



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

I'll begin this month with the results of a survey conducted among members of the American Society of Anesthesiologists exploring the important issue of burnout. Dr. Anoushka Afonso of Memorial Sloan Kettering Cancer Center and colleagues there and at Harvard Medical School conducted the study. Their objective was to improve understanding of burnout in anesthesiologists. They also wanted to identify work-

place and personal factors associated with burnout among anesthesiologists, and to quantify those associations. As the pandemic began in March 2020, the authors used the Maslach Burnout Inventory Human Services Survey to assess burnout. Nearly 29,000 anesthesiologists were surveyed. The results showed that nearly 60% were at high risk of burnout. And nearly 14% met the World Health Organization criteria for burnout syndrome, in which all three aspects of the Maslach Burnout Inventory were abnormal. Multivariable logistic regression modeling showed that burnout syndrome most strongly associated with a perceived lack of support at home, and particularly at work. Physician age was the only personal factor that was associated with burnout syndrome. The authors suggested that focused workplace interventions may be effective in reducing burnout.

This article is accompanied by an editorial, titled "Burnout: The 'Other' pandemic", written by Dr. Steve Hyman, of Vanderbilt University School of Medicine. The editorial notes that this study is novel because it is the first large-scale evaluation of burnout in anesthesiologists. It also notes that the ability of anesthesiologists to perform a broad range of duties, particularly in the COVID era, and to contribute positively to hospitals' financial well-being, often comes at the steep price of anesthesiologists' own well-being. It also provocatively notes that institutions often turn a "blind eye" to dysfunctional workplace characteristics which exacerbate burnout and thus have negative employee consequences. And it challenges these institutions to spend less time holding wellness and resilience seminars, and spend more time correcting the institutional causes of burnout. To address individual issues without addressing workplace issues does not provide a comprehensive solution to the problem.

Our next study is a perioperative clinical trial. It was a double-blind randomized trial that tested the effectiveness of the opioid methadone and the N-methyl-D-aspartate receptor antagonist ketamine to improve postoperative pain control. Dr. Glenn Murphy, then at NorthShore University HealthSystem and now at Illinois Masonic Hospital in Chicago and colleagues elsewhere conducted the study. They tested the hypothesis that patients undergoing spinal fusion surgery who were given intraoperative and postoperative ketamine and intraoperative methadone, would use less hydromorphone on the first postoperative day, compared with those given intraoperative methadone alone. The authors randomized 130 spinal surgery patients. All patients received methadone 0.2 mg/kg ideal body weight intraoperatively. Half the patients also received an intraoperative ketamine infusion (0.3 mg/kg/hr), followed by an infusion of ketamine (0.1 mg/kg/hr) for the first 48 hr postoperatively. The other half of the patients received a placebo infusion for 48 hr postoperatively. The primary outcome was postoperative day one intravenous hydromorphone use. Patients in the methadone/ketamine group required less hydromorphone on postoperative day one, with a median of 2 mg, compared with 5 mg in the methadone-only group. They also used less hydromorphone throughout the entire 3d follow-up period. Patients in the methadone/ketamine group also required fewer oral opioid tablets. Pain scores were lower in the methadone/ketamine group at 23 of 24 postoperative assessment times. Patient satisfaction scores were high in both study groups. The authors concluded that the combination of methadone and ketamine could be considered in patients having spine surgery.

This article is accompanied by an editorial, titled "Methadone and ketamine: Boosting benefits and still more to learn", written by Dr. David Clark of Stanford University, and I. The editorial notes that less is known about methadone and perioperative drug combinations, compared with other opioids. Ketamine did appear to have "boosted" the effects of methadone. And, the magnitude of the effect of adding ketamine to methadone

was much greater than is commonly reported for adding ketamine to other opioids. While these clinical observations were important, and interesting, the mechanism of the ketamine-methadone interaction remains unknown.

Our next study is also a perioperative clinical trial. This was a prospective, randomized, double-blind, placebo-controlled trial that explored optimal pain management following hip arthroplasty. Recently, the quadratus lumborum block has been proposed as an analgesic option. Dr. Sophia Margareta Brixel and colleagues at University of Montpellier, Montpellier, France, conducted the study. They tested the hypothesis that the posterior quadratus lumborum block would result in less postoperative morphine consumption after hip arthroplasty compared with placebo. One hundred patients scheduled for elective total hip arthroplasty were studied. Fifty patients were randomized to receive a 30 mL injection of 0.33% ropivacaine posterior to the quadratus lumborum muscle, prior to general anesthesia. Fifty patients received an injection of normal saline. All patients also received a multimodal analgesic regimen consisting of acetaminophen, ketoprofen, and a morphine intravenous patient-controlled analgesia pump. The primary outcome was total intravenous morphine consumption in the first 24 hours. The results found no significant difference between the groups in 24-hour total morphine consumption. Similarly, pain scores did not differ between the groups. The authors concluded that the addition of a posterior quadratus lumborum block to a multimodal analgesic regimen did not reduce morphine consumption or pain scores among patients who had total hip replacement surgery.

Next, we have an observational study. It explored the impact of mechanical ventilation on expiratory muscles, in mechanically ventilated patients in mixed medical-surgical academic intensive care units. Dr. Zhong-Hua Shi of the Amsterdam University Medical Centers, The Netherlands, and colleagues there and in China conducted the study. The objective was to evaluate changes in expiratory muscle thickness during mechanical ventilation, and to compare this to changes in diaphragm thickness. There were two substudies. The first, a reproducibility study, tested the feasibility and reproducibility of expiratory muscle ultrasound. It investigated inter- and intra-rater variability of lateral abdominal wall muscle measurements in 30 mechanically ventilated patients. Then it assessed the effects of lung volume on expiratory muscle thickness. The second substudy was a cohort study, investigating the evolution of expiratory muscle thickness during the mechanical ventilation in critically ill patients. It used the threshold values from the reproducibility cohort to evaluate these temporal changes. Muscle thickness remained stable in the majority of subjects. But muscle thickness decreased in 22% of patients and increased in 12%. The authors concluded that these changes were unrelated to changes in diaphragmatic thickness. Increased expiratory muscle thickness resulted from increased thickness of the fasciae.

This article is accompanied by an editorial, written by Dr. Franco Laghi, of Loyola University Hospital, entitled "Expiratory muscles, neglected no more". Dr. Laghi notes that expiratory muscle thickness is important because they are necessary for cough, and for successful weaning from mechanical ventilation. It makes a strong case for the use of ultrasound imaging to assess expiratory muscle thickness in ventilated patients.

Our next study is a subanalysis of a multiple crossover cluster trial. This trial examined the effects of supplemental intraoperative oxygen on long-term postoperative mortality. Dr. Qiliang Jiang of Shanghai Jiao Tong University in China and colleagues at the Cleveland Clinic conducted the study. The authors tested the hypothesis that supplemental oxygen increases the hazard for long-term mortality. The authors conducted a *post hoc* analysis of a large multiple crossover cluster trial in which adults who had colorectal surgery were randomized to receive either 80% or 30% inspired oxygen during general anesthesia. The authors assessed the effect of 80% versus 30% target-inspired oxygen on long-term mortality. Among 3,920 colorectal surgeries, the incidence of death after a median of 3 yrs of follow-up was 14% with 80% oxygen, and 15% with 30% oxygen. The authors concluded that supplemental oxygen does not increase mortality.

Next, we have an animal study. It explored the extent to which implicit memory formation is possible under sedation. Dr. Nir Samuel of the Weizmann Institute of Science, Rehovot, Israel, and colleagues there and elsewhere in Israel conducted the study. They tested the hypothesis that

the amygdala and dorsal anterior cingulate cortex participate in forging emotional and valence-driven memory formation – even under sedation with ketamine or midazolam. The primary outcome was behavioral and neural evidence that suggested memory formation. The experiment used a classical tone-odor conditioning task, which allows for invasive neural recording under sedation or anesthesia. The paradigm measures respiratory responses, and does not require conscious volition, making it suitable as an implicit measure of learning and memory in awake, sedated, and anesthetized conditions. The study simultaneously measured conditioned inspiratory changes and changes in firing rate of single neurons in the amygdala and the dorsal anterior cingulate cortex. The study was conducted in two non-human primates. The authors introduced an expected aversive olfactory stimulus during sedation with ketamine or midazolam, and tested retention after recovery. The authors found that aversive memory formation occurred in 26 of 59 sessions under sedation. There was a positive correlation between acquisition and retention, of single-neuron responses in the amygdala and dorsal anterior cingulate cortex. The authors also found that neural responses during acquisition under sedation were stronger in sessions exhibiting memory formation than those that did not. The firing rate of neurons in the amygdala and the dorsal cingulate cortex during memory acquisition under sedation predicted the memory retention response after sedation. These observations suggest that implicit memory formation can occur under sedation. Moreover, memory formation appeared to follow similar rules and engage the same structures and mechanisms as in the awake state.

Next, our Clinical Focus Review article this month considers the clinical applications of near-infrared spectroscopy monitoring in cardiovascular surgery. Dr. Charles Hogue and colleagues at Northwestern University Feinberg School of Medicine, Chicago, authored this review. They summarize the applications of cerebral oximetry monitoring for adult patients undergoing cardiovascular surgery. Near-infrared spectroscopy provides a clinically feasible method for monitoring cerebral oxygen saturation. Cerebral oximetry has entered clinical practice in response to greater concerns about the effects of neurologic complications on patient outcomes after cardiac surgery. Nevertheless, adoption in the United States remains low. Other applications continue to evolve, including monitoring during noncardiac surgery such as shoulder surgery in the

beach chair position or during one-lung ventilation for thoracic surgery. The review suggests that limitations with the technology and inter-individual variations must be acknowledged, such that cerebral oximetry should be interpreted as a trend not an absolute monitor. Additionally, current evidence is insufficient to prove or disprove that optimizing cerebral oxygen saturation during cardiac surgery can improve patient outcomes. New applications of cerebral oximetry might expand its clinical utility, including for patients undergoing extracorporeal membrane oxygenation and as a bedside monitor of cerebral autoregulation.

I'll close this month with a review article that explores whether alpha-1-antitrypsin is a key factor or a bystander in acute respiratory distress syndrome. Grace Hogan and colleagues at the Royal College of Surgeons in Dublin, Ireland, authored this review. They note that acute respiratory distress syndrome is characterized by hypoxemia, altered alveolar-capillary permeability, and a neutrophil-dominated inflammatory pulmonary edema. Despite decades of research, an effective drug-therapy remains elusive. The ideal pharmacotherapy for this condition should demonstrate anti-protease activity. It should also target injurious inflammatory pathways, while maintaining host defense against infection. Other desirable traits would be a reputable safety profile, low possibility of off-target effects, and well-understood pharmacokinetics. The endogenous 52kDa serine protease alpha-1 antitrypsin has the potential to be a novel treatment option for acute respiratory distress syndrome. The main function of alpha-1 antitrypsin is as an anti-protease, targeting neutrophil elastase in particular. However, studies have also highlighted the role of alpha-1 antitrypsin in the modulation of inflammation and bacterial clearance. In light of the current pandemic, our need for a treatment for acute respiratory distress syndrome is more pressing than ever. This need is even greater considering that alpha-1 antitrypsin has been implicated in the inflammatory response to SARS-CoV-2 infection.

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.