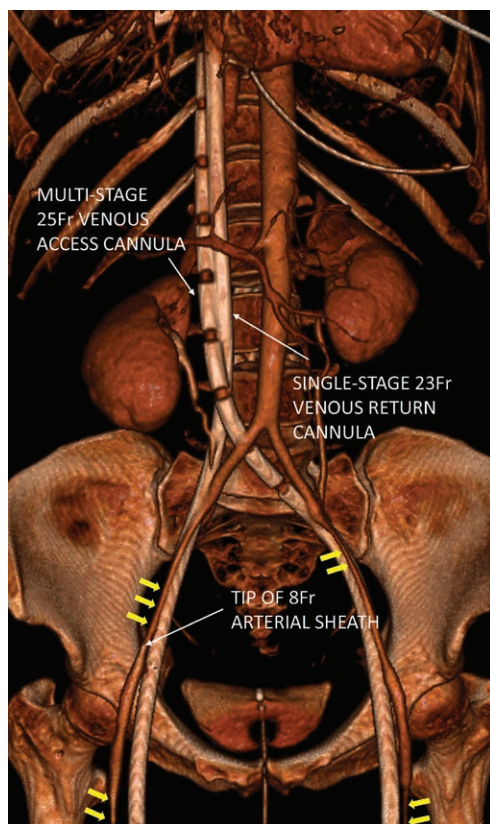
IN the management of severe respiratory failure, veno-venous extracorporeal membrane oxygenation is an increasingly used therapy that presents a unique challenge for anesthesiologists.[1] Veno-arterial-venous extracorporeal membrane oxygenation is emerging as a strategy to treat refractory respiratory failure with coexisting cardiogenic shock.[2] This image demonstrates profound constrictive effects of high-dose vasopressor therapy on arterial caliber and implications for percutaneous arterial access.

The accompanying computed tomography angiogram demonstrates a patient established on veno-venous extracorporeal membrane oxygenation using a bifemoral percutaneous approach. A 25Fr multistage access cannula and a 23Fr return cannula can be seen ascending the inferior vena cava *via* the left and right femoral veins, respectively, with their tips lying at the cavoatrial junction. A 8Fr arterial sheath was inserted percutaneously *via* the right femoral artery at time of extracorporeal membrane oxygenation cannulation to allow rapid arterial access if circulatory support was required in the form of veno-arterial-venous extracorporeal membrane oxygenation; the tip of the arterial sheath is labeled. At time of image acquisition, the patient was on high-dose vasopressor therapy (norepinephrine 0.8 mcg · kg · min and epinephrine 0.5 mcg · kg · min). Severe vasoconstriction of the femoral and iliac arteries can be seen (yellow arrows) and is present bilaterally.

Anesthesiologists should be aware of the importance of gaining arterial access early in a patient on veno-venous extracorporeal membrane oxygenation with coexistent septic cardiomyopathy. Percutaneous arterial access may be very challenging when a patient is on high-dose vasopressor therapy. This image also demonstrates why distal limb perfusion must be monitored closely for ischemic complications if indwelling arterial devices are *in situ*.[3]

Competing Interests

The authors declare no competing interests.

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References

1. Fierro MA, Daneshmand MA, Bartz RR: Perioperative management of the adult patient on venovenous extracorporeal membrane oxygenation requiring noncardiac surgery. ANESTHESIOLOGY 2018; 128:181–201
2. Vogel DJ, Murray J, Czapran AZ, Camporota L, Ioannou N, Meadows CIS, Sherren PB, Daly K, Gooby N, Barrett N: Veno-arteriovenous ECMO for septic cardiomyopathy: A single-centre experience. Perfusion 2018; 33(1 suppl):57–64
3. Brown SM, Lanspa MJ, Jones JP, Kuttler KG, Li Y, Carlson R, Miller RR III, Hirshberg EL, Grissom CK, Morris AH: Survival after shock requiring high-dose vasopressor therapy. Chest 2013; 143:664–71

Brian P. Kavanagh, M.B., F.R.C.P.C., Editor

Interscalene Brachial Plexus Block

"Stoplight" That Lit Up Red

Adam W. Amundson, M.D., Hugh M. Smith, M.D., Ph.D.

SONOGRAPHIC guidance has increased the efficacy of regional anesthesia and improved safety by reducing the minimum effective local anesthetic volume[1]; however, block failures still occur due to anomalous anatomy and/or sonographic misidentification of relevant structures.[2] The ultrasound image presented (image *A*) demonstrates the typical "stoplight" pattern of three vertically oriented hypoechoic structures denoting C5 and C6 of the brachial plexus, lying between the anterior and middle scalene muscles.[3] However, color Doppler imaging (image *B*) reveals blood flowing through a transverse cervical artery viewed in cross section, mimicking the sonographic appearance of the C5 nerve root (see the Supplemental Digital Content, http://links.lww.com/ALN/B769, a video that demonstrates color Doppler flow through the artery). Because ultrasound works by detecting differences in tissue density, anatomic structures with tissue homogeneity typically produce hypoechoic signals. In this case, blood inside an artery and solid neural tissue are both homogenous and of similar size, and misidentification may occur. Arterial and venous structures can be sonographically differentiated from neural structures through compressibility, pulsatility, and application of color Doppler. Image *B* highlights the importance of sonographic guidance, but underscores the need for awareness of anatomic features and their interpretation throughout interventional procedures.

Competing Interests

The authors declare no competing interests.

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References

1. McNaught A, Shastri U, Carmichael N, Awad IT, Columb M, Cheung J, Holtby RM, McCartney CJL: Ultrasound reduces the minimum effective local anaesthetic volume compared with peripheral nerve stimulation for interscalene block. Br J Anaesthesia 2010; 106:124–30
2. Sites BD, Brull R, Chan VWS, Spence BC, Gallagher J, Beach ML, Sites VR, Abbas S, Hartman GS: Artifacts and pitfall errors associated with ultrasound-guided regional anesthesia. Part II: A pictorial approach to understanding and avoidance. Reg Anesth Pain Med 2007; 32:419–33
3. Franco CD, Williams JM: Ultrasound-guided interscalene block: Reevaluation of the "stoplight" sign and clinical implications. Reg Anesth Pain Med 2016; 41:452–9

Thoracoscopic and Ultrasound Guidance for Optimization of Medication Spread during Thoracic Paravertebral Nerve Blockade

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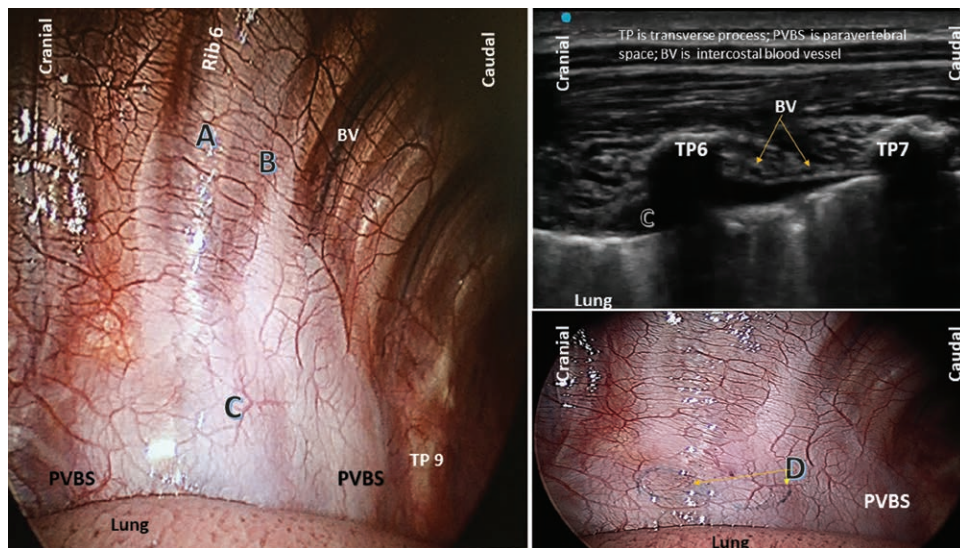
MEDICATION spread after transverse ultrasound-guided thoracic paravertebral block has been studied in cadavers[1] and on volunteers with magnetic resonance imaging[2] and it can be highly variable. Ultrasound-guided thoracic paravertebral block can be performed under direct thoracoscopic visualization to monitor the dynamic spread of medication to achieve optimal anesthetic coverage and confirm correct catheter placement.

We present images of a 17-yr-old boy (52.9 kg) who had a T6 ultrasound-guided thoracic paravertebral block catheter placed as described by Boretsky *et al.*[3] Correct needle and catheter placement into the paravertebral space was confirmed with simultaneous sonographic (See video, Supplemental Digital Content, http://links.lww.com/ALN/B771) and thoracoscopic visualization (See video, Supplemental Digital Content, http://links.lww.com/ALN/B770). Initially, 10 ml saline was injected into the paravertebral space, but spread was seen only over one single intercostal space (*A*). Injection of an additional 15 ml ropivacaine led initially to more caudal intercostal spread (*B*), which was then followed by further filling (*C*) of the paravertebral space. A heart-shaped bulge of the parietal pleura was observed, which remained consistent after more saline was injected through the catheter in an attempt to achieve an even wider distribution. As seen with the thoracoscope, a total of two intercostal spaces (6 to 7) and four paravertebral levels (T5 to T8) were covered after injection of 0.5 ml/kg medication. The medication preferentially distributed in the caudal direction rather than cephalad within the paravertebral space. In contrast to previous reports[1] and to our own experience, the catheter (*D*) was easy to place and could be seen coiling in the paravertebral space at the desired level (T6). Our thoracoscopic and ultrasound-guided thoracic paravertebral block approach helped understanding of dermatomal mapping and confirmation of correct paravertebral catheter placement.

Competing Interests

Dr. Visoiu is a consultant at Hospira (Lake Forest, Illinois). The remaining author declares no competing interests.

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References

1. Cowie B, McGlade D, Ivanusic J, Barrington MJ: Ultrasound-guided thoracic paravertebral blockade: A cadaveric study. Anesth Analg 2010; 110:1735–9

2. Marhofer D, Marhofer P, Kettner SC, Fleischmann E, Prayer D, Schernthaner M, Lackner E, Willschke H, Schwetz P, Zeitlinger M: Magnetic resonance imaging analysis of the spread of local anesthetic solution after ultrasound-guided lateral thoracic paravertebral blockade: A volunteer study. ANESTHESIOLOGY 2013; 118:1106–12

3. Boretsky K, Visoiu M, Bigeleisen P: Ultrasound-guided approach to the paravertebral space for catheter insertion in infants and children. Paediatr Anaesth 2013; 23:1193–8

Brian P. Kavanagh, M.B., F.R.C.P.C., Editor

Blue Rubber Bleb Nevus Syndrome

Cornelius A. Sullivan, M.D., F.A.C.S.
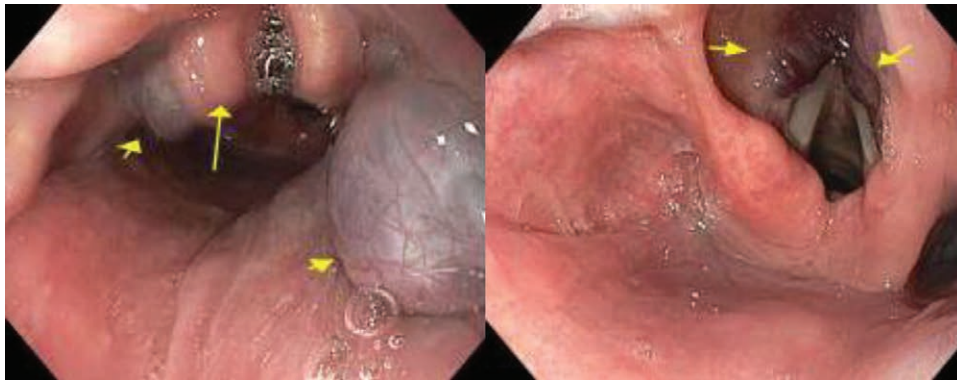
BLUE Rubber Bleb Nevus Syndrome is a rare anomaly of developmental vascular biology that can occur in any part of the body, most commonly the skin and gastrointestinal tract. The accompanying images show the typical appearance of these firm but compressible lesions (*short arrows*) in the pyriform sinuses, the anterior laryngeal wall, and in relation to the aryepiglottic fold (left panel, *long arrow*). These locations would be at risk for injury during direct laryngoscopy and intubation, or even with placement of a laryngeal mask, which could result in potentially catastrophic hemorrhage.

Sometimes called "Bean Syndrome" following its original description in 1958, this entity can involve dozens of these lesions, which are felt to be congenital venous malformations rather than true vascular neoplasms.[1] Although cutaneous lesions are often present at birth or develop in early childhood, the diagnosis has been made in an octogenarian. Of approximately 300 cases in the literature, approximately 10% showed definite airway involvement; central nervous system involvement was almost twice as common.[2] Clinical manifestations are secondary to chronic occult blood loss, or rarely, intussusception from a bleb acting as a lead point. Although surgical extirpation of symptomatic lesions has been the mainstay of therapy, recent reports describe regression after sirolimus treatment.[3] Patients presenting for endoscopy or surgical intervention should be assessed preoperatively for anemia and assumed to have lesions in the upper aerodigestive tract. Blind nasal intubation should be avoided, and because involvement of the lower airways has been observed, fiberoptic intubation may be prudent.

Acknowledgments

Competing Interests

The author declares no competing interests.

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References

1. Xue-Li Jin, Zhao-Hong Wang, Xi-Bin Xiao, Lian-Sheng Huang, Xiao-Ying Zhao: Blue rubber bleb nevus syndrome: A case report and literature review. World J Gastroenterol 2014; 20:17254–9
2. González-Pizarro P, García-Fernández J: Blue rubber bleb nevus syndrome: Airway management. Paediatr Anaesth 2010; 20:285–7
3. Salloum R, Fox CE, Alvarez-Allende CR, Hammill AM, Dasgupta R, Dickie BH, Mobberley-Schuman P, Wentzel MS, Chute C, Kaul A, Patel M, Merrow AC, Gupta A, Whitworth JR, Adams DM: Response of Blue Rubber Bleb Nevus Syndrome to sirolimus treatment. Pediatr Blood Cancer 2016; 63:1911–4

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Brian P. Kavanagh, M.B., F.R.C.P.C., Editor

Simultaneous Color Change at Opposite Ends of Carbon Dioxide Absorbent Canisters

Robert G. Loeb, M.D., Nikolaus Gravenstein, M.D.
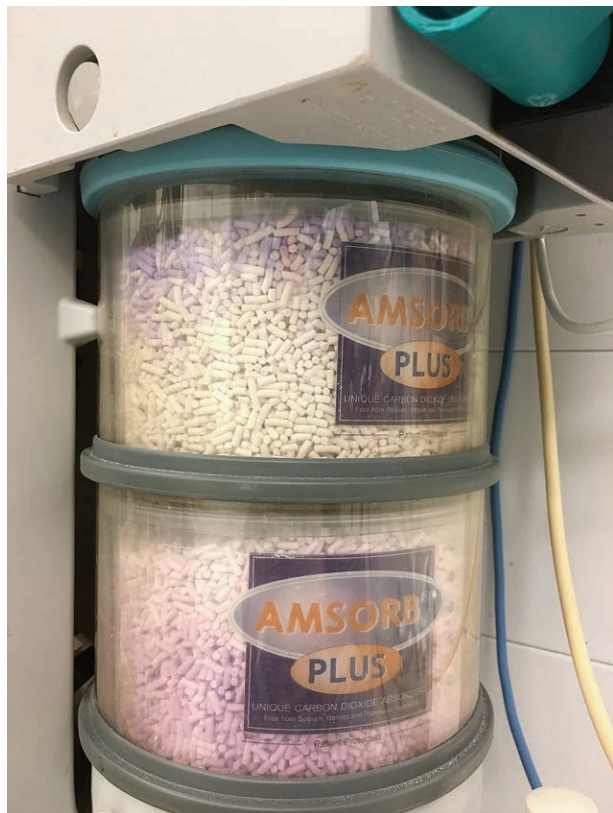
T HE image shows carbon dioxide absorbent that is violet at the top and bottom of the canisters. This was observed on a Monday after a weekend of nonuse when fresh gas was left flowing. Like other absorbents, Amsorb Plus (Armstrong Medical, Ireland)[1] changes color when exhausted because alkaline absorbents convert carbon dioxide to carbonic acid, and the ethyl violet indicator changes color when the pH drops to less than 10.3. During use of this anesthesia breathing circuit, exhaled gas flows through the canisters from top to bottom. The absorbent at the top of the upper canister in this image is violet, indicating that it is exhausted. During nonuse, fresh gas can flow retrograde through the canisters, causing desiccation. Unlike other absorbents, Amsorb Plus also changes color when desiccated,[2] so the absorbent at the bottom of the lower canister in this image is violet because it is desiccated. The absorbent in this image is still perfectly safe for use because it is not totally exhausted and the absorbent will not produce toxic substances. Armstrong Medical recommends replacing the absorbent in this dual-canister system when the top canister and half of the bottom canister have changed color.

Desiccated Amsorb Plus, unlike some other absorbents, does not interact with volatile anesthetics to produce carbon monoxide or compound A.[3] The desiccated absorbent in this image will change back to its original color when rehydrated by humidified exhaled gas during use.

Competing Interests

The authors declare no competing interests.

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References

1. Murray JM, Renfrew CW, Bedi A, McCrystal CB, Jones DS, Fee JP: Amsorb: A new carbon dioxide absorbent for use in anesthetic breathing systems. ANESTHESIOLOGY 1999; 91:1342–8
2. Knolle E, Linert W, Gilly H: Using Amsorb to detect dehydration of CO_2 absorbents containing strong base. ANESTHESIOLOGY 2002; 97:454–9
3. Kharasch ED, Powers KM, Artru AA: Comparison of Amsorb®, sodalime, and Baralyme® degradation of volatile anesthetics and formation of carbon monoxide and compound A in swine in vivo. ANESTHESIOLOGY 2002; 96:173–82

Deborah J. Culley, M.D., Editor

Prothrombin Complex Concentrates for Perioperative Vitamin K Antagonist and Non–vitamin K Anticoagulant Reversal

Jerrold H. Levy, M.D., F.A.H.A., F.C.C.M., James Douketis, M.D., Thorsten Steiner, M.D., Joshua N. Goldstein, M.D., Ph.D., Truman J. Milling, M.D.

ABSTRACT

Vitamin K antagonist therapy is associated with an increased bleeding risk, and clinicians often reverse anticoagulation in patients who require emergency surgical procedures. Current guidelines for rapid anticoagulation reversal for emergency surgery recommend four-factor prothrombin complex concentrate and vitamin K coadministration. The authors reviewed the current evidence on prothrombin complex concentrate treatment for vitamin K antagonist reversal in the perioperative setting, focusing on comparative studies and in the context of intracranial hemorrhage and cardiac surgery. The authors searched Cochrane Library and PubMed between January 2008 and December 2017 and retrieved 423 English-language papers, which they then screened for relevance to the perioperative setting; they identified 36 papers to include in this review. Prothrombin complex concentrate therapy was consistently shown to reduce international normalized ratio rapidly and control bleeding effectively. In comparative studies with plasma, prothrombin complex concentrate use was associated with a greater proportion of patients achieving target international normalized ratios rapidly, with improved hemostasis. No differences in thromboembolic event rates were seen between prothrombin complex concentrate and plasma, with prothrombin complex concentrate also demonstrating a lower risk of fluid overload events. Overall, the studies the authors reviewed support current recommendations favoring prothrombin complex concentrate therapy in patients requiring vitamin K antagonist reversal before emergency surgery. **(ANESTHESIOLOGY 2018; 129: 1171-84)**

DESPITE the increasing use of non–vitamin K antagonist oral anticoagulants, vitamin K antagonists, such as warfarin, are still widely used in patients with atrial fibrillation, venous thromboembolism, and mechanical heart valves. In 2015, approximately 3 million patients were prescribed warfarin in the United States alone.[1] As with all anticoagulants, the main risk associated with vitamin K antagonist therapy is an increased risk for bleeding. Thus, annual rates of major hemorrhagic events ranged from 1.0 to 7.4% in a systematic review of patients with atrial fibrillation receiving vitamin K antagonist therapy for stroke prevention, while rates of intracranial hemorrhage in the same population ranged from 0.1 to 2.5%.[2]

Patients receiving vitamin K antagonist therapy who require surgery or an invasive procedure present a specific challenge to clinicians, with an estimated 250,000 to 400,000 patients

affected per year in North America alone.[3] Data from the Randomized Evaluation of Long-Term Anticoagulation Therapy trial demonstrated that major bleeding (defined as 2g/dl or more reduction in hemoglobin, transfusion of two or more units of red blood cells, or a critical area or organ bleed) occurred in 3.3% of warfarin-treated patients undergoing elective surgery, increasing to 21.6% in patients who required emergency surgery.[4] Consequently, effective perioperative management is a key consideration in this population. In patients undergoing elective surgery, current guidelines recommend discontinuing vitamin K antagonist therapy 5 days before the procedure to restore patients' international normalized ratio to a normal range and to minimize the risk of perioperative bleeding.[3] However, in patients who require an emergency surgical procedure, rapid vitamin K antagonist reversal is recommended by replacing the vitamin K–dependent coagulation factors II, VII, IX, and X.[5]

Table 1. Composition of Available Prothrombin Complex Concentrates

Product (Manufacturer)	Coagulation Factor Content (U)				Antithrombotic Content (U)		
	II	VII	IX	X	Protein C	Protein S	ATIII
Beriplex P/N (CSL Behring, Germany)	400–960	200–500	400–620	440–1200	300–900	240–760	4–30
Octaplex (Octapharma, Switzerland)	280–760	180–480	500	360–600	260–620	240–640	0
Prothromplex Total (Shire/Baxalta, USA)	480–900	500	600	600	400	Not declared	Not declared
Cofact/PPSB SD/ Kanokad (Sanquin/ CAF, The Netherlands)	280–700	140–400	500	280–700	222–780	20–160	≤ 0.6
Uman Complex (Kedrion, Italy)	500	Not declared	500	400	Not declared	Not declared	2.5
Profilnine (Grifols, Spain)	150	35	100	100	Not declared	Not declared	Not declared
Bebulin (Shire/Baxalta)	Not declared	Not declared (low)	Not declared	Not declared	Not declared	Not declared	Not declared
FEIBA (Shire/Baxalta)	Present,* mainly nonactivated	Present,* activated	Present,* mainly nonactivated	Present,* mainly nonactivated	Not declared	Not declared	Not declared

Data are based on the prescribing information of each product, as of January 2017.
*Indicates that values are not provided in the prescribing information, just the presence or absence of the coagulation factor.
ATIII, antithrombin III.

Intravenous vitamin K monotherapy is recommended only for vitamin K antagonist reversal in patients in whom surgery can be delayed[6] because it can take more than 48 h to normalize functional factor levels and restore them to the normal range.[5] Therefore, in situations requiring rapid vitamin K antagonist reversal, treatment with prothrombin complex concentrates, concomitantly with vitamin K, is more commonly administered. Although fresh frozen plasma (plasma frozen within 8 h of collection) or plasma (frozen within 24 h of collection) was traditionally used for rapid reversal of anticoagulation with vitamin K antagonists, there are multiple limitations to its use, including the need for blood type matching before administration; time required to thaw the product; and risks of fluid overload, pathogen transmission, and transfusion-related acute lung injury.[5] Furthermore, only minimal benefits have been shown from plasma when reducing the international normalized ratio to less than 1.7 in adults, as well as minimal efficacy for anticoagulation reversal.[7,8]

Prothrombin complex concentrates, which are classed as either four-factor prothrombin complex concentrates (containing coagulation factors II, VII, IX, and X) or three-factor prothrombin complex concentrate (containing factors II, IX and X, but only minimal levels of factor VII; table 1), are stored at room temperature, administered in a smaller volume and shorter infusion time than plasma, and are virally inactivated to minimize the risk of pathogen transmission. Current treatment guidelines recommend prothrombin complex concentrates, specifically four-factor prothrombin complex concentrates, with concomitant intravenous vitamin K, as the preferred therapy for urgent vitamin K antagonist reversal (table 2).[5,6,9,10]

The perioperative management of hemostasis in patients receiving vitamin K antagonists was previously reviewed in this journal in 2008.[11] Since then, multiple new studies have investigated vitamin K antagonist reversal in perioperative and periprocedural settings, and prothrombin complex concentrates have become more widely available in the United States and are recommended in guidance documents. Despite the fact that prothrombin complex concentrate is recommended in all guidelines, plasma is still frequently administered for vitamin K antagonist reversal.[12] This article provides an update on the latest evidence for the use of prothrombin complex concentrates in patients requiring urgent vitamin K antagonist reversal for emergency surgery, but it also reviews current use for non–vitamin K antagonist oral anticoagulant reversal.

Materials and Methods

A Cochrane Library and PubMed search for publications between January 2008 and December 2017 was conducted with the following search terms: prothrombin complex concentrate* AND (warfarin OR [vitamin K antagonist*]). The search retrieved 423 English-language papers, which were then screened for relevance to the perioperative setting (fig. 1). We excluded preclinical studies and reviews but included all other studies, including case studies.

In total, 35 papers investigating the use of prothrombin complex concentrate for vitamin K antagonist reversal in perioperative settings were identified and included in this review. A further paper investigating prothrombin complex concentrate use in cardiac surgery was identified through a recent meta-analysis of warfarin reversal with prothrombin complex concentrate or fresh frozen plasma,[13] bringing the total number of papers included to 36. Of these papers, six studies in cardiac surgery and three in neurosurgical settings were identified.

Table 2. Current Guideline Recommendations for Reversal of Vitamin K Antagonist Anticoagulation in Patients with Bleeding Events or Requiring Surgery

Condition	Guidance	
	U.S. Guidelines[3,9,55,107]	European Guidelines[6,10]
Elective surgery	• Cessation of VKAs approximately 5 days before surgery	• VKAs should not be taken for 5 days before surgery • PCC should not be used to enable elective surgery
Emergency surgery		• Intravenous vitamin K should be administered in patients whose surgery can be delayed for 6 to 12 h • In patients with life-threatening bleeding and an INR > 1.5, 20 to 40 U/kg 4F-PCC and 10 mg intravenous vitamin K should be administered
Nonmajor bleeding		• 1 to 3 mg intravenous vitamin K should be administered

Major or life-threatening bleeding	• 25 to 50 U/kg 4F-PCC concomitant with 5 to 10 mg intravenous vitamin K should be administered
	• In patients with VKA-associated ICH
	  ○ PCCs might be considered over FFP
	  ○ If INR ≥ 1.4: 10 mg intravenous vitamin K plus 3F- or 4F-PCC should be administered
		• 25 to 50 U/kg 4F-PCC concomitant with 5 to 10 mg intravenous vitamin K should be administered
		• rFVIIa is not recommended for anticoagulation in this setting
		• 4F-PCC is preferred over plasma

3F, three-factor; 4F, four-factor; FFP, fresh frozen plasma; ICH, intracranial hemorrhage; INR, international normalized ratio; PCC, prothrombin complex concentrate; rFVIIa, activated recombinant factor VII; VKA, vitamin K antagonist.
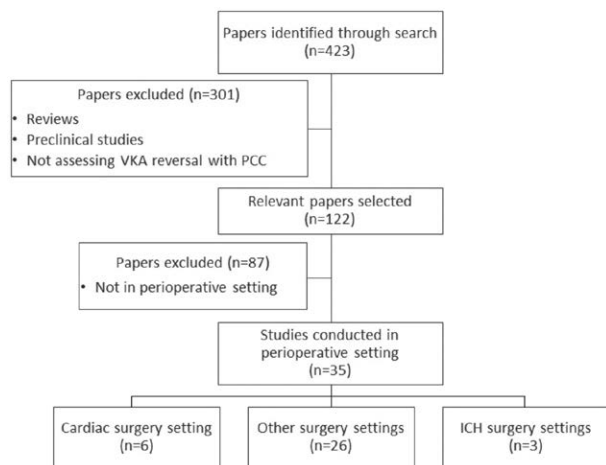
Fig. 1. Literature search process. ICH, intracranial hemorrhage; PCC, prothrombin complex concentrate; VKA, vitamin K antagonist.

Results

Noncomparative Studies of Prothrombin Complex Concentrates

The majority of studies identified in the search were of a retrospective observational design, with limited numbers of patients and lacking a comparator treatment arm. In general, perioperative bleeding episodes were well controlled with prothrombin complex concentrate therapy. The percentage of patients achieving effective hemostasis (no reports of excessive bleeding or bleeding controlled with no requirement for additional products) ranged from 90 to 100%,[14–19] while in a study of 20 patients treated with a four-factor prothrombin complex concentrate, blood loss decreased significantly, from an average of 829 ml in the 6 h preceding four-factor prothrombin complex concentrate administration to 283 ml 6 h after administration.[20]

Reversing vitamin K antagonist anticoagulation, as reflected by a normalized international normalized ratio, is often required for most surgeries and procedures. In the studies identified, prothrombin complex concentrate therapy consistently reduced patients' international normalized ratio to 1.1 to 1.9 from baseline values of 1.6 to 4.2.[15,16,20–35] These reduced international normalized ratios are in line with the target international normalized ratio for patients undergoing surgery of less than 1.5.[3]

As well as reducing the risk for bleeding during surgery, rapid vitamin K antagonist reversal with prothrombin complex concentrates may also reduce time to surgery. For minor procedures such as a lumbar puncture, the time between administration of prothrombin complex concentrate and the start of the procedure was as short as 15 to 30 min.[16,24] In patients requiring more extensive surgery (e.g., heart transplantation, neurosurgery), this period ranged from 2.5 to 5.2 h.[22,23,36]

All-cause mortality rates were generally between 10% and 25%,[14,22,23,30,37] although one study in patients requiring neurosurgery because of a life-threatening intracranial hemorrhage reported a mortality rate of 43.5%.[21] It should be noted that this study included high-risk patients with serious head trauma; the authors also highlighted that delays in therapy administration, subtherapeutic doses of prothrombin complex concentrate, and incorrect vitamin K use may also have been factors contributing to this high mortality rate.[21]

Studies Comparing Prothrombin Complex Concentrate and Fresh Frozen Plasma or Plasma

Given that fresh frozen plasma or plasma is still often used by clinicians for the urgent reversal of vitamin K antagonist

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anticoagulation, it is pertinent to look at studies that specifically compared this treatment option with prothrombin complex concentrate in patients undergoing emergency surgical procedures. Overall, three randomized trials[38–40] and one retrospective study[41] comparing these treatment options in this setting were identified. Outside of the literature search, a further study was identified that investigated the administration of prothrombin complex concentrate *versus* fresh frozen plasma in patients who experienced coagulopathy while undergoing elective pulmonary endarterectomy (table 3).[42] All studies used either fresh frozen plasma or plasma frozen within 24 h of collection (frozen plasma). Compared with fresh frozen plasma, only levels of factors V and VIII are slightly reduced in frozen plasma; therefore, for the purposes of this review, the terms *fresh frozen plasma* and *plasma* can be used interchangeably.

Effect of Prothrombin Complex Concentrate versus Plasma on International Normalized Ratio

In the randomized trials, prothrombin complex concentrate was consistently shown to reduce the international normalized ratio more rapidly than plasma. One study, by Goldstein *et al.*, in various surgical indications demonstrated superiority of four-factor prothrombin complex concentrate over plasma for rapid international normalized ratio reduction, with 55% of patients treated with a four-factor prothrombin complex concentrate achieving a target international normalized ratio of 1.3 or less *versus* 10% of patients in the plasma group at 30 min after the end of infusion (treatment difference, 45.3%; 95% CI, 31.9 to 56.4%; $P < 0.0001$).[40] Patients undergoing cardiac surgery with cardiopulmonary bypass demonstrated a significant treatment difference 15 min after infusion, with 17.5% of patients receiving four-factor prothrombin complex concentrate achieving a target international normalized ratio of 1.5 or less compared to no patients who received fresh frozen plasma ($P = 0.0068$).[38] These quicker international normalized ratio reduction times seen with prothrombin complex concentrate compared with plasma should also be considered in the context of the smaller volume that needs to be administered (40 to 100 ml with prothrombin complex concentrate compared with 520 to 1,200 ml with plasma), which leads to a shorter infusion time.[38–40] Thus, in the Goldstein *et al.* study, mean infusion times were 21 min for four-factor prothrombin complex concentrate and 141 min for plasma. Therefore, despite plasma having almost two additional hours to start exerting a treatment effect, international normalized ratio reduction 30 min after end of infusion was still superior with four-factor prothrombin complex concentrate.[40]

An important advantage of a more rapid and predictable international normalized ratio reduction is the ability to proceed to surgery quickly in emergency situations. The length of time from start of infusion to start of surgery was reported in one study: patients who received four-factor prothrombin complex concentrate had a significantly shorter median time to surgery than did patients who received plasma (3.6 h *vs.* 8.5 h, respectively; $P = 0.0098$).[40] In a *post hoc* analysis of patients with gastrointestinal bleeding requiring procedures in the Goldstein *et al.* study and in another study investigating four-factor prothrombin complex concentrate for warfarin reversal in patients with acute bleeding,[43] the mean time between the start of treatment and the first procedure was significantly shorter in patients given four-factor prothrombin complex concentrate than in those given plasma ($P = 0.037$).[44]

Unlike the randomized trials, the retrospective analysis comparing prothrombin complex concentrate *versus* fresh frozen plasma in patients undergoing emergency neurosurgery did not investigate the time taken to achieve international normalized ratio reversal. However, both prothrombin complex concentrate and fresh frozen plasma were shown to significantly decrease the international normalized ratio from baseline ($P < 0.001$), with no significant difference between either group for posttreatment values.[41]

Effect of Prothrombin Complex Concentrate versus Plasma on Clinical Outcomes

As well as demonstrating more rapid international normalized ratio reduction, four-factor prothrombin complex concentrates have also been associated with greater clinical efficacy than plasma. In a study by Goldstein *et al.* in patients undergoing various surgical or invasive procedures, effective hemostasis (defined as intraoperative blood loss not exceeding predicted loss by 50 ml or 30%, normal hemostasis, and no requirement for additional coagulation products) was achieved in 90% of patients who received four-factor prothrombin complex concentrate compared with 75% of patients who received plasma. This treatment difference was significant ($P = 0.0142$) and demonstrated the superiority of four-factor prothrombin complex concentrate over plasma.[40] In another study involving patients who received four-factor prothrombin complex concentrate or plasma for vitamin K antagonist reversal while undergoing elective pulmonary endarterectomy, cumulative blood loss was significantly lower up to 12 h postoperatively in the four-factor prothrombin complex concentrate group than in the plasma group (277 ml and 650 ml, respectively; $P = 0.0078$).[42]

In general, similar numbers of patients receiving prothrombin complex concentrate and plasma required transfusions of additional blood products (*i.e.*, platelets, erythrocytes, cryoprecipitate).[40,42] However, one study in patients undergoing cardiopulmonary bypass reported a significantly greater proportion of patients who received plasma requiring additional doses of plasma or four-factor prothrombin complex concentrate *versus* patients who originally received four-factor prothrombin complex concentrate (100% *vs.* 30% of patients receiving plasma or four-factor prothrombin complex concentrate, respectively; $P < 0.001$).[38]

Mortality rates were reported in two studies. Although fewer deaths occurred among patients who received

Table 3. Comparative Studies of PCC *versus* Plasma for Urgent VKA Reversal in Perioperative Settings, 2008 to 2017

Citation and Location of Study	Study Design	Surgical Indication	Patients (N)	PCC Used (Manufacturer)	Comparator	Key Efficacy Results	Key Safety Results
Agarwal et al.[41] (United States)	Retrospective cohort analysis	Neurosurgery	PCC: 28 FFP: 35	Not specified	FFP	• INR decreased from 3.36 to 1.36 with PCC and 2.92 to 1.33 with FFP • No significant difference between post-treatment INR for the PCC and FFP groups	• 1 and 0 TEEs were reported in the PCC and FFP groups within 72 h after infusion • No significant difference in inhospital mortality rates were observed (PCC, 17.9%; FFP, 14.3%)
Demeyere et al.[38] (Belgium)	Prospective, randomized, two-arm, open-label	Cardiac surgery	PCC: 18 FFP: 20	Cofact (Sanquin, The Netherlands)	FFP	• 15 min after CPB, INR ≤ 1.5 was reached by 7 and 0 patients receiving PCC and FFP, respectively • Median INR decrease was greater with PCC (from 2.7 to 1.6) than with FFP (2.6 to 2.3) 15 min after CPB • 6 and 20 patients required an additional dose to reach INR target in the PCC and FFP groups, respectively	• 7 and 9 AEs were reported in the PCC and FFP groups, respectively • 2 patients in the FFP group reported excessive oozing
Fariboz Farsad et al.[39] (Iran)	Randomized study comparing PCC with FFP	Cardiac procedure	PCC: 25 FFP: 25	Uman Complex (Kedrion, Italy)	FFP	• 30 min after infusion, mean INR decreased from 4.02 to 2.34 for the PCC group and from 4.88 to 3.1 for FFP • 76% and 20% of patients achieved INR < 2.5 in the PCC and FFP groups, respectively • 20% and 68% of patients needed additional doses to achieve target INR in the PCC and FFP groups, respectively	• No cases of hemorrhage were reported
Goldstein et al.[40] (United States, Belarus, Bulgaria, Lebanon, Romania, Russia)	Phase 3b, prospective randomized, open-label, active-control, multicenter study	Urgent surgery	PCC: 89 FFP: 90	Beriplex/Kcentra (CSL Behring, Germany)	FFP	• Effective hemostasis was achieved in 90% and 75% of patients in the PCC and plasma groups, respectively • INR ≤ 1.3 at 30 min after administration was achieved in 55% and 10% of patients in the PCC and plasma groups, respectively • Median time from start of infusion to start of surgery was significantly shorter in the PCC group (P = 0.0098)	• AEs were seen in 56% and 60% of patients in the PCC and plasma groups, respectively • TEEs occurred in 7% and 8%, fluid overload developed in 3% and 13%, and late bleeding occurred in 3% and 5% of patients in the PCC and plasma groups, respectively • By day 45, 3 and 8 deaths were reported in the PCC and plasma groups, respectively. Only one death (plasma group) was deemed related to treatment
Ortmann et al.[42] (United Kingdom)	Exploratory cohort study	Cardiac surgery	PCC: 45 FFP: 55	Beriplex/Kcentra (CSL Behring) and Octaplex (Octapharma, Switzerland)	FFP	• Cumulative blood loss was lower in the PCC group 1 at 12 h after surgery than in the FFP group • Similar numbers of units of erythrocytes were transfused in both groups	• No DVT, pulmonary embolisms, or MIs were seen in either group • Rates of cerebral infarction, hemorrhage, and 30-day mortality were similar between the two groups
Refaai et al.[44]	Post hoc analysis	GI bleeding	PCC: 22 FFP: 20	Beriplex/Kcentra (CSL Behring)	FFP	• INR ≤ 1.3 30 min after infusion was achieved in 65% of patients with PCC vs 0% in patients with FFP • Median time between start of treatment and first procedure was 17.5 h with PCC vs 23.9 h with FFP	• TEEs occurred in 1 and 2 patients in the PCC and FFP groups, respectively • 1 and 4 fluid overload events occurred in the PCC and FFP groups, respectively

AE, adverse event; CPB, cardiopulmonary bypass; DVT, deep vein thrombosis; FFP, fresh frozen plasma; INR, international normalized ratio; MI, myocardial infarction; PCC, prothrombin complex concentrate; TEE, thromboembolic event.

four-factor prothrombin complex concentrate than among patients who received plasma (3.4% *vs.* 9.1%[40] and 6.7% *vs.* 7.3%[42]), this difference did not reach statistical significance.[40,42] A recent systematic review and meta-analysis of 13 studies comparing prothrombin complex concentrate *versus* plasma in patients with warfarin-related bleeding also demonstrated a nonsignificant reduction in mortality outcomes in a subgroup analysis of studies evaluating patients who underwent urgent surgical procedures.[13] By contrast, when all warfarin-related bleeding events were included, and not just those in the perioperative setting, this meta-analysis demonstrated that prothrombin complex concentrate therapy was associated with a significant reduction in all-cause mortality compared with plasma ($P = 0.006$).[13]

Studies Comparing Three-factor Prothrombin Complex Concentrates and Four-factor Prothrombin Complex Concentrates

Both three- and four-factor prothrombin complex concentrates were used in the studies identified in our search, although no studies directly compared these different formulations in a surgical setting. However, current guidelines recommend the use of four-factor prothrombin complex concentrates for patients who require rapid vitamin K antagonist reversal.[6,9] These recommendations are aligned with the findings of retrospective studies conducted in patients experiencing major bleeding, which have demonstrated that a greater proportion of patients achieved vitamin K antagonist reversal (as measured by achievement of target international normalized ratios ranging from 1.3 or less to 1.5) with four-factor prothrombin complex concentrate than three-factor prothrombin complex concentrate,[45–48] reaching statistical significance in two studies.[45,47] One study also reported a significantly higher mortality rate ($P = 0.001$) in patients who received three-factor than in patients who received four-factor prothrombin complex concentrate.[48]

Studies Comparing Prothrombin Complex Concentrate and Recombinant FVIIa

Despite being off label, use of recombinant FVIIa has been reported for vitamin K antagonist reversal. Although recombinant FVIIa completely normalizes the international normalized ratio, it does not correct the coagulation defect based on peak thrombin levels and endogenous thrombin potential.[49,50] Two retrospective studies investigated the use of recombinant FVIIa in comparison with a three-factor prothrombin complex concentrate. In one analysis, recombinant FVIIa was shown to reduce the international normalized ratio more rapidly than prothrombin complex concentrates, although this difference did not result in clinical benefit, with a greater proportion of patients receiving recombinant FVIIa experiencing hematoma expansion.[51] The second study also reported more rapid international normalized ratio reduction with recombinant FVIIa *versus* prothrombin complex concentrate; however, there were no

significant differences in thromboembolic events or mortality rates.[52] In another retrospective review, a significantly greater proportion of patients achieved a target international normalized ratio of less than 1.3 when receiving a combination of three-factor prothrombin complex concentrate and recombinant FVIIa (79.4%) compared with patients who received either recombinant FVIIa (45.7%) or four-factor prothrombin complex concentrate (50%) alone; however, this combination therapy was associated with a significantly higher proportion of deep vein thromboses (18.7%) than was associated with either recombinant FVIIa (4.2%) or four-factor prothrombin complex concentrate (6.1%).[53] The high number of patients achieving international normalized ratio less than 1.3 and experiencing deep vein thromboses with the combination therapy might be indicative of "double dosing" of coagulation factors and the fact that three-factor prothrombin complex concentrates lack small amounts of anticoagulant factors (protein C and S) present in four-factor prothrombin complex concentrates.[53]

Current guidelines do not recommend recombinant FVIIa for urgent vitamin K antagonist anticoagulation reversal.[5,6] Further investigative studies would be beneficial to compare the efficacy and safety of prothrombin complex concentrates and rFVIIa to help inform future practice.

Studies Conducted in Specific Surgical Indications

The majority of surgeries carry an inherent risk of bleeding; however, certain surgical indications are associated with an increased bleeding risk in patients receiving vitamin K antagonists.[3] Furthermore, uncontrolled bleeding in patients undergoing cardiac, intracranial, or spinal surgery can result in serious clinical consequences.[3]

Intracranial Hemorrhage. Intracranial hemorrhage is a particular concern in patients treated with vitamin K antagonists. A report from a large U.S. cohort of more than 13,500 patients with atrial fibrillation demonstrated that almost 88% of deaths resulting from warfarin-associated bleeding were intracranial hemorrhage events, and more than 40% in patients who developed an intracranial hemorrhage died.[54] Although surgical intervention in cases of intracranial hemorrhage remains controversial, it can be considered in patients who are deteriorating neurologically, have brainstem compression or hydrocephalus as a result of ventricular obstruction,[55] or those with supratentorial intracranial hemorrhage and a Glasgow coma score of 9 to 12.[56]

Few studies have investigated vitamin K antagonist reversal in patients with intracranial hemorrhage in the perioperative setting, and a comprehensive examination of prothrombin complex concentrate use in patients presenting with intracranial hemorrhage, not just those requiring surgical intervention, is outside the scope of this review. A retrospective analysis by Agarwal *et al.* investigated prothrombin complex concentrate use *versus* plasma in warfarin-treated patients undergoing emergency surgery

for treatment of intracranial hemorrhage.[41] As highlighted earlier, both prothrombin complex concentrate and plasma significantly reduced the international normalized ratio from baseline ($P < 0.001$); however, no difference between the posttreatment international normalized ratio values were seen between prothrombin complex concentrate and plasma. In-hospital mortality rates were similar between the two treatments with a rate of 17.9% and 14.3% in the prothrombin complex concentrate and plasma groups, respectively.[41]

In studies investigating plasma and prothrombin complex concentrate treatment in warfarin-treated patients presenting with intracranial hemorrhage and not just patients undergoing neurosurgery, prothrombin complex concentrate use *versus* plasma resulted in more rapid international normalized ratio reversal,[57–60] and a greater proportion of patients achieved the target international normalized ratio.[58,59,61,62] Mortality rates were not significantly different between treatments,[41,57,59,63,64] and fewer patients experienced neurologic deterioration[63] or required neurosurgical intervention after prothrombin complex concentrate treatment.[57] In a study comparing plasma, three-factor prothrombin complex concentrate, and recombinant FVIIa in patients with intracranial hemorrhage, time to anticoagulation reversal was almost twice as long with plasma than with three-factor prothrombin complex concentrate or recombinant FVIIa; international normalized ratio rebound was seen more frequently in patients who received recombinant FVIIa than in those who received either plasma or prothrombin complex concentrate, and the mortality rate was lowest in patients who received three-factor prothrombin complex concentrate (although it should be noted that the population size for these groups was small).[65] In another retrospective study conducted in the intracranial hemorrhage setting, recombinant FVIIa was shown to reduce the international normalized ratio to 1.3 or less in 83% of patients, compared with only 20% of patients treated with three-factor prothrombin complex concentrate. However, this improved international normalized ratio reversal did not translate into clinical efficacy, with hematoma expansion occurring in a greater proportion of patients receiving recombinant FVIIa.[51]

Cardiac Surgery. Major bleeding events in patients undergoing cardiac surgery have been shown to significantly increase the risk of operative mortality and are also a precursor to reoperation and increased erythrocyte transfusions, both of which are associated with increased morbidity and mortality.[66] As such, rapid vitamin K antagonist reversal is essential for patients requiring emergency cardiac surgery. In a study in patients undergoing cardiopulmonary bypass, international normalized ratio reversal to 1.5 or less within 15 min was achieved in 35% of patients who were administered four-factor prothrombin complex concentrate compared with 0% of plasma recipients,[38] whereas another study of prothrombin complex concentrate in patients undergoing

heart transplantation showed that 12% and 75% of patients achieved an international normalized ratio less than 1.5 and less than 1.7, respectively, before transplantation.[67] International normalized ratio reduction to less than 1.5 was achieved in all four patients in a small case series of patients undergoing heart transplantation; however, the average time to achieve this was 2.45 h (still within the recommended 2- to 3-h window between dosing and incision).[36]

In comparison with plasma, prothrombin complex concentrate treatment was associated with a more rapid international normalized ratio decrease,[38] a greater proportion of patients achieving the target international normalized ratio before cardiac surgery,[39] and less cumulative postoperative blood loss.[38,42] Nonsignificant decreases in blood product use (*e.g.*, red blood cells, plasma, platelets, and cryoprecipitate), patients requiring reoperation for bleeding, and in-hospital mortality were also seen in patients undergoing heart transplantation treated with four-factor prothrombin complex concentrate compared with a nonfactor concentrate historical control group.[67]

In a retrospective analysis of patients undergoing orthotopic heart transplantation, significantly fewer units of cryoprecipitate and packed erythrocytes were transfused in patients who received four-factor prothrombin complex concentrate than in those who did not ($P < 0.001$).[68] Furthermore, the median time to chest closure was significantly shorter in patients receiving four-factor prothrombin complex concentrate (547.9 min) *versus* those who did not (618.8 min; $P = 0.008$).[68] No significant difference in in-hospital mortality was observed.[68]

Reversing Vitamin K Antagonist Therapy in Trauma Patients

Patients who receive vitamin K antagonist therapy and present with trauma represent a challenging medical emergency. In the United States, the proportion of trauma patients who take warfarin has been shown to be approximately 4%, which increases to almost 13% when considering patients older than 65 yr.[69] Furthermore, anticoagulant use before trauma has been associated with an increased risk of mortality, even when adjusting for confounders such as age and preexisting medical conditions.[69,70]

While rapid reversal of the anticoagulant effect is essential in any vitamin K antagonist–treated patient suffering a traumatic injury, simply replenishing the vitamin K–dependent coagulation factors does not provide volume replacement, which is often required in patients who are in hypovolemic shock after major blood loss. For patients with a suspected massive bleed, current European guidelines recommend transfusion of fresh frozen plasma (or pathogen-inactivated plasma) in conjunction with packed erythrocytes in a plasma–erythrocyte ratio of at least 1:2.[71] The recent Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial investigated the effectiveness and safety of a 1:1:1 plasma, platelet, erythrocyte transfusion ratio

compared with a 1:1:2 ratio.[72] No significant differences were seen in overall mortality after 24 h or 30 days; however, the 1:1:1 transfusion ratio was associated with a significantly greater proportion of patients achieving hemostasis (86.1% *vs.* 78.1%; $P = 0.006$) and significantly fewer patients dying from exsanguination (9.2% *vs.* 14.6%; $P = 0.03$).[72]

However, the administration of large amounts of fresh frozen plasma and erythrocytes to restore blood volume can lead to a dilution of the coagulation factors, which delays coagulopathy reversal.[71] As such, the administration of prothrombin complex concentrate in conjunction with fresh frozen plasma has been proposed as an alternative therapeutic option for the rapid correction of traumatic coagulopathy while also restoring volume and should be considered in a vitamin K antagonist–treated patient. While studies have also investigated three-factor prothrombin complex concentrate for the treatment of traumatic coagulopathy,[73,74] four-factor prothrombin complex concentrate is recommended by current guidelines for the reversal of vitamin K antagonist–related anticoagulation,[5,6,9,10] and a number of studies have investigated the use of four-factor prothrombin complex concentrate to reverse the anticoagulant effect in vitamin K antagonist–treated trauma patients.[47,60,75–77] In a retrospective study of four-factor prothrombin complex concentrate administered to 26 trauma patients on warfarin, the mean international normalized ratio was shown to significantly decrease from 5.7 to 1.5 ($P < 0.001$), and this decrease was sustained for more than 2 days.[75] No patients developed venous thromboembolic events, and no in-hospital mortality was reported.[75] A prospective study investigated four-factor prothrombin complex concentrate treatment for warfarin-associated coagulopathy after traumatic brain injury.[60] In five patients treated with four-factor prothrombin complex concentrate, the international normalized ratio was corrected to 1.2 or less from a baseline of more than 2.0 in all patients; for patients requiring surgery, the time to anesthesia induction was 159 min, which compared favorably to patients who received fresh frozen plasma (307 min).[60] Administration of four-factor prothrombin complex concentrate has also been shown to result in significantly lower transfusion requirements of erythrocyte and platelet concentrate units ($P < 0.001$), as well as fewer trauma patients requiring transfusion compared with patients receiving fresh frozen plasma.[76]

When comparing with prothrombin complex concentrates, four-factor prothrombin complex concentrate has been shown to result in a significantly lower international normalized ratio (1.3 *vs.* 1.6; $P < 0.001$) and a significantly greater proportion of trauma patients achieving successful reversal of anticoagulation (83% *vs.* 50%; $P = 0.022$).[47] Three-factor prothrombin complex concentrate was also associated with a greater number of venous thromboembolic events in patients, compared with four-factor prothrombin complex concentrate (15% *vs.* 0%), although this difference did not reach statistical significance.[47] In a retrospective analysis of warfarin-treated trauma patients comparing four-factor prothrombin complex concentrate with three-factor prothrombin complex concentrate plus recombinant FVIIa, the combination therapy of a three-factor prothrombin complex concentrate and recombinant FVIIa achieved a significantly lower international normalized ratio than did four-factor prothrombin complex concentrate (0.75 *vs.* 1.28; $P < 0.001$); however, no difference was seen between treatments for patients achieving a target international normalized ratio less than 1.5.[77] Furthermore, the combination therapy was associated with a significantly increased risk of deep vein thrombosis development compared with the four-factor prothrombin complex concentrate group (22.6% *vs.* 2.9%; $P = 0.01$).

These studies demonstrate that prothrombin complex concentrate results in a rapid reversal of the coagulopathy, as measured by the international normalized ratio. However, as stated earlier, it is important to remember that because of its concentrated nature, prothrombin complex concentrate does not provide the volume support that can be required to correct hypoperfusion associated with major blood loss, and, therefore, administration of plasma is still recommended in this patient population.[71]

Safety

Thromboembolic and Bleeding Events. Historically, the use of prothrombin complex concentrates has been associated with a potential increase in venous thromboembolic events, possibly because activated coagulation factors were included in the previous formulations of prothrombin complex concentrates[78] but also because patients on anticoagulants are treated for hypercoagulable disorders. Current formulations use nonactivated clotting factors and include antithrombotic components (protein C and S), which may mitigate the risk of developing venous thromboembolic events.[79] In a meta-analysis of 27 studies investigating prothrombin complex concentrate therapy for vitamin K antagonist–treated patients in various settings, the overall risk of venous or arterial venous thromboembolic events was only 1.4%, which decreased to 0.8% in the subset of patients undergoing a surgical procedure.[80]

In the studies identified in our search, rates of venous thromboembolic events in patients receiving prothrombin complex concentrates varied considerably, from 0 to 26.3%.[19,22,23,25,31,37,41,64,81–83] We also identified two case studies that each reported a patient undergoing surgery who developed a venous thromboembolic event within 1 h after three-factor prothrombin complex concentrate administration.[35,84] It should be noted that many of these studies included few patients, and the patient populations investigated often had a number of comorbidities; moreover, once vitamin K antagonist therapy is reversed, the underlying risk that first necessitated anticoagulation is restored, and as a result, caution should be taken when interpreting these findings.

In a comparative study of patients requiring vitamin K antagonist reversal before heart transplantation, venous

thromboembolic events were reported more frequently in patients receiving three-factor prothrombin complex concentrate than with a historical cohort who received vitamin K and plasma (18.7% *vs.* 10%, respectively), although this difference was not significant.[67] In another comparative study of four-factor prothrombin complex concentrate and plasma in patients undergoing emergency surgery, no significant difference was noted in the percentage of patients with venous thromboembolic events, with 7% and 8% of patients who received prothrombin complex concentrate and plasma, respectively, experiencing a venous thromboembolic event,[40] which is in line with a recent meta-analysis demonstrating no increase in risk of venous thromboembolic events with prothrombin complex concentrates compared with plasma.[13] However, none of the studies were designed to compare the incidence of thromboembolic events between prothrombin complex concentrates and plasma.

Across four studies, no significant differences in overall adverse event rates were seen in patients who received prothrombin complex concentrate compared with patients who received plasma.[38–40,42] One study reported similar rates of late bleeding events in four-factor prothrombin complex concentrate–treated patients and plasma-treated patients,[40] whereas another study reported abnormal bleeding in two patients who received plasma but none in those treated with four-factor prothrombin complex concentrate.[38] These abnormal bleeding events were likely linked to plasma's lower effectiveness at reducing patients' international normalized ratio.[38]

Because rapid infusion of prothrombin complex concentrates have potential safety concerns, a multinational trial evaluated 43 patients given prothrombin complex concentrates for emergency warfarin reversal to evaluate the effect of the infusion rate on international normalized ratio correction and thrombogenicity.[85] The infusion speed ranged from 2.0 to 40.0 ml/min (median of 7.5 ml/min). The investigators noted that the speed of infusion did not affect the international normalized ratio measured at 30 min after prothrombin complex concentrate completion, and measured thrombogenicity parameters were not affected by infusion speed.[85] Currently, recommendations for four-component prothrombin complex concentrate administration is reconstitution in 20 ml, and the solution should be administered intravenously (not more than $3 \text{ U} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, maximum 210 U/min, approximately 8 ml/min).

Fluid Overload. Owing to the increased volumes administered with plasma compared with prothrombin complex concentrate, there is a greater risk of fluid overload in patients treated with plasma.[86] In the study by Goldstein *et al.,* fluid overload or similar cardiac events were reported in 3% of patients who received four-factor prothrombin complex concentrate, compared with 13% of patients who received plasma.[40] In another study, one patient who received plasma experienced a significant increase in pulmonary and/or atrial pressure after plasma administration, which is indicative of fluid overload; no patients treated with four-factor prothrombin complex concentrate demonstrated fluid overload events.[38] Taken together, these safety findings are in line with those reported in a recent meta-analysis of warfarin-treated patients who required urgent reversal owing to major bleeding or urgent surgical intervention: no significant difference between prothrombin complex concentrate and plasma was seen in relation to thromboembolic risk, and fluid overload was less likely in patients treated with prothrombin complex concentrate than in patients treated with plasma.[13] In summary, large volumes of plasma are required to reverse vitamin K antagonists; however, they ineffectively increase the concentration of coagulation factors, expose patients to allogeneic blood products with all the inherent risks, and should not be recommended or used for vitamin K antagonist reversal as also recommended in guidelines.

Future Directions: Role of Prothrombin Complex Concentrates for Reversal of Oral Factor Xa Anticoagulants

In contrast with vitamin K antagonists, the non–vitamin K oral anticoagulants specifically inhibit either coagulation factors IIa or Xa, and unlike vitamin K antagonists, have few drug–drug interactions.[87] However, as with vitamin K antagonists, increased bleeding risk remains a concern with non–vitamin K oral anticoagulants.[88] In cases of emergency surgical intervention, there are currently no approved specific reversal agents for factor Xa inhibitors, although andexanet alfa, a recombinant factor Xa decoy receptor protein, was approved in May 2018 for patients treated with rivaroxaban and apixaban, when reversal of anticoagulation is needed because of life-threatening or uncontrolled bleeding. The use of specific reversal strategies for non–vitamin K oral anticoagulants, also called antidotes, is an evolving strategy for treating bleeding with these agents.[89] However, andexanet has not been studied in surgical patients and will be available initially in a limited number of medical centers; its role for perioperative use remains to be determined.

Based on preclinical evidence and recent reports, current guidelines suggest that prothrombin complex concentrates could be used as part of a multimodal approach in patients requiring urgent surgery or experiencing life-threatening bleeding.[10,90–93] Infusion of four-factor prothrombin complex concentrate has been shown to reduce prothrombin time and/or increase endogenous thrombin potential in studies of healthy volunteers or patients who received apixaban, edoxaban, or rivaroxaban.[94–98] Furthermore, infusion of four-factor prothrombin complex concentrate after edoxaban administration demonstrated a dose-dependent effect on reducing bleeding duration and volume within 30 min, with a dose of 50 U/kg decreasing bleeding duration and volume below baseline levels in patients receiving therapeutic doses.[98]

An increasing amount of clinical data on prothrombin complex concentrate use for treatment of acute major bleeding associated with factor Xa anticoagulation is emerging from large patient registries and observational studies. Data from

a large prospective registry of patients receiving non–vitamin K oral anticoagulants, the Dresden registry,[99] demonstrated the rates, management, and outcome of rivaroxaban-related bleeding. Of 1,776 patients, 66 patients experienced a major bleeding event and six patients received prothrombin complex concentrates (dose range, 18 to 47 U/kg). Only one patient had a significant improvement in coagulation parameters (international normalized ratio, prothrombin time ratio, and activated partial thromboplastin time); however, five of the six patients demonstrated hemorrhage stabilization.[99] In a retrospective review of patients developing hemorrhage secondary to dabigatran or rivaroxaban therapy, a median dose of 40 U/kg prothrombin complex concentrate was administered in 3 of 25 patients.[100] All three patients had rivaroxaban-associated bleeds (one major, two life threatening), and administration of prothrombin complex concentrate successfully resolved the bleeding in all cases.[100] With regards to the perioperative setting, a retrospective, multicenter study investigated patients who received four-factor prothrombin complex concentrate for treatment of the anticoagulation effects of factor Xa inhibitors when developing a pericardial effusion during or after atrial fibrillation ablation.[101] In total, 11 patients were administered four-factor prothrombin complex concentrate. Two patients required further surgery for treatment of the pericardial effusion, and the other nine patients were hemodynamically stable and there was no recurrence of the pericardial effusion, demonstrating that four-factor prothrombin complex concentrate is an effective management option in this patient population.[101]

There have also been a few case reports of patients on factor Xa inhibitors (either apixaban or rivaroxaban) being treated with prothrombin complex concentrate before undergoing a surgical procedure.[102–104] Overall, administration of prothrombin complex concentrate was associated with successful completion of surgery and no bleeding complications were reported.[102–104]

A recent prospective evaluation reported 84 patients receiving rivaroxaban or apixaban who were treated with prothrombin complex concentrates for major bleeding and evaluated for thromboembolic events and all-cause mortality within 30 days.[105] Prothrombin complex concentrates were administered at a median dose of 2,000 U (1,500 to 2,000 U) for patients with an intracranial hemorrhage (n = 59; 70.2%) or gastrointestinal bleeding (n = 13; 15.5%). Treatment to stop bleeding was considered effective in 58 (69.1%) and ineffective in 26 (30.9%) treated patients. The majority of the patients with ineffective hemostasis had intracranial hemorrhage (n = 16; 61.5%), and two patients developed an ischemic stroke 5 and 10 days after prothrombin complex concentrate administration. A total of 27 (32%) patients died within 30 days; however, there was no control group in the report.[105]

An additional report from Canada evaluated major bleeding in 66 apixaban- or rivaroxaban-treated patients treated with 2,000 units of prothrombin complex concentrates and evaluated thromboembolism or mortality 30 days later.[106] Using a specific evaluation scale, the investigators reported cessation of bleeding was good in 65%, moderate in 20%, and poor or none in 15% of patients and included patients with intracranial hemorrhage or gastrointestinal bleeding. Overall reversal was considered to be effective in 68% of patients and ineffective in 32%, and mortality was 14% in 30 days, with an 8% risk of thromboembolic events.[106]

Conclusions

Overall, the studies identified in this review support current guideline recommendations that four-factor prothrombin complex concentrate is a preferred treatment option for urgent reversal of vitamin K antagonist anticoagulation in patients requiring urgent surgical or invasive procedures. Prothrombin complex concentrates consistently and rapidly reduced patients' international normalized ratio. Comparative studies with plasma demonstrated greater clinical efficacy with prothrombin complex concentrates in patients requiring emergency surgery. Furthermore, prothrombin complex concentrate treatment was associated with lower rates of fluid overload owing to its lower infusion volume compared to plasma and no instances of viral transmission. Prothrombin complex concentrates are recommended in guidelines for rapid reversal of anticoagulation in vitamin K antagonist–treated patients and represent an important therapeutic option for emergency surgical interventions.

Research Support

Competing Interests

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References

1. IMS data Global Prescription Audit: MAT (moving annual total) 2014/15 to 2015/16. Danbury, Connecticut, IMS Health.

2. Lip GY, Andreotti F, Fauchier L, Huber K, Hylek E, Knight E, Lane D, Levi M, Marín F, Palareti G, Kirchhof P; European Heart Rhythm Association: Bleeding risk assessment and management in atrial fibrillation patients. Executive summary of a position document from the European Heart Rhythm Association [EHRA], endorsed by the European Society of Cardiology [ESC] Working Group on Thrombosis. Thromb Haemost 2011; 106:997–1011

3. Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckman MH, Dunn AS, Kunz R; American College of Chest Physicians: Perioperative management of antithrombotic therapy: Antithrombotic therapy and prevention of thrombosis, 9th edition. American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012; 141:e326S–50S

4. Healey JS, Eikelboom J, Douketis J, Wallentin L, Oldgren J, Yang S, Themeles E, Heidbuchel H, Heidbuchle H, Avezum A, Reilly P, Connolly SJ, Yusuf S, Ezekowitz M; RE-LY Investigators: Periprocedural bleeding and thromboembolic events with dabigatran compared with warfarin: Results from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) randomized trial. Circulation 2012; 126:343–8

5. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G; American College of Chest Physicians: Oral anticoagulant therapy: Antithrombotic therapy and prevention of thrombosis, 9th edition. American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012; 141:e44S–88S

6. Keeling D, Baglin T, Tait C, Watson H, Perry D, Baglin C, Kitchen S, Makris M; British Committee for Standards in Haematology: Guidelines on oral anticoagulation with warfarin, 4th edition. Br J Haematol 2011; 154:311–24

7. Holland LL, Brooks JP: Toward rational fresh frozen plasma transfusion: The effect of plasma transfusion on coagulation test results. Am J Clin Pathol 2006; 126:133–9

8. Dzik WH: The James Blundell Award Lecture 2006: Transfusion and the treatment of haemorrhage: Past, present and future. Transfus Med 2007; 17:367–74

9. Holbrook A, Schulman S, Witt DM, Vandvik PO, Fish J, Kovacs MJ, Svensson PJ, Veenstra DL, Crowther M, Guyatt GH; American College of Chest Physicians: Evidence-based management of anticoagulant therapy: Antithrombotic therapy and prevention of thrombosis, 9th edition: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012; 141:e152S–84S

10. Kozek-Langenecker SA, Ahmed AB, Afshari A, Albaladejo P, Aldecoa C, Barauskas G, De Robertis E, Faraoni D, Filipescu DC, Fries D, Haas T, Jacob M, Lancé MD, Pitarch JVL, Mallett S, Meier J, Molnar ZL, Rahe-Meyer N, Samama CM, Stensballe J, Van der Linden PJF, Wikkelsø AJ, Wouters P, Wyffels P, Zacharowski K: Management of severe perioperative bleeding: Guidelines from the European Society of Anaesthesiology: First update 2016. Eur J Anaesthesiol 2017; 34(6):332–95

11. Levy JH, Tanaka KA, Dietrich W: Perioperative hemostatic management of patients treated with vitamin K antagonists. ANESTHESIOLOGY 2008; 109:918–26

12. Halbritter K, Beyer-Westendorf J, Nowotny J, Pannach S, Kuhlisch E, Schellong SM: Hospitalization for vitamin-K-antagonist-related bleeding: Treatment patterns and outcome. J Thromb Haemost 2013; 11:651–9

13. Chai-Adisaksopha C, Hillis C, Siegal DM, Movilla R, Heddle N, Iorio A, Crowther M: Prothrombin complex concentrates versus fresh frozen plasma for warfarin reversal. A systematic review and meta-analysis. Thromb Haemost 2016; 116:879–90

14. Altorjay A, Szabo E, Boda Z, Kramer L, Ngo LY, Engl W, Firth CL, Ahlstrom ER, Gelmont DM, Pabinger I: An international, multicenter, prospective study of a prothrombin complex concentrate, Prothromplex Total®, in anticoagulant reversal. Thromb Res 2015; 135:485–91

15. Majeed A, Eelde A, Agren A, Schulman S, Holmström M: Thromboembolic safety and efficacy of prothrombin complex concentrates in the emergency reversal of warfarin coagulopathy. Thromb Res 2012; 129:146–51

16. Morimoto Y, Niwa H, Nakatani T: On the use of prothrombin complex concentrate in patients with coagulopathy requiring tooth extraction. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010; 110:e7–10

17. Varga C, Al-Touri S, Papadoukakis S, Caplan S, Kahn S, Blostein M: The effectiveness and safety of fixed low-dose prothrombin complex concentrates in patients requiring urgent reversal of warfarin. Transfusion 2013; 53:1451–8; quiz 1450

18. Wozniak M, Kruit A, Padmore R, Giulivi A, Bormanis J: Prothrombin complex concentrate for the urgent reversal of warfarin. Assessment of a standard dosing protocol. Transfus Apher Sci 2012; 46:309–14

19. Kushimoto S, Fukuoka T, Kimura A, Toyoda K, Brainsky A, Harman A, Chung T, Yasaka M: Efficacy and safety of a 4-factor prothrombin complex concentrate for rapid vitamin K antagonist reversal in Japanese patients presenting with major bleeding or requiring urgent surgical or invasive procedures: A prospective, open-label, single-arm phase 3b study. Int J Hematol 2017; 106:777–86

20. Leal-Noval SR, López-Irizo R, Bautista-Paloma J, Casado M, Arellano-Orden V, Leal-Romero M, Fernández-Hinojosa E, Puppo-Moreno A, Muñoz M: Efficacy of the prothrombin complex concentrate prothromplex in patients requiring urgent reversal of vitamin K antagonists or presenting with uncontrolled bleeding: A retrospective, single center study. Blood Coagul Fibrinolysis 2013; 24:862–8

21. Barillari G, Pasca S, Barillari A, De Angelis V: Emergency reversal of anticoagulation: From theory to real use of prothrombin complex concentrates. A retrospective Italian experience. Blood Transfus 2012; 10:87–94

22. Beynon C, Potzy A, Jungk C, Unterberg AW, Sakowitz OW: Rapid anticoagulation reversal with prothrombin complex concentrate before emergency brain tumor surgery. J Neurosurg Anesthesiol 2015; 27:246–51

23. Beynon C, Potzy A, Unterberg AW, Sakowitz OW: Prothrombin complex concentrate facilitates emergency spinal surgery in anticoagulated patients. Acta Neurochir (Wien) 2014; 156:741–7

24. Butler JJ: Use of low-dose prothrombin complex concentrate before lumbar puncture. Am J Health Syst Pharm 2015; 72:203–5

25. Carvalho MC, Rodrigues AG, Conceição LM, Galvão ML, Ribeiro LC: Prothrombin complex concentrate (Octaplex): A Portuguese experience in 1152 patients. Blood Coagul Fibrinolysis 2012; 23:222–8

26. Hurlburt L, Roscoe A, van Rensburg A: The use of prothrombin complex concentrates in two patients with non-pulsatile left ventricular assist devices. J Cardiothorac Vasc Anesth 2014; 28:345–6

27. Kar R, Abel E, Burcham P, Firstenberg MS: Prothrombin complex concentrate for warfarin-induced bleeding in a patient

with a mechanical aortic valve. Interact Cardiovasc Thorac Surg 2013; 17:421–2

28. Pabinger I, Brenner B, Kalina U, Knaub S, Nagy A, Ostermann H; Beriplex P/N Anticoagulation Reversal Study Group: Prothrombin complex concentrate (Beriplex P/N) for emergency anticoagulation reversal: A prospective multinational clinical trial. J Thromb Haemost 2008; 6:622–31

29. Skerritt C, Mannion S: Prothrombin complex concentrate for rapid reversal of warfarin anticoagulation to allow neuraxial blockade. Case Rep Anesthesiol 2014; 2014:126864

30. Sridharan M, Wysokinski WE, Pruthi R, Oyen L, Freeman WD, Rabinstein AA, McBane RD: Periprocedural warfarin reversal with prothrombin complex concentrate. Thromb Res 2016; 139:160–5

31. Laible M, Beynon C, Sander P, Purrucker J, Müller OJ, Möhlenbruch M, Ringleb PA, Rizos T: Treatment with prothrombin complex concentrate to enable emergency lumbar puncture in patients receiving vitamin K antagonists. Ann Emerg Med 2016; 68:340–4

32. Burk DR, Smith JL, Wild JR: Prothrombin complex concentrates: An alternative to fresh frozen plasma. Orthopedics 2017; 40:e367–9

33. Chaudhuri K, Phillips CW, Chaudhuri S, Wasnick J: Use of prothrombin complex concentrate for warfarin reversal before the performance of an epidural blood patch in a patient with cortical vein thrombosis and subdural hematoma: A case report. A A Case Rep 2017; 8:36–8

34. Farley TM, Andreas EM: Reversal of anticoagulation with four-factor prothrombin complex concentrate without concurrent vitamin K (phytonadione) for urgent surgery in a patient at moderate-to-high risk for thromboembolism. BMJ Case Rep 2016; 2016; pii: bcr2016217092

35. Keung CYY, Metz AJ, Sood S: Rapid large pulmonary embolism after prothrombin complex concentrate for warfarin reversal during colonoscopy. Intern Med J 2017; 47:710–1

36. Nuckles KB, Pratt JH, Cameron CM, Ingemi AI: Case series of four-factor prothrombin complex concentrate for warfarin reversal before heart transplantation. Transplant Proc 2015; 47:841–3

37. Joseph R, Burner J, Yates S, Strickland A, Tharpe W, Sarode R: Thromboembolic outcomes after use of a four-factor prothrombin complex concentrate for vitamin K antagonist reversal in a real-world setting. Transfusion 2016; 56:799–807

38. Demeyere R, Gillardin S, Arnout J, Strengers PF: Comparison of fresh frozen plasma and prothrombin complex concentrate for the reversal of oral anticoagulants in patients undergoing cardiopulmonary bypass surgery: A randomized study. Vox Sang 2010; 99:251–60

39. Fariborz Farsad B, Golpira R, Najafi H, Totonchi Z, Salajegheh S, Bakhshandeh H, Hashemian F: Comparison between prothrombin complex concentrate (PCC) and fresh frozen plasma (FFP) for the urgent reversal of warfarin in patients with mechanical heart valves in a tertiary care cardiac center. Iran J Pharm Res 2015; 14:877–85

40. Goldstein JN, Refaai MA, Milling TJ Jr, Lewis B, Goldberg-Alberts R, Hug BA, Sarode R: Four-factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions: A phase 3b, open-label, non-inferiority, randomised trial. Lancet 2015; 385:2077–87

41. Agarwal P, Abdullah KG, Ramayya AG, Nayak NR, Lucas TH: A retrospective propensity score-matched early thromboembolic event analysis of prothrombin complex concentrate vs fresh frozen plasma for warfarin reversal prior to emergency neurosurgical procedures. Neurosurgery 2018; 82:877–86

42. Ortmann E, Besser MW, Sharples LD, Gerrard C, Berman M, Jenkins DP, Klein AA: An exploratory cohort study comparing prothrombin complex concentrate and fresh frozen plasma for the treatment of coagulopathy after complex cardiac surgery. Anesth Analg 2015; 121:26–33

43. Sarode R, Milling TJ Jr, Refaai MA, Mangione A, Schneider A, Durn BL, Goldstein JN: Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: A randomized, plasma-controlled, phase IIIb study. Circulation 2013; 128:1234–43

44. Refaai MA, Kothari TH, Straub S, Falcon J, Sarode R, Goldstein JN, Brainsky A, Omert L, Lee ML, Milling TJ: Four-factor prothrombin complex concentrate reduces time to procedure in vitamin K antagonist-treated patients experiencing gastrointestinal bleeding: A post hoc analysis of two randomized controlled trials. Emerg Med Int 2017; 2017:8024356

45. Al-Majzoub O, Rybak E, Reardon DP, Krause P, Connors JM: Evaluation of warfarin reversal with 4-factor prothrombin complex concentrate compared to 3-factor prothrombin complex concentrate at a tertiary academic medical center. J Emerg Med 2016; 50:7–13

46. Jones GM, Erdman MJ, Smetana KS, Mohrien KM, Vandigo JE, Elijovich L: 3-Factor *versus* 4-factor prothrombin complex concentrate for warfarin reversal in severe bleeding: A multicenter, retrospective, propensity-matched pilot study. J Thromb Thrombolysis 2016; 42:19–26

47. Mangram A, Oguntodu OF, Dzandu JK, Hollingworth AK, Hall S, Cung C, Rodriguez J, Yusupov I, Barletta JF: Is there a difference in efficacy, safety, and cost-effectiveness between 3-factor and 4-factor prothrombin complex concentrates among trauma patients on oral anticoagulants? J Crit Care 2016; 33:252–6

48. Voils SA, Holder MC, Premraj S, Catlin JR, Allen BR: Comparative effectiveness of 3- versus 4-factor prothrombin complex concentrate for emergent warfarin reversal. Thromb Res 2015; 136:595–8

49. Skolnick BE, Mathews DR, Khutoryansky NM, Pusateri AE, Carr ME: Exploratory study on the reversal of warfarin with rFVIIa in healthy subjects. Blood 2010; 116:693–701

50. Tanaka KA, Szlam F, Dickneite G, Levy JH: Effects of prothrombin complex concentrate and recombinant activated factor VII on vitamin K antagonist induced anticoagulation. Thromb Res 2008; 122:117–23

51. Pinner NA, Hurdle AC, Oliphant C, Reaves A, Lobo B, Sills A: Treatment of warfarin-related intracranial hemorrhage: A comparison of prothrombin complex concentrate and recombinant activated factor VII. World Neurosurg 2010; 74:631–5

52. Chapman SA, Irwin ED, Abou-Karam NM, Rupnow NM, Hutson KE, Vespa J, Roach RM: Comparison of 3-factor prothrombin complex concentrate and low-dose recombinant factor VIIa for warfarin reversal. World J Emerg Surg 2014; 9:27

53. DeLoughery E, Avery B, DeLoughery TG: Retrospective study of rFVIIa, 4-factor PCC, and a rFVIIa and 3-factor PCC combination in improving bleeding outcomes in the warfarin and non-warfarin patient. Am J Hematol 2016; 91:705–8

54. Fang MC, Go AS, Chang Y, Hylek EM, Henault LE, Jensvold NG, Singer DE: Death and disability from warfarin-associated intracranial and extracranial hemorrhages. Am J Med 2007; 120:700–5

55. Hemphill JC 3rd, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, Fung GL, Goldstein JN, Macdonald RL, Mitchell PH, Scott PA, Selim MH, Woo D; American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology: Guidelines for the management of spontaneous intracerebral hemorrhage: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2015; 46:2032–60

56. Steiner T, Al-Shahi Salman R, Beer R, Christensen H, Cordonnier C, Csiba L, Forsting M, Harnof S, Klijn CJ, Krieger D, Mendelow AD, Molina C, Montaner J, Overgaard K, Petersson J, Roine RO, Schmutzhard E, Schwerdtfeger K, Stapf C, Tatlisumak T, Thomas BM, Toni D, Unterberg

A, Wagner M; European Stroke Organisation: European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage. Int J Stroke 2014; 9:840–55

57. Edavettal M, Rogers A, Rogers F, Horst M, Leng W: Prothrombin complex concentrate accelerates international normalized ratio reversal and diminishes the extension of intracranial hemorrhage in geriatric trauma patients. Am Surg 2014; 80:372–6

58. Siddiq F, Jalil A, McDaniel C, Brock DG, Pineda CC, Bell RD, Lee K: Effectiveness of Factor IX complex concentrate in reversing warfarin associated coagulopathy for intracerebral hemorrhage. Neurocrit Care 2008; 8:36–41

59. Steiner T, Poli S, Griebe M, Hüsing J, Hajda J, Freiberger A, Bendszus M, Bösel J, Christensen H, Dohmen C, Hennerici M, Kollmer J, Stetefeld H, Wartenberg KE, Weimar C, Hacke W, Veltkamp R: Fresh frozen plasma versus prothrombin complex concentrate in patients with intracranial haemorrhage related to vitamin K antagonists (INCH): A randomised trial. Lancet Neurol 2016; 15:566–73

60. Yanamadala V, Walcott BP, Fecci PE, Rozman P, Kumar JI, Nahed BV, Swearingen B: Reversal of warfarin associated coagulopathy with 4-factor prothrombin complex concentrate in traumatic brain injury and intracranial hemorrhage. J Clin Neurosci 2014; 21:1881–4

61. Alonso de Lecinana M, Huertas N, Egido JA, Muriel A, Garcia A, Ruiz-Ares G, Diez-Tejedor E, Fuentes B: Questionable reversal of anticoagulation in the therapeutic management of cerebral haemorrhage associated with vitamin K antagonists. Thromb Haemost 2013; 110: 1145–51

62. Frontera JA, Gordon E, Zach V, Jovine M, Uchino K, Hussain MS, Aledort L: Reversal of coagulopathy using prothrombin complex concentrates is associated with improved outcome compared to fresh frozen plasma in warfarin-associated intracranial hemorrhage. Neurocrit Care 2014; 21:397–406

63. Fong WC, Lo WT, Ng YW, Cheung YF, Wong GC, Ho HF, Chan JH, Li PC: The benefit of prothrombin complex concentrate in decreasing neurological deterioration in patients with warfarin-associated intracerebral haemorrhage. Hong Kong Med J 2014; 20:486–94

64. Majeed A, Meijer K, Larrazabal R, Arnberg F, Luijckx GJ, Roberts RS, Schulman S: Mortality in vitamin K antagonist-related intracerebral bleeding treated with plasma or 4-factor prothrombin complex concentrate. Thromb Haemost 2014; 111:233–9

65. Woo CH, Patel N, Conell C, Rao VA, Faigeles BS, Patel MC, Pombra J, Akins PT, Axelrod YK, Ge IY, Sheridan WF, Flint AC: Rapid Warfarin reversal in the setting of intracranial hemorrhage: A comparison of plasma, recombinant activated factor VII, and prothrombin complex concentrate. World Neurosurg 2014; 81:110–5

66. Ranucci M, Baryshnikova E, Castelvecchio S, Pelissero G; Surgical and Clinical Outcome Research (SCORE) Group: Major bleeding, transfusions, and anemia: The deadly triad of cardiac surgery. Ann Thorac Surg 2013; 96:478–85

67. Kantorovich A, Fink JM, Militello MA, Wanek MR, Smedira NG, Soltesz EG, Moazami N: Low-dose 3-factor prothrombin complex concentrate for warfarin reversal prior to heart transplant. Ann Pharmacother 2015; 49:876–82

68. Sun GH, Patel V, Moreno-Duarte I, Zahedi F, Ursprung E, Couper G, Chen FY, Welsby IJ, Comenzo R, Kao G, Cobey FC: Intraoperative administration of 4-factor prothrombin complex concentrate reduces blood requirements in cardiac transplantation. J Cardiothorac Vasc Anesth 2018; 32:161–7

69. Dossett LA, Riesel JN, Griffin MR, Cotton BA: Prevalence and implications of preinjury warfarin use: An analysis of the National Trauma Databank. Arch Surg 2011; 146:565–70

70. Lecky FE, Omar M, Bouamra O, Jenks T, Edwards A, Battle CE, Evans PA: The effect of preinjury warfarin use on mortality rates in trauma patients: A European multicentre study. Emerg Med J 2015; 32:916–20

71. Rossaint R, Bouillon B, Cerny V, Coats TJ, Duranteau J, Fernandez-Mondejar E, Filipescu D, Hunt BJ, Komadina R, Nardi G, Neugebauer EA, Ozier Y, Riddez L, Schultz A, Vincent JL, Spahn DR: The European guideline on management of major bleeding and coagulopathy following trauma, 4th edition. Crit Care 2016; 20:100

72. Holcomb JB, Tilley BC, Baraniuk S, Fox EE, Wade CE, Podbielski JM, del Junco DJ, Brasel KJ, Bulger EM, Callcut RA, Cohen MJ, Cotton BA, Fabian TC, Inaba K, Kerby JD, Muskat P, O'Keeffe T, Rizoli S, Robinson BR, Scalea TM, Schreiber MA, Stein DM, Weinberg JA, Callum JL, Hess JR, Matijevic N, Miller CN, Pittet JF, Hoyt DB, Pearson GD, Leroux B, van Belle G; PROPPR Study Group: Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: The PROPPR randomized clinical trial. JAMA 2015; 313:471–82

73. Joseph B, Aziz H, Pandit V, Hays D, Kulvatunyou N, Yousuf Z, Tang A, O'Keeffe T, Green D, Friese RS, Rhee P: Prothrombin complex concentrate *versus* fresh-frozen plasma for reversal of coagulopathy of trauma: Is there a difference? World J Surg 2014; 38:1875–81

74. Joseph B, Khalil M, Harrison C, Swartz T, Kulvatunyou N, Haider AA, Jokar TO, Burk D, Mahmoud A, Latifi R, Rhee P: Assessing the efficacy of prothrombin complex concentrate in multiply injured patients with high-energy pelvic and extremity fractures. J Orthop Trauma 2016; 30:653–8

75. Berndtson AE, Huang WT, Box K, Kobayashi L, Godat LN, Smith AM, Weingarten D, Coimbra R: A new kid on the block: Outcomes with Kcentra 1 year after approval. J Trauma Acute Care Surg 2015; 79:1004–8

76. Innerhofer P, Westermann I, Tauber H, Breitkopf R, Fries D, Kastenberger T, El Attal R, Strasak A, Mittermayr M: The exclusive use of coagulation factor concentrates enables reversal of coagulopathy and decreases transfusion rates in patients with major blunt trauma. Injury 2013; 44:209–16

77. Martin DT, Barton CA, Dodgion C, Schreiber M: Emergent reversal of vitamin K antagonists: Addressing all the factors. Am J Surg 2016; 211:919–25

78. Köhler M: Thrombogenicity of prothrombin complex concentrates. Thromb Res 1999; 95(4 Suppl 1):S13–7

79. Kalina U, Bickhard H, Schulte S: Biochemical comparison of seven commercially available prothrombin complex concentrates. Int J Clin Pract 2008; 62:1614–22

80. Dentali F, Marchesi C, Giorgi Pierfranceschi M, Crowther M, Garcia D, Hylek E, Witt DM, Clark NP, Squizzato A, Imberti D, Ageno W: Safety of prothrombin complex concentrates for rapid anticoagulation reversal of vitamin K antagonists. A meta-analysis. Thromb Haemost 2011; 106:429–38

81. Desmettre T, Dubart AE, Capellier G, Fanara B, Puyraveau M, Kepka S, Coquart J, Sheppard F, Tazarourte K: Emergency reversal of anticoagulation: The real use of prothrombin complex concentrates: A prospective multicenter two year French study from 2006 to 2008. Thromb Res 2012; 130:e178–83

82. Sin JH, Berger K, Lesch CA: Four-factor prothrombin complex concentrate for life-threatening bleeds or emergent surgery: A retrospective evaluation. J Crit Care 2016; 36:166–72

83. Toth P, van Veen JJ, Robinson K, Maclean RM, Hampton KK, Laidlaw S, Makris M: Real world usage of PCC to "rapidly" correct warfarin induced coagulopathy. Blood Transfus 2013; 11:500–5

84. Goldhammer JE, Bakowitz MJ, Milas BL, Patel PA: Intracardiac thrombosis after emergent prothrombin complex concentrate administration for warfarin reversal. ANESTHESIOLOGY 2015; 123:458

85. Pabinger I, Tiede A, Kalina U, Knaub S, Germann R, Ostermann H; Beriplex P/N Anticoagulation Reversal Study Group: Impact of infusion speed on the safety and

effectiveness of prothrombin complex concentrate: A prospective clinical trial of emergency anticoagulation reversal. Ann Hematol 2010; 89:309–16

86. Refaai MA, Goldstein JN, Lee ML, Durn BL, Milling TJ Jr, Sarode R: Increased risk of volume overload with plasma compared with four-factor prothrombin complex concentrate for urgent vitamin K antagonist reversal. Transfusion 2015; 55:2722–9

87. Levy JH, Key NS, Azran MS: Novel oral anticoagulants: Implications in the perioperative setting. ANESTHESIOLOGY 2010; 113:726–45

88. Sarich TC, Seltzer JH, Berkowitz SD, Costin' J, Curnutte JT, Gibson CM, Hoffman M, Kaminskas E, Krucoff MW, Levy JH, Mintz PD, Reilly PA, Sager PT, Singer DE, Stockbridge N, Weitz JI, Kowey PR: Novel oral anticoagulants and reversal agents: Considerations for clinical development. Am Heart J 2015; 169:751–7

89. Levy JH, Ageno W, Chan NC, Crowther M, Verhamme P, Weitz JI; Subcommittee on Control of Anticoagulation: When and how to use antidotes for the reversal of direct oral anticoagulants: Guidance from the SSC of the ISTH. J Thromb Haemost 2016; 14:623–7

90. Faraoni D, Levy JH, Albaladejo P, Samama CM; Groupe d'Intérêt en Hémostase Périopératoire: Updates in the perioperative and emergency management of non-vitamin K antagonist oral anticoagulants. Crit Care 2015; 19:203

91. Tomaselli GF, Mahaffey KW, Cuker A, Dobesh PP, Doherty JU, Eikelboom JW, Florido R, Hucker W, Mehran R, Messé SR, Pollack CV Jr., Rodriguez F, Sarode R, Siegal D, Wiggins BS: 2017 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants: A report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol 2017; 70:3042–67

92. Levy JH, Douketis J, Weitz JI: Reversal agents for non-vitamin K antagonist oral anticoagulants. Nat Rev Cardiol 2018; 15:273–81

93. Raval AN, Cigarroa JE, Chung MK, Diaz-Sandoval LJ, Diercks D, Piccini JP, Jung HS, Washam JB, Welch BG, Zazulia AR, Collins SP; American Heart Association Clinical Pharmacology Subcommittee of the Acute Cardiac Care and General Cardiology Committee of the Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; and Council on Quality of Care and Outcomes Research: Management of patients on non-vitamin K antagonist oral anticoagulants in the acute care and periprocedural setting: A scientific statement from the American Heart Association. Circulation 2017; 135:e604–33

94. Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, Levi M: Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: A randomized, placebo-controlled, crossover study in healthy subjects. Circulation 2011; 124:1573–9

95. Levi M, Moore KT, Castillejos CF, Kubitza D, Berkowitz SD, Goldhaber SZ, Raghoebar M, Patel MR, Weitz JI, Levy JH: Comparison of three-factor and four-factor prothrombin complex concentrates regarding reversal of the anticoagulant effects of rivaroxaban in healthy volunteers. J Thromb Haemost 2014; 12:1428–36

96. Nagalla S, Thomson L, Oppong Y, Bachman B, Chervoneva I, Kraft WK: Reversibility of apixaban anticoagulation with a four-factor prothrombin complex concentrate in healthy volunteers. Clin Transl Sci 2016; 9:176–80

97. Schultz NH, Tran HTT, Bjørnsen S, Henriksson CE, Sandset PM, Holme PA: The reversal effect of prothrombin complex concentrate (PCC), activated PCC and recombinant activated factor VII against anticoagulation of Xa inhibitor. Thromb J 2017; 15:6

98. Zahir H, Brown KS, Vandell AG, Desai M, Maa JF, Dishy V, Lomeli B, Feussner A, Feng W, He L, Grosso MA, Lanz HJ, Antman EM: Edoxaban effects on bleeding following punch biopsy and reversal by a 4-factor prothrombin complex concentrate. Circulation 2015; 131:82–90

99. Beyer-Westendorf J, Förster K, Pannach S, Ebertz F, Gelbricht V, Thieme C, Michalski F, Köhler C, Werth S, Sahin K, Tittl L, Hänsel U, Weiss N: Rates, management, and outcome of rivaroxaban bleeding in daily care: Results from the Dresden NOAC registry. Blood 2014; 124:955–62

100. Pahs L, Beavers C, Schuler P: The real-world treatment of hemorrhages associated with dabigatran and rivaroxaban: A multicenter evaluation. Crit Pathw Cardiol 2015; 14:53–61

101. Gianni C, DI Biase L, Mohanty S, Trivedi C, Bai R, Al-Ahmad A, Burkhardt JD, Gallinghouse GJ, Horton RP, Sanchez JE, Hranitzky PM, Lakkireddy D, Mansour MC, Santangeli P, Zado ES, Marchlinski FE, Beheiry S, Hao SC, Couts L, Gibson D, Natale A: Management of periprocedural and early pericardial effusions with tamponade following ablation of atrial fibrillation with uninterrupted factor Xa inhibitors: A case series. J Cardiovasc Electrophysiol 2016; 27:399–403

102. Beynon C, Potzy A, Unterberg AW, Sakowitz OW: Emergency neurosurgical care in patients treated with apixaban: Report of 2 cases. Am J Emerg Med 2015; 33:858.e5–7

103. Chic Acevedo C, Velasco F, Herrera C: Reversal of rivaroxaban anticoagulation by nonactivated prothrombin complex concentrate in urgent surgery. Future Cardiol 2015; 11:525–9

104. Liu M, Aguele C, Darr U: Use of four-factor prothrombin complex concentrate for the mitigation of rivaroxaban-induced bleeding in an emergent coronary artery bypass graft. Clin Case Rep 2017; 5:636–9

105. Majeed A, Ågren A, Holmström M, Bruzelius M, Chaireti R, Odeberg J, Hempel EL, Magnusson M, Frisk T, Schulman S: Management of rivaroxaban- or apixaban-associated major bleeding with prothrombin complex concentrates: A cohort study. Blood 2017; 130:1706–12

106. Schulman S, Gross PL, Ritchie B, Nahirniak S, Lin Y, Lieberman L, Carrier M, Crowther MA, Ghosh I, Lazo-Langner A, Zondag M; Study Investigators: Prothrombin complex concentrate for major bleeding on factor Xa inhibitors: A prospective cohort study. Thromb Haemost 2018; 118:842–51

107. Frontera JA, Lewin 3rd JJ, Rabinstein AA, Aisiku IP, Alexandrov AW, Cook AM, del Zoppo GJ, Kumar MA, Peerschke EI, Stiefel MF, Teitelbaum JS, Wartenberg KE, Zerfoss CL. Guideline for reversal of antithrombotics in intracranial hemorrhage: A statement for healthcare professionals from the Neurocritical Care Society and Society of Critical Care Medicine. Neurocrit Care 2016; 24:6–46

MIND TO MIND

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

Stephen T. Harvey, M.D., Editor

KW

Jo Dereske

He felt a backache in springtime
Moving bricks to build a garden wall
For me.

Persistent. Not backrubs
Nor Ben-Gay nor bed.
X-rays, blood tests, CT scan,
As big as a grapefruit.

New scars, new words:
5-FU, Leucovorin.
Deadly music:
Camptosar, Oxaliplatin.

Devil child's poem:
Thoracentesis, Pleuradesis
Hepatic metastasis.

Coffee in sunlight, each sip
A gift. One year.
Green grass growing in my
New garden.

This poem is one of the finalists of ANESTHESIOLOGY's first annual creative writing competition, The Letheon.

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Stephen T. Harvey, M.D., Editor

Among Body Parts and Colleagues

Finding My Team in the Rubble on 9/11

Jesse M. Raiten, M.D.

We stood in silence and watched as a bright blue sky slowly turned black with ash. The sense of anxiety was nearly palpable as the distant sounds of ambulance sirens slowly grew louder. My hands fidgeted in the pockets of my short white coat, bulging with reference books and other tools, still clean enough to identify me as a medical student early in my clinical rotations. No one knew what to expect, but the mass of students, physicians, nurses, and staff was a formidable sight in the otherwise empty ambulance bay at Bellevue Hospital.

Everyone has his or her own story of the morning of September 11, 2001. Where they were when the first tower fell, whom they called first. I heard it from our waiter at breakfast in the café in Bellevue Hospital, the flagship hospital of New York City's Health and Hospitals Corporation, located a few miles from the site of the attacks. I turned to see the tiny television screen beyond the cash register showing fire rising from the South Tower. Over the next hours my colleagues and I would reinvent ourselves time and again, our responsibilities evolving at a lightning pace. My patients would change from those with congestive heart failure and pneumonia to another type all together—the literal fragments of humanity. A charred body part, a ring attached to a severed hand. They were faces plastered on telephone poles, and missing persons reports on CNN.

The hours and days after 9/11 were full of chaos and confusion, yet my memories remain vivid, even raw. The smell of smoke and burned flesh mixed, permeating into my clothing, rising above and wafting through the windows of my seventh-floor dormitory room, which now overlooked the makeshift triage tents of the medical examiner's office. Hours after the towers fell, a group of medical students rode in an ambulance to Ground Zero. As we passed a giant tire on the side of the road, deep in soot, I wondered what size truck used a wheel that big. Chills ran down my back when, hours later, I realized it was the wheel of an airplane.

Of all the images of horror that I associate with 9/11, so too were there lessons of courage, and the power of a medical community coming together. As rumors swirled of countless injuries and traumas, we gathered in the emergency department to await a rush of patients. Medical students, interns, residents, nurses, junior faculty, and senior faculty, shoulder-to-shoulder, waiting. It was then, in a cloud of confusion and uncertainty, that I learned the true meaning of being a team.

The onslaught of patients that we expected never materialized, although we rapidly mobilized our resources to prepare for the worst and adapted as the realities of the events gained clarity. In the coming days, my colleagues and I would become forensic examiners, cafeteria workers, patient transporters, and counselors. I triaged body bags of rubble as they arrived in a virtual bucket brigade from ambulances, and helped catalog bone fragments opposite a pathology resident. My colleagues would do the same heartbreaking work, then serve food to volunteers on the sidewalks along First Avenue.

We had no blueprint to follow. I was only two years out of anatomy class, and hardly the best person to identify human remains mixed among the rubble of the Manhattan skyline. But we were a team—each of us with different skills and specialties, experience levels and titles—but all with the same responsibility: to do anything, and everything, we were able. Over the ensuing hours and days, in the backdrop of a city literally rising from the flames, we came together for our patients, and for each other. Being a team is more than picking up where someone left off or lending a helping hand. It is finding the silver lining in a ghastly situation to make things a little easier for a colleague. It is the pathologist who paused for a moment as we triaged body bags when a teaching opportunity presented, offering, if only for a moment, a much-needed escape from the gravity of the situation. It is the ambulance crew agreeing to take you to Ground Zero on the night of 9/11, knowing there is nothing you could do there to help, but understanding that you needed to go, just to be sure.

Much of the study of medicine is individually driven. Success is achieved through exam scores and grades that allow you to move from college to medical school, and into residency. But success in medicine ultimately comes in the healing of your patients, something that rarely happens in isolation, but through the harmonious work of physicians, nurses, pharmacists, and the plethora of team members that patients require. Teamwork on 9/11 required acknowledging a new perspective—one where treating our patients meant reuniting their bodies with their loved ones, understanding that everyone was grappling with a new, nearly inconceivable reality where a wheel on the sidewalk in lower Manhattan could come from an airplane, and where we would need to look out for each other as much as we did for our patients and their families.

Life gradually assumed a new normalcy as the weeks and months passed after the attacks. The smoke from the towers slowed and we returned to our clinical rotations and assignments. But the tragedy of 9/11 remained a tangible presence in our lives, the medical examiner's triage tent still active outside our windows, and the hospital walls still plastered with the faces of the missing. They are experiences and images that will forever tie those of us who were there on 9/11 together. For many of us, it was the first time in our brief medical careers that we were ever truly depended on. And while I had yet to write my first prescription or place my first suture in the operating room, I learned that being a team was as much dependent on adaptability and respect for your colleagues, as on medical knowledge and skills. And while no one wants to learn these skills in the aftermath of a terrorist attack, ironically for my colleagues and I, little did we know how soon we would be using them again.

Two months and one day after 9/11, an American Airlines plane crashed only miles from the site of the World Trade Center. All over again, with many questions but few answers, we searched out opportunities to help—medical students, residents, and faculty, many still actively working on the aftermath of 9/11. As the events unfolded and we realized there would be no survivors, I found myself in a familiar position alongside a medical student colleague and a pathologist, triaging the remains of patients from arriving ambulances into the morgue. Once again, the images of flames and debris played on repeat on the television screen, and once again, the ambulance sirens screamed. And once again, we were a team.

In-training Exams, Performance, and Exam Fatigue

To the Editor:

I read with great interest Dr. Zhou *et al.*'s article regarding the effect of instituting the BASIC examination on anesthesiology knowledge acquisition.[1] The authors should be commended for their hard work and dedication to educating future leaders of our specialty.

As a recent graduate of anesthesiology residency in a large tertiary academic medical center, and as a member of the second class to take the American Board of Anesthesiology BASIC examination, my perspective on the examination differs somewhat from that of its developers. Scores on the in-training examination have been shown to correlate poorly with clinical performance in a variety of medical specialties and practice environments,[2–4] and therefore a statistically significant increase in these scores may not translate into any real clinical improvement. In addition, the advent of frequent standardized testing is a likely factor of the burnout epidemic among anesthesiology trainees. I was not immune to this phenomenon, and personally experienced intense periods of detachment and depersonalization during my residency as a result of exam fatigue. This problem is only likely to worsen with the rollout of the new American Board of Anesthesiology Applied examination, which includes an Objective Structured Clinical Exam component in addition to the Standardized Oral Examination exam.

The rollout of the United States Medical Licensing Examination Step 2 Clinical Skills should be a cautionary tale to all in the world of medical education. Initially used as a method for ascertaining the bedside manner and communication skills of foreign medical graduates, it was expanded to include all U.S. graduates. The costs associated with finding a "legitimate failure" are estimated at over $1 million per failure,[5] a sum financed largely by examinees mired in worsening educational debt. Much ink has been spilled (including by the authors of the article under discussion)[6,7] about the rollout of the Objective Structured Clinical Exam exam, but it is important to put a human face to the discussion. The majority of residents experience burnout at some point during their time in education, and most anesthesiology residents personally know someone whose training was interrupted for mental health reasons. Maybe this would happen less if we had to jump through fewer hoops to prove our baseline competence—or maybe not. But we cannot afford to keep adding on exam after exam without serious thought to the toll it's taking on our trainees.

Although an increase in in-training examination scores is impressive and laudable, like everything else in medicine there should be a constant examination of the risks and benefits of our interventions. The question we should be asking ourselves is not whether additional exams raise performance on our exams: Instead, maybe we should think about whether it will make us better anesthesiologists in the long run. We do what we do for the benefit of our patients, and they deserve us to be at our best educationally and in terms of our mental health.

Competing Interests

The author declares no competing interests.

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References

1. Zhou Y, Sun H, Lien CA, Keegan MT, Wang T, Harman AE, Warner DO: Effect of the BASIC examination on knowledge acquisition during anesthesiology residency. Anesthesiology 2018; 128:813–20

2. Ryan JG, Barlas D, Pollack S: The relationship between faculty performance assessment and results on the in-training examination for residents in an emergency medicine training program. J Grad Med Educ 2013; 5:582–6

3. Quattlebaum TG, Darden PM, Sperry JB: In-training examinations as predictors of resident clinical performance. Pediatrics 1989; 84:165–72

4. Hawkins RE, Sumption KF, Gaglione MM, Holmboe ES: The in-training examination in internal medicine: Resident perceptions and lack of correlation between resident scores and faculty predictions of resident performance. Am J Med 1999; 106:206–10

5. Lehman EP IV, Guercio JR: The Step 2 Clinical Skills exam—a poor value proposition. N Engl J Med 2013; 368:889–91

6. Rathmell JP, Lien C, Harman A: Objective structured clinical examination and board certification in anesthesiology. Anesthesiology 2014; 120:4–6

7. Rathmell JP, Lien CA, Harman A: In reply. Anesthesiology 2014; 121:432

(Accepted for publication August 31, 2018.)

Does the American Board of Anesthesiology BASIC Examination Really Affect Anesthesiology Resident Knowledge Acquisition?

To the Editor:

We applaud Zhou *et al.* for their recent publication of American Board of Anesthesiology data suggesting that after implementation of the BASIC certification examination, anesthesiology residents' performance improved on the subsequent in-training examination.[1] As opined by Murray in an accompanying editorial, increased transparency and sharing of data from the American Board of Anesthesiology is welcome and useful to the specialty, training programs, and community at

large that physician anesthesiologists serve.[2] Our program, as we suspect many others have, is focusing educational preparation for the BASIC exam over the two years of clinical base and clinical anesthesia year 1 training, an acknowledged potential benefit and goal.

Both the editorial and article discuss the small effect size (two points in scaled score) in this initial evaluation of the examination process restructure. In the mixed effects model, residents with in-training examination scores were considered, thus implying that a large proportion not taking the in-training examination during the clinical base year and any resident not sitting for subsequent in-training examinations was not accounted for. The method similarly confirms that only residents "who maintained a regular progression of training level" were included. Thus, it is likely that residents lost from the program through attrition (whether for medical knowledge, professionalism, or another competency) may have affected the small signal. This and an additional unintended consequence of the new examination structure is explored.

1. Most programs have incorporated success on the BASIC examination as an objective milestone measure of medical knowledge and many are offering residents only two unsuccessful opportunities, in the summer and fall of the rising clinical anesthesia year 2 year. As such, any deficiency will be apparent *prior* to the next spring in-training examination in the clinical anesthesia year 2 year and any loss of residents (who would naturally be presumed also to be poor performers on the in-training examination) may have *de facto* resulted in an apparent improvement in the cohort's second compared in-training examination score.
2. Similarly, with appropriate increased academic attention and focus on the BASIC exam, it is likely that many clinical base and clinical anesthesia year 1 residents are more committed to the higher stakes first certification BASIC examination, which has implications for successful maturation through the program. The more specific curriculum for the BASIC exam and time required for preparation may unintentionally distract attention from the preceding in-training examination, which for many programs is not a high-stakes examination for satisfactory academic progress. Thus, the in-training examination in the clinical anesthesia year 1 year as the first comparison point may be artificially lower, this also appearing to accentuate the "improvement" in the subsequent in-training examination.

Addition of the BASIC exam as the first step in anesthesiology resident certification appears to be appropriate and useful to residents and programs in the milestone era. Optimism for objective markers of success should remain restrained, however, until the impact of unintended consequences in resident exam preparation priorities and residents missing from the in-training examination through attrition are accounted for. We eagerly anticipate continued

distribution of data from the American Board of Anesthesiology on these and other certification processes.

Competing Interests

The authors declare no competing interests.

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References

1. Zhou Y, Sun H, Lien CA, Keegan MT, Wang T, Harman AE, Warner DO: Effect of the BASIC examination on knowledge acquisition during anesthesiology residency. ANESTHESIOLOGY 2018; 128:813–20
2. Murray DJ, Boulet JR: Anesthesiology board certification changes: A real-time example of "assessment drives learning." ANESTHESIOLOGY 2018: 128:704–6

In Reply:

The letter from Pivalizza *et al.* confirms that residency programs do respond rapidly to changes in certification requirements.[1] The program directors at this relatively large residency program suggest that both attrition of residents earlier in their training and changes to the curriculum could impact the conclusions about knowledge acquisition in the study by Zhou *et al.*[2] The letter suggests that these factors, especially attrition of residents who likely had lower in-training examination scores, may have contributed to higher in-training examination scores in clinical anesthesia year 2, potentially tainting the "acceleration of knowledge" argument.[2] Information about the training outcomes of residents who do not successfully pass their BASIC exam, either on initial or further attempts, could help alleviate the concerns regarding the representativeness of the resident cohort.

The more important question that this letter, the original article by Zhou *et al.*,[2] and the editorial[1] all allude to is, "What measures would confirm that the changes in examination resulted in increased knowledge acquisition?" As noted in our editorial, if certification requirements stay the same, the ultimate outcome measure would be that a cohort of graduates would be more successful in their first attempt following the move to administering BASIC and ADVANCED examinations.[1] Ideally, this cohort would need to include and account for those residents who entered training but were not allowed to take the ADVANCED examination because they were unsuccessful in passing the BASIC examination.

The letter by Pivalizza *et al.* also highlights an additional implied outcome that will result from a change in the certification requirements. The first certification requirement

now occurs early in training; residents who do not pass the BASIC examination would be more likely to leave (or be dismissed from) training prior to completing residency. The remaining residents who have passed their BASIC examination are more likely to be successful in their initial attempt to pass the ADVANCED certification examination, leading to a greater proportion of residents successful on their first attempt to become certified. From a patient safety perspective, this may be a desirable long-term outcome, because a prior investigation by Zhou *et al.* indicated that anesthesiologists who obtained their certification on the first attempt had a lower likelihood of having an action against their medical license than those who required more than one attempt.[3] Under previous certification rules, the initial certification examination occurred after residents had successfully completed their training. Prior to the change in certification, residents who did not successfully pass their written examination could enter practice and potentially never achieve certification.

Residency programs and program directors are likely to be the first to identify the desirable as well as the unintended consequences of changes in certification. It is hoped that additional investigations from residency programs will follow the letter by Pivalizza *et al.* and provide information about how the introduction of the BASIC examination impacts training, certification, and patient safety outcomes.

Competing Interests

The authors declare no competing interests.

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References

1. Murray DJ, Boulet JR: Anesthesiology board certification changes: A real-time example of "assessment drives learning." Anesthesiology 2018; 128:704–6
2. Zhou Y, Sun H, Lien CA, Keegan MT, Wang T, Harman AE, Warner DO: Effect of the BASIC examination on knowledge acquisition during anesthesiology residency. Anesthesiology 2018; 128:813–20
3. Zhou Y, Sun H, Culley DJ, Young A, Harman AE, Warner DO: Effectiveness of written and oral specialty certification examinations to predict actions against the medical licenses of anesthesiologists. Anesthesiology 2017; 126:1171–9

(Accepted for publication August 31, 2018.)

In Reply:

We appreciate the interest in our publication[1] and the opportunity to respond to these two Letters to the Editor.

Dr. Pivalizza and colleagues have questions about our methodology and inclusion criteria, and we would like to clarify. Their first question related to not accounting for those residents who did not take the in-training examination in their clinical base year in the analysis. There were actually two different models employed in the analysis of changes in in-training examination scores from the clinical base year to the clinical anesthesia year 1, and from the clinical anesthesia year 1 to year 2. The latter analysis (and our main conclusion) did not depend upon whether the residents had taken the in-training examination during their clinical base year. Second, given the study question of in-training examination score increment, residents who did not take the in-training examination in both clinical anesthesia years 1 and 2 could not be analyzed, and concerns were raised regarding the possibility of those who had failed the BASIC examination leaving training before taking the in-training examination in their clinical anesthesia year 2, thus biasing the composition of the cohort. We note that three failures of the BASIC examination are required for mandatory extension of training, and that for the 2013 cohort, only 0.2% failed twice. Thus, we think it is unlikely that this factor significantly affected the analysis. Dr. Pivalizza and colleagues also question whether preparing for the BASIC examination may have distracted residents from preparing for the preceding in-training examination, lowering in-training examination performance at clinical anesthesia year 1 and biasing toward an increase in performance from clinical anesthesia year 1 to year 2. As shown in table 1 and figure 2 of our article,[1] there is no evidence that the introduction of the staged examination system in the 2013 cohort was associated with lower in-training examination scores at clinical anesthesia year 1; indeed, the 2014 cohort had higher in-training examination scores at clinical anesthesia year 1. Finally, it is our perspective that what constitutes a "small" effect size is a matter of interpretation. The in-training examination performance of clinical anesthesia year 2 residents after the introduction of the staged examination system was similar to that of clinical anesthesia year 3 residents in the traditional examination system; we leave it to the readers to judge the significance of this finding.

Dr. Berman is concerned with "exam fatigue" associated with the introduction of new examination components in the primary certification process, and its potential to contribute to psychologic distress in residents. We appreciate his raising this important issue, given that a variety of studies have shown that residents in training can exhibit high levels of stress and burnout.[2,3] Each of the physician directors of the American Board of Anesthesiology is a practicing anesthesiologist, well aware of the demands of training and practice. Consideration of the impact of changes in the certification process on residency training is an essential factor in American Board of Anesthesiology decisions. Dr. Berman questions the clinical significance of improved in-training examination performance. Our prior work has shown that in-training examination performance is a significant predictor of achieving timely board certification,[4] and that board certification (or rather the lack thereof) predicts relevant outcomes such as disciplinary actions against the medical licenses

of anesthesiologists.[5] Nonetheless, we agree that our goal should always be focused on improving patient care, not on test scores *per se*. This study focused on whether knowledge acquisition was accelerated with the advent of the BASIC examination, not on whether the ultimate clinical performance of residency graduates is improved (an important question that remains to be answered in future research). We very much agree that changes such as the staged examination system, including the introduction of the Objective Structured Clinical Examination (also mentioned by Dr. Berman), require continued evaluation. As evidenced by this and other publications, the American Board of Anesthesiology is committed to ongoing rigorous and transparent analyses of its systems and processes. These analyses include evaluation of the unintended consequences on our trainees and, ultimately, on the abilities of anesthesiologists to provide excellent patient care. Such analyses will be essential to the consideration of any future system and process modifications desired to better meet the goal of fulfilling the American Board of Anesthesiology's mission to advance the highest standards of the practice of anesthesiology. We thank the authors of the letters for their comments, and we welcome further feedback from the community of anesthesiologists whom we serve.

Competing Interests

Drs. Sun and Zhou are staff members of the American Board of Anesthesiology; Drs. Keegan and Warner are American Board of Anesthesiology directors and receive a stipend for their participation in American Board of Anesthesiology activities; Dr. Lien is a former director of the American Board of Anesthesiology.

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References

1. Zhou Y, Sun H, Lien CA, Keegan MT, Wang T, Harman AE, Warner DO: Effect of the BASIC examination on knowledge acquisition during anesthesiology residency. ANESTHESIOLOGY 2018; 128:813–20

2. de Oliveira GS Jr, Chang R, Fitzgerald PC, Almeida MD, Castro-Alves LS, Ahmad S, McCarthy RJ: The prevalence of burnout and depression and their association with adherence to safety and practice standards: A survey of United States anesthesiology trainees. Anesth Analg 2013; 117:182–93

3. Royal College of Anaesthetists: A report on the welfare morale and experiences of anaesthetists in training: The need to listen. Royal College of Anaesthetists, London, UK, December 2017

4. McClintock JC, Gravlee GP: Predicting success on the certification examinations of the American Board of Anesthesiology. ANESTHESIOLOGY 2010; 112:212–9

5. Zhou Y, Sun H, Culley DJ, Young A, Harman AE, Warner DO: Effectiveness of written and oral specialty certification examinations to predict actions against the medical licenses of anesthesiologists. ANESTHESIOLOGY 2017; 126:1171–9

(Accepted for publication August 31, 2018.)

When Checklists Fail: Human Factors Learning from Aviation and Safety by Design

To the Editor:

There has been appreciable literature on the use of checklists to prevent errors that could lead to patient harm.[1] In this letter, we use a recent commercial aviation event to explore the limitations of checklists and introduce the concept of engineering design to prevent error, and examine parallels in health care. In April 2018, following a cabin depressurization on Southwest Airlines, images were posted online showing passengers wearing oxygen masks incorrectly, covering their mouths only. This provoked debate blaming passengers for not listening to the preflight briefing during which the instructions, "place the mask over your nose and mouth and breathe normally," are given.[2] There are many reasons why this simplistic analysis of the error and blame is counterproductive, and why other solutions, such as engineering safety into the design of the oxygen masks, are more likely to succeed than using checklists alone. The Southwest Airlines preflight announcement[2] is a checklist that imparts 34 pieces of information, providing a high cognitive load in a situation in which other distractions and anxiety may be present. Only exceptional individuals have a working memory that tolerates retention of more than half a dozen pieces of information. Information retention of frequent flyers may be blunted over time due to a phenomenon known as "creeping complacency" and "alert/warning fatigue." We propose a simple, safety-design engineered solution for these rare events to improve compliance. Currently the airline oxygen mask is cylindrical with a round aperture. The elongated shape of a simple face mask and its elastic strap, however, can be presented to unaccustomed users in the correct vertical orientation, providing the visual and haptic signals to nudge appropriate placement covering the nose and mouth.

Similar rare events in health care are "serious adverse events" or "never events." Despite the introduction of education and checklists, the incidence of reported never events has increased. With rare but serious errors, the same problems of cognitive load, creeping complacency, and alert/warning fatigue come into play. The additional time and cognitive load upon an operator, performing complex procedures in distracting and stressful environments, from the use of formalized checklists, may be detrimental. This may have a greater overall absolute negative impact for the thousands of uncomplicated procedures outweighing the benefit of preventing a single rare error. Two-person checks are commonly instituted for preventing rare errors. However, distraction and creeping complacency manifest here, wherein both operators tend to rely on the other to complete the procedure correctly, along with inattentional blindness in which the checkers see what they expect to see, rather than what is in plain sight. Warning fatigue is commonplace and

particularly problematic for rare events. For rare errors, an engineered solution in equipment design not only prevents the error but sustains the safety benefit over time. Through the introduction of simple design adaptations in health care, it may be possible to make specific rare serious events either less likely or impossible when checklists or human practice fail.

Research Support

Dr. Mariyaselvam is undertaking an M.D. in Human Factors under the supervision of the University Department of Anaesthesia, University of Cambridge, Cambridge, United Kingdom.

Competing Interests

The authors declare no competing interests.

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References

1. Gillespie BM, Chaboyer W, Thalib L, John M, Fairweather N, Slater K: Effect of using a safety checklist on patient complications after surgery: A systematic review and meta-analysis. ANESTHESIOLOGY 2014; 120:1380–9

2. Southwest Airlines pre-flight public announcements: Transcription of opening, emergency, service, final descent and arrivals announcements. https://quizlet.com/36754761/pas-for-swa-flash-cards/. Accessed May 3, 2018

(Accepted for publication September 6, 2018.)

Alan Jay Schwartz, M.D., M.S.Ed., Editor

The Basics of Anesthesia, 7th Edition. Edited by Manuel Pardo, M.D., and Ronald D. Miller, M.D., M.S. New York, Elsevier, 2017. Pages: 936. Price: $95.99.
Miller's Anesthesia Review, 3rd Edition. Written by Lorraine M. Sdrales, M.D., and Ronald D. Miller, M.D., M.S. New York, Elsevier, 2017. Pages: 544. Price: $87.36.

In the world of anesthesia, very few textbooks resonate with anesthesiologists the way that *The Basics of Anesthesia* does. This is the 7th edition of this classic, and the timing of this edition coincides with release of an update of the companion study guide, *Miller's Anesthesia Review.* The book honors the 33-yr stewardship of Dr. Miller, and ushers in a changing of the guard with Dr. Pardo assuming the role of lead editor. One will quickly notice the growth and far reaching collection of authors that have contributed to this version; there are a total of 87 authors in this edition. There are many familiar names, with the addition of new authors adding a unique and updated perspective.

At first glance, this book looks like previous versions. The organization of the book is what we have come to expect. For an introductory book it is robust: 936 pages. On further inspection, the reader will immediately notice that this edition is much more visually pleasing, with better illustrations and important information more usefully highlighted. Each chapter is organized better than in previous editions, which leads to improved flow overall. Gone is the history chapter. Gone are the numerous appendices and "Please refer to…" comments. Although this is touted as a basics book, there is nothing basic about this book; it is dense with information and, while easy to read, it is not a quick read.

The sections of the book are organized similarly to previous editions. Most of the information in the basic science and pharmacology sections remain the same, but rather than presenting a dry litany of scientific fact, there is a concerted effort to relate the information in a more clinical fashion. The detailed introduction gives the topic a clinical focus, and in some sections a brief historical perspective is provided to make up for the loss of the chapter on anesthesia history. The addition of a physical diagnoses segment in each chapter is welcome, providing more opportunities to tie the scientific facts to clinical practice. The pharmacology section is also enhanced with additional focus on the pharmacologic implications of obesity and advanced age. The updates to common practice, with the exclusion of halothane from clinical practice and the addition of newer drugs like sugammadex, brings the text into alignment with the current state

of practice, as well as provides insightful clinical pearls in each section.

The evolution of our specialty and the changing context of anesthesiology practice is reflected in this new edition. There is an expanded and improved section on outpatient sedation, an updated section on hyperalgesia and the opioid crisis in the pain chapter, and a beautifully organized trauma section. Chapter 12 is a welcomed addition, providing an outstanding summary of the current state of the controversial topic of anesthetic neurotoxicity. The addition of the "Human Induced and Natural Disasters" chapter sheds light on important aspects of our current geopolitical realities. In the context of the anesthesiologist as the "perioperative physician," the text highlights the importance of anesthesiologists as in-hospital physicians whose clinical skills and leadership provide value to the system as a whole. The "Palliative Care" and "Sleep Medicine and Anesthesia" chapters are brief introductions to worlds not very familiar to most; providing succinct, yet complete, overviews of new subspecialties that are evolving and gaining importance in our specialty. One of the most innovative chapters is "New Models of Anesthesia Care: Perioperative Medicine, the Perioperative Surgical Home, and Population Health," encompassing new initiatives that provide value beyond the operating room, with a focus on the perioperative surgical home. For someone new to the field, it is an excellent introduction to the landscape of health care and the anesthesiologist's future and role in this rapidly evolving world.

The negatives in this book are few, and most are related to the electronic version of the text. The eBook, while adding convenient access, does not offer anything additive or innovative. In fact, it is essentially a digital copy of the hardcopy book. While there is the ability to highlight text and save "notes," the search functionality is essentially a word search. On the whole, the regional section was perhaps the most disappointing. Both the paper and digital versions would have benefited from a more through catalogue and description of basic blocks. This could have been an area where the digital version distinguished itself with an enhanced library of digital images or video clips.

As a companion to this text, Drs. Sdrales and Miller offer *Miller's Anesthesia Review,* in its 3rd edition. It again has a familiar format to previous versions and is laid out in chapters that match the text. It serves as a very thorough study guide when used in conjunction with the textbook, with open ended questions and detailed explanations that highlight key points. For trainees looking for help in preparation for the American Board of Anesthesiology Part 1A Exam, this book provides an excellent synopsis of the fundamentals; however, this is not the traditional test prep book with multiple choice questions. The use of open ended questions, coupled with the discussions that tie basic science concepts

to clinical scenarios, makes this an excellent text to review in preparation for the American Board of Anesthesiology Part 2 Exam as well. It is also available as an eBook, providing convenient access; although it shares *The Basics of Anesthesia* eBook's problem of being cumbersome to navigate.

In summary, the 7th edition of *The Basics of Anesthesia* continues to be an excellent textbook as it offers something to everyone. It remains "must read" for all trainees. Coupled with the study guide, Pardo, Miller, and Sdrales have created an outstanding and up-to-date clinical resource and education tool that provides a strong foundation of knowledge in anesthesiology. For the practicing physician it offers a good refresher and quick reference. This book serves to honor previous versions and shows that the future of this classic is in good hands.

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Erratum

Brian Bateman, M.D., Recipient of the 2018 James E. Cottrell, M.D., American Society of Anesthesiologists Presidential Scholar Award: Erratum

In the article "Brian Bateman, M.D., Recipient of the 2018 James E. Cottrell, M.D., American Society of Anesthesiologists Presidential Scholar Award" (Rathmell JP: ANESTHESIOLOGY 2018; 129:646–8), there was an error in the title. The corrected title is "Brian Bateman, M.D., Recipient of the 2018 James E. Cottrell, M.D., Presidential Scholar Award."

The online version and PDF of the article have been corrected.

Reference

Rathmell JP: Brian Bateman, M.D., Recipient of the 2018 James E. Cottrell, M.D., American Society of Anesthesiologists Presidential Scholar Award. ANESTHESIOLOGY 2018; 129:646–8.

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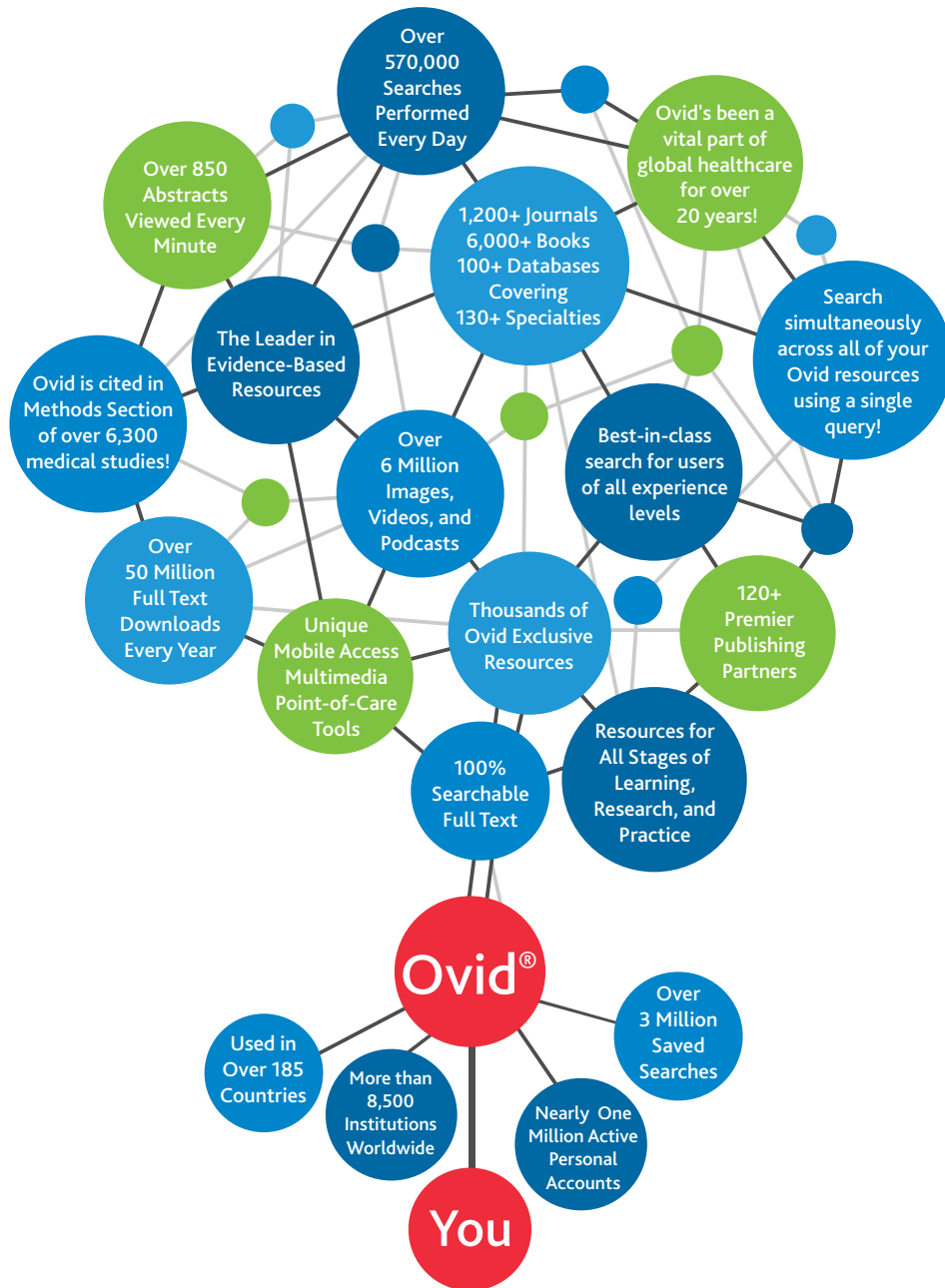For more information about advertising and the next available issue, contact your sales managers:

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