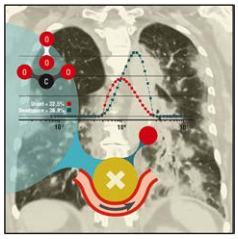
THIS MONTH IN
ANESTHESIOLOGY®



251 Causes of Hypoxemia in COVID-19 Acute Respiratory Distress Syndrome: A Combined Multiple Inert Gas Elimination Technique and Dual-energy Computed Tomography Study

Hypoxemia can arise from shunt, ventilation–perfusion ($\dot{V}_A/\dot{Q}_T$) mismatch, and diffusion limitation. Hypoxemia in acute respiratory distress syndrome (ARDS) is mainly due to shunt through the atelectasis. However, the pathogenesis of oxygenation impairment in COVID-19 ARDS might be more complex because alterations of the pulmonary vasculature are particularly prominent in COVID-19. This study sought to understand the relative contribution of the different mechanisms of hypoxemia in COVID-19 ARDS and the relationship between the alterations of ventilation and perfusion and the anatomical distribution of air, tissue, and blood within the lung. Ten patients with COVID-19 ARDS who had been intubated for fewer than 7 days were studied using the multiple inert gas elimination technique (MIGET) to measure the ventilation–perfusion distribution and dual-energy computed tomography (DECT) to quantify the anatomical distribution of tissue and blood volume. The pathogenesis of hypoxemia in COVID-19 ARDS was found to be exceptionally multifactorial, combining alveolar factors, typical of ARDS, with vascular factors, more typical of pulmonary macro- and microembolism. *See the accompanying Editorial on **page 186**.* *(Summary: M. J. Avram. Image: A. Johnson, Vivo Visuals Studio.)*

195 Perioperative Mortality of the COVID-19 Recovered Patient Compared to a Matched Control: A Multicenter Retrospective Cohort Study

Patients with recent COVID-19 infection have been reported to have an increased risk of perioperative morbidity and mortality. The hypothesis that patients testing positive for COVID-19 before undergoing elective inpatient surgery between April 2020 and April 2021 would have an increased all-cause 30-day mortality compared to a propensity-matched cohort of patients without a known prior diagnosis of COVID-19 was tested in a multicenter retrospective observational study. Early in the pandemic, 30-day mortality occurred in 4.6% (229 of 4,951) of COVID-19 exposed patients and 2.5% (122 of 4,951) of controls; the adjusted odds ratio (95% CI) for 30-day mortality was 1.63 (1.38 to 1.91). COVID-19 exposure was also associated with an increased odds of postoperative pulmonary complications (1.60 [1.36 to 1.88]) but not increased odds of postoperative acute kidney injury (1.03 [0.87 to 1.22]). Surgery performed within 2 weeks of a positive COVID-19 test was associated with elevated risk of mortality and pulmonary complications, but the effect was not observed after 2 weeks. *See the accompanying Editorial on **page 183**.* *(Summary: M. J. Avram. Image: J. P. Rathmell.)*

207 Target-controlled Infusion of Remimazolam in Healthy Volunteers Shows Some Acute Tolerance

Remimazolam is a short-acting benzodiazepine that is administered as repeated bolus doses for procedural sedation and as a continuous infusion for general anesthesia in adults. The pharmacokinetics of remimazolam administered as a bolus dose as well as a continuous infusion have been well characterized. The pharmacokinetic–pharmacodynamic relationships between remimazolam concentrations and Modified Observer's Assessment of Alertness and Sedation scores and bispectral index were assessed in 24 healthy volunteers using step-up and step-down target-controlled infusions to determine clinically appropriate target concentrations. Target concentration–dependent sedation was observed with little effect on vital signs. A difference in the sedative effects of remimazolam at identical target concentrations was observed between the step-up and step-down parts of the titration scheme that could not be explained by a bias in the predicted target concentrations. Pharmacodynamic models for Modified Observer's Assessment of Alertness and Sedation scores and bispectral index that assumed tolerance development described the observed difference in the sedative effects between the step-up and step-down parts of the titration scheme. *(Summary: M. J. Avram. Image: J. P. Rathmell.)*

261 Monitoring of Argatroban in Critically Ill Patients: A Prospective Study Comparing Activated Partial Thromboplastin Time, Point-of-Care Viscoelastic Testing with Ecarin Clotting Time and Diluted Thrombin Time to Mass Spectrometry

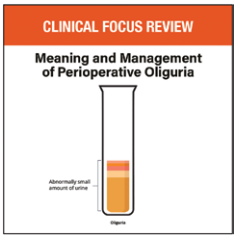
Argatroban is a direct thrombin inhibitor used to treat heparin-induced thrombocytopenia type II and reduce thrombin overload in this and (off label) other prothrombotic states. Precise argatroban dosing depends on monitoring its anticoagulant effect, which is routinely done using the activated partial thromboplastin time (PTT). Alternative tests include diluted thrombin time (TT) and ecarin-dependent assays. This study compared established argatroban monitoring tests (activated PTT and diluted TT) with a point-of-care viscoelastic ecarin-test and validated their performance against measured plasma argatroban concentrations. The adequacies of the results of the tests relative to measured plasma concentrations were classified as lower, concordant, or higher. Twenty-two critically ill patients with acute respiratory distress syndrome due to COVID-19 and treated with argatroban provided 205 blood samples for plasma concentration measurement and more than 100 assessments of the adequacies of each of the monitoring tests. Activated PTT–based argatroban monitoring was inaccurate and unable to detect argatroban overdosing. The viscoelastic ecarin test more reliably detected argatroban overdosing but was less accurate than diluted TT, which predicted correct plasma concentrations in more than 80% of measurements. *See the accompanying Editorial on **page 189**.* *(Summary: M. J. Avram. Image: Adobe Stock.)*

220 Association of Patient Race and Hospital with Utilization of Regional Anesthesia for Treatment of Postoperative Pain in Total Knee Arthroplasty: A Retrospective Analysis Using Medicare Claims

Use of regional anesthesia for total knee arthroplasty is associated with improved postoperative analgesia and decreased opioid use as well as decreased risk of serious complications, including end-organ damage, blood loss, and surgical site infection. The hypotheses that Black patients who underwent primary total knee arthroplasty between 2011 and 2016 were less likely to receive regional anesthetic techniques for postoperative analgesia than White patients and that variability in regional anesthesia utilization would more likely be attributable to hospital than race were tested using a large national claims dataset representing 100% of Medicare fee-for-service enrollees. The final dataset included 733,406 surgeries across 644,117 patients and 2,507 hospitals. Black patients did not have a different likelihood of receiving a regional anesthetic compared to White patients after accounting for demographic variables, comorbidities, year of surgery, and hospital; 53.3% of Black patients received regional anesthesia, as did 52.7% of White patients. Hospital and year accounted for 42.0% and 0.1% of variation in the use of regional anesthesia, respectively, while patient-level factors in aggregate accounted for 0.01% of variation. *(Summary: M. J. Avram. Image: J. P. Rathmell.)*

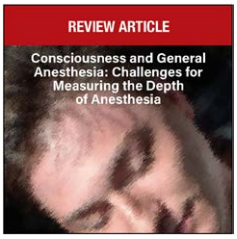
272 Opposing Effects on Descending Control of Nociception by μ and κ Opioid Receptors in the Anterior Cingulate Cortex

The loss of descending control of nociception/diffuse noxious inhibitory controls response observed in a spinal nerve ligation rat model of neuropathic pain was restored by microinjection of a μ opioid receptor agonist or a κ opioid receptor blocker in the right central amygdala nucleus. The hypothesis that μ opioid receptor and κ opioid receptor signaling in the anterior cingulate cortex would have similar effects on descending control of nociception was tested in naive male rats and male rats after undergoing spinal nerve ligation or sham surgeries. Descending control of nociception was lost in the ipsilateral hind paw of rats with spinal nerve ligation–induced chronic pain. Pharmacologic activation of μ opioid receptors and blockade of κ opioid receptors in the anterior cingulate cortex did not alter mechanical hypersensitivity in the ipsilateral hind paw of ligation-injured rats but restored ligation-induced impairment of descending control of nociception. Blockade of anterior cingulate cortex μ opioid receptors in ligation-injured rats did not affect hypersensitivity or the descending control of nociception response. Activation of anterior cingulate cortex κ opioid receptors in naive animals diminished the descending control of nociception response without producing hypersensitivity. *See the accompanying Editorial on **page 192**.* *(Summary: M. J. Avram. Image: Adobe Stock.)*



304 Meaning and Management of Perioperative Oliguria (Clinical Focus Review)

Perioperative oliguria can be a useful alarm signal for potential complications. Indeed, oliguria meeting criteria for acute kidney injury has been associated with complications including increased length of hospital stay, costs, and mortality. The risk associated with oliguria varies with the duration and degree of oliguria; the definition of acute kidney injury includes a urine output lower than 0.5 ml · kg^{-1} · h^{-1} for more than 6 h. Transient intraoperative oliguria, a urine output of less than 0.5 ml · kg^{-1} · h^{-1} for at least 1 h, has been associated with an increased risk of postoperative acute kidney injury, but its predictive value was low. Although several intrinsic causes of acute kidney injury have a higher likelihood in the perioperative setting, perioperative factors can affect urine output without direct kidney injury. Therefore, perioperative oliguria should not be interpreted as an automatic indication for fluid administration. The decision to give fluids should be based on the clinical context, indicators of fluid responsiveness, risk of developing fluid overload, and previous responses to fluid challenge. *(Summary: M. J. Avram. Image: Adobe Stock.)*



313 Consciousness and General Anesthesia: Challenges for Measuring the Depth of Anesthesia (Review Article)

Anesthesia has been loosely defined as a drug-induced impairment of consciousness. To address the problem of unintentional awareness or excessive hypnosis, it is necessary to define the target of consciousness and be able to measure and monitor the target. To help clarify the definition of wakefulness, three concepts relevant to clinical anesthesia have been introduced: consciousness (a subjective experience of existence), connectedness (perception of input from the body or the environment), and responsiveness (ability to signal their state to others). The authors of this review suggest that disconnected consciousness, experienced while dreaming under general anesthesia, could be considered an ideal state for certain surgeries, because it lies between full consciousness and internal unconsciousness. The depth of anesthesia may be inadequate or excessive for some patients because currently used technologies are unable to reliably assess the state of consciousness. Until there are technologies that reliably differentiate environmentally connected consciousness (experience of the surgery) from disconnected consciousness (dreaming), it will be difficult to optimize anesthesia for all patients. *(Summary: M. J. Avram. Image: J. P. Rathmell.)*