Hi, this is Evan Kharasch, Editor-in-Chief of Anesthesiology, with some highlights from the April 2021 issue, as selected by the journal editors.

This month's issue contains 2 articles and an editorial on the topic of opioid-free anesthesia. There has been increasing discussion about this approach to perioperative care. We bring trusted evidence to the discussion.

Our first article this month examines the topic of opioid-free anesthesia. It reports a randomized clinical trial that investigated whether opioid-free anesthesia affects the frequency of postoperative adverse events. Dr. Helene Beloeil of the University of Rennes and colleagues elsewhere in France conducted the study, which is known as the POFA trial. They compared opioid-free balanced anesthesia with dexmedetomidine versus balanced anesthesia with remifentanil plus morphine. They tested the hypothesis that opioid-free anesthesia would result in fewer postoperative opioid-related adverse events. The primary outcome was a composite of opioid-related adverse events within the first 48 hours after extubation. These events included hypoxemia, ileus or cognitive dysfunction. The authors found that postoperative hypoxemia occurred significantly more often in the opioid-free dexmedetomidine group compared with the opioid group. There were no differences in ileus and cognitive dysfunction. The main secondary outcomes were postoperative pain, opioid consumption and postoperative nausea and vomiting. Both postoperative opioid consumption and postoperative nausea and vomiting were significantly less in the dexmedetomidine group, while analgesia did not differ. Dexmedetomidine patients did have delayed extubation and prolonged stays in the postoperative care unit. The most striking result of the investigation, however, was the incidence of unanticipated severe adverse events. There were 5 cases of severe bradycardia in the dexmedetomidine group, including 3 cases of asystole. The study was stopped early because of safety concerns with the dexmedetomidine group. The POFA trial refuted the hypothesis that balanced opioid-free anesthesia with dexmedetomidine would result in fewer postoperative opioid-related adverse events compared with remifentanil.

Our next clinical study pertains to regional anesthesia. It was a dose-finding exploration to define the optimal volume of 0.5% ropivacaine needed for a successful ultrasound-guided costoclavicular block for surgical anesthesia. Dr. Anu Kewlani and colleagues at the Postgraduate Institute of Medical Education and Research in Chandigarh, India, conducted the study. Their objective was to determine the median effective dose of 0.5% ropivacaine, that is, the volume of ropivacaine required for surgical anesthesia in 50% of the patients. They also wanted to determine the calculated dose required for effective blockade in 95% of patients. This prospective, single-arm study enrolled adult patients who were scheduled to undergo forearm and hand surgeries under ultrasound-guided costoclavicular block. The extents of sensory and motor block were assessed in the median, radial, ulnar and musculocutaneous nerve distributions and graded using 3-point scales. Following a successful or unsuccessful block, the volume of local anesthetic correspondingly decreased or increased by 2ml in the next patient. The authors considered anesthesia to be successful if the surgeon was able to proceed with surgery without needing to supplement anesthesia. Among 38 patients, the volume of local anesthetic administered ranged from 8ml to 26ml. The authors concluded that the median effective dose of 0.5% ropivacaine was 14 ml, and 19ml is likely to produce an effective ultrasound guided costoclavicular block for providing adequate surgical anesthesia to 95% of patients.

Our next study was a database evaluation, to assess whether a one lung ventilation using a lung-protective approach would affect patient outcomes following major surgery. Dr. Douglas Colquhoun of the University of Michigan and colleagues there and elsewhere conducted the study. They tested the hypothesis that a one lung protective ventilation regimen would be independently associated with lesser odds of pulmonary complications following thoracic surgery. One lung protective ventilation was defined as the combination of two criteria: median tidal volume <5 ml/kg predicted body weight and positive end expiratory pressure >5 cm H2O. The authors used data from two databases for 3,200 lung resection procedures using one lung ventilation across five institutions. The primary outcome was a composite of 30-day major postoperative pulmonary complications. Pulmonary complications were one or more of the following: initial ventilator support greater than 48 hours, reintubation, pneumonia, atelectasis requiring bronchoscopy, ARDS, air leak greater than 5 days, bronchopleural fistula, respiratory failure, tracheostomy, pulmonary embolism or empyema requiring treatment. The authors found that during the study period, from 2012 to 2016, there was an overall decrease in tidal volume. Additionally, positive end expiratory pressure increased from 4 to 5 cm H_2O. And, a protective ventilation strategy was increasingly used during the study period - 6% in 2012 versus 18% in 2016. The main finding was that despite this increase in the use of lung-protective ventilation, there was no change in the prevalence of postoperative pulmonary complications. The authors concluded that using a low tidal volume lung protective ventilation regimen or modified airway driving pressure during 1-lung ventilation was not associated with the odds of major postoperative pulmonary complications.

Next, we have a retrospective cohort study that examines the association between preoperative frailty and postoperative complications and mortality. We know that moderate-to-severe complications are common after major surgery, and can have substantial impact on long-term outcomes. We also know that postoperative complications and mortality are strongly associated with preoperative frailty. However we do not understand well the relationships between frailty and postoperative complications, and mortality. Dr. Daniel McIsaac and colleagues at the University of Ottawa, Canada, conducted this retrospective study to examine that relationship. They tested the hypothesis that a substantial proportion of the total effect of frailty on mortality after elective noncardiac surgery would be mediated by postoperative complications. They used data from the National Surgical Quality Improvement Program, to estimate the total effect of frailty on mortality. They also estimated the proportion of the frailty–mortality association that appeared to be mediated by complications. Out of 200,000 intermediate-risk to high-risk patients, about 10 percent developed complications. Complications mediated slightly more than half, 57%, of the association between frailty and postoperative mortality. Cardiopulmonary complications were more likely to contribute to this association than renal or infectious complications. The authors concluded that half of the association of frailty with postoperative mortality appears to be mediated by the occurrence of postoperative complications, and that a substantial proportion may also be related to non-complication-mediated mechanisms.

Next, we have another retrospective cohort study which examines complications after surgery. This one asked whether the risk of cardiac-related complications after cardiac surgery differed between cases performed in the morning vs afternoon. Dr. Ryan Hijazi and colleagues at the Cleveland Clinic conducted the single-center study. They analyzed the data from three common types of cardiac surgery performed at their institution during an eight-year period from 2011 to 2018, specifically, aortic and/or mitral valve repair/replacement and/or coronary artery bypass grafting. They devised a composite outcome of in-hospital mortality and low cardiac output syndrome. The authors compared the composite outcome of patients who had surgery in the morning versus the afternoon. Among 9,700 surgeries, the composite of in-hospital mortality and low cardiac output syndrome occurred in 2.8% of morning patients and 3.4% of afternoon patients. This difference was not statistically significant. There was also no difference in the surgical subgroups. The authors concluded that patients who had cardiac surgery with aortic cross-clamping in the morning or afternoon did not have significantly different outcomes. They found no evidence to suggest that morning or afternoon surgical timing alters postoperative risk.

Our next article reports a laboratory study designed to assess the role of acetylcholine in the effects of the general anesthetics isoflurane and ketamine. Dr. L. Stan Leung and colleagues at the University of Western Ontario conducted the study. They tested the hypothesis that mice with genetic deficiency of forebrain acetylcholine would show increased anesthetic sensitivity to isoflurane and ketamine. The authors also sought to determine whether these mice may also show decreased brain electroencephalogram, EEG, activity. The authors compared wild-type mice with two experimental types of mice. One type had heterozygous knockdown of the vesicular acetylcholine transporter in the brain, and the other type had homozygous knockout of the transporter in the basal forebrain. The authors administered various doses of isoflurane and ketamine and determined the dose needed to achieve anesthesia or unconsciousness, defined

as loss of the righting reflex. In genetically modified mice lacking the vesicular acetylcholine transporter in the forebrain, lower doses of isoflurane and ketamine were necessary to induce the loss of the righting reflex, compared to wild-type counterparts. No differences were observed in mice with knockdown of the acetylcholine transporter in the brain. EEG gamma activity in the hippocampus after isoflurane or ketamine was lower in both the knockout and knockdown mice compared to wild-type mice. However, EEG gamma activity in the frontal cortex with either isoflurane or ketamine was not different among knockout, knockdown and wildtype mice. The authors concluded that cholinergic neurons in the forebrain modulate anesthetic sensitivity during isoflurane and ketamine anesthesia.

Our Clinical Focus Review article this month focuses on the management of patient-ventilator asynchrony. This is sometimes referred to as a patient "fighting the ventilator". Dr. James Bailey of Northeast Georgia Physicians Group, Northeast Georgia Health System, Gainesville, Georgia, authored this review. Patient–ventilator asynchrony reflects a mismatch between patient demand for flow, volume, or pressure, and, what the ventilator is delivering. Asynchrony can impede adequate oxygenation and ventilation. It may also reflect patient distress and discomfort. When asynchrony happens, clinicians are obligated to find methods to reduce patient distress. The review details the need to first understand the reason for the asynchrony, and second how to correct it as a component of patient management. Asynchrony can be corrected by understanding the nature of the patient demand-ventilator delivery mismatch and adjusting the ventilator mode and settings. However patient-ventilator asynchrony is commonly addressed by increasing the depth of patient sedation or using a neuromuscular blocking drug. However, this can have unintended consequences. Specifically, deeper sedation is associated with increasing length of stay and mortality, and use of neuromuscular blocking drugs have been specifically associated with severe weakness and critical illness myopathy, which makes weaning the patient from mechanical ventilation very difficult. The article advocates first analyzing the nature of the patient demand–ventilator delivery mismatch, and then adjusting the ventilator accordingly. This approach may facilitate management of the spontaneously ventilating patient in both critical care and in the operating room. Anesthesiologists can expect a variety of monitoring trends to help combat patient-ventilator asynchrony in the future. Additionally, new ventilator modes are being investigated that may improve our ability to both detect and prevent asynchronies. Modes under investigation include assist ventilation and neurally adjusted ventilatory assist.

I'll close this month with a return to our opening topic – opioid-free anesthesia. Specifically, a review article that provides a critical look at opioid-free versus opioid-sparing approaches to anesthesia and analgesia. Dr. Harsha Shanthanna of McMaster University, Hamilton, Ontario, Canada and colleagues elsewhere authored this review. They report that opioid-free strategies, however noble their cause, do not fully acknowledge the limitations and gaps within existing evidence and clinical practice considerations. Opioid-free strategies do not allow analgesic titration based on patient needs. No clinical consensus has yet been reached about optimal components of opioid-free regimens and their role in different settings and phases of care. Opioid-free strategies do not allow analgesic titration based on patient needs, nor do they decrease the risk of persistent postoperative opioid use. There is no evidence that opioid-free strategies have benefits beyond those of opioid-sparing strategies. The focus on opioid-free anesthesia distracts anesthesiologists from alleviating pain and minimizing realistic long-term harms. Various safe and feasible opioid-based options can be successfully adapted to individual patient needs. The authors advocate for a clinical framework that involves patient education, preoperative opioid minimization, use of multimodal analgesia strategies, and postoperative analgesia titrated to transitional pain needs. This multipronged approach can successfully decrease the risk of persistent opioid use and persistent postsurgical pain.

As always, thank you for interest in and support of our journal. I hope that you will use the information published in Anesthesiology to guide and improve your clinical practice. I look forward to keeping you informed as Anesthesiology continues to publish important research and trusted evidence each month.