Hi, this is Evan Kharasch, Editor-in-Chief of Anesthesiology, with some highlights from the March 2022 issue, as selected by the journal editors.

In this month's podcast, we'll take a look at an antioxidant intervention to reduce myocardial injury. We'll explore new information about the association between propofol and brain network connectivity. We'll discuss a study of how end-tidal CO2 can help identify anaphylaxis in patients with post-induction hypotension. And we'll close this month with a review of the latest opinions on the effect of anesthesia on the developing brain.

Let's begin this month with a clinical study of potential oxygen toxicity and an antioxidant intervention to reduce myocardial injury. We know that excess oxygen can lead to hyperoxia, but it is unknown if there is any clinical effect of excess oxygen on cardiac function. Patients with cardiac disease might theoretically be at additional risk of long-term cardiac complications because of a possible link with high perioperative inspiratory oxygen fraction during anesthesia. Dr. Cecilie Holse and colleagues at the University of Copenhagen, Denmark, conducted a randomized trial to assess the effect of different perioperative oxygen fractions on myocardial injury. They also assess the effect of an antioxidant intervention versus placebo. They studied 600 patients older than 45 years, and used a 2x2 factorial design, to test both interventions at once. Patients were randomized to receive either 80% oxygen or 30% oxygen perioperatively, and were then randomized further to either an antioxidant injection or placebo. Patients randomized to antioxidants received intravenous vitamin C prior to anesthesia. They also received an N-acetylcysteine infusion over 4 hours after induction of anesthesia. The primary outcome was myocardial injury, which was defined as area under the curve of high-sensitive troponin for the first 3 days after surgery. The first major result was that there was no significant difference between 30% and 80% oxygen groups in the primary outcome of myocardial injury. The second major result was that there was no significant difference between antioxidant and placebo groups in the primary outcome of myocardial injury. Secondary outcomes including all-cause mortality within 30 days were similar between the oxygen groups, and between patients who received antioxidants or placebo. Incidence of nonfatal myocardial infarction and nonfatal serious adverse events within 30 days also were not different between the groups. The authors said their results show no difference in the safety of different oxygen concentrations, and no benefits from an antioxidant intervention. An editorial by Dr. Peter Nagele accompanies this article. Dr. Nagele noted several strengths of the study, including the large sample size, and the inclusion of patients undergoing elective and emergent surgeries. Also, the 2x2 study design allowed assessment of two interventions, oxygen concentration and antioxidant administration. Although the study showed no effect of either intervention, it was large enough to be conclusive. "For conclusive studies, it does not matter whether results are positive or negative—they will be informative," Dr. Nagele said. Check out the full article for free in this month's issue.

We next look at a clinical study of local anesthetics in regional anesthesia. This was a noninferiority trial to compare interscalene brachial plexus block with liposomal bupivacaine to interscalene block with standard bupivacaine and perineural dexamethasone. Perineural dexamethasone is often used to extend the duration of interscalene nerve blocks and provide sufficient anesthesia while minimizing opioid use. However, data on liposomal bupivacaine, which is an extended-release formula, are limited, according to Dr. David Kim and colleagues at Weill Cornell Medical College. The authors tested the hypothesis that average pain scores in the first 72 hours after surgery would be noninferior for patients who received liposomal bupivacaine and those who received bupivacaine with dexamethasone, in patients undergoing shoulder surgery. The authors found this to be the case—the average pain VAS score was 2.4 in the liposomal bupivacaine group and 3.4 in bupivacaine plus dexamethasone group. These were not significantly different. Other factors including duration of analgesia, motor and sensory resolutions, and opioid consumption were not different between the groups. The authors concluded that bupivacaine with dexamethasone can be used interchangeably with liposomal bupivacaine for shoulder surgery analgesia. This article is available for free in this month's issue.

Our next clinical study explored the association between propofol anesthesia and changes in brain network connectivity. We know that propofol prompts decreases in brain connectivity over time periods of seconds to tens of seconds. However, the effect on brain network dynamics for shorter periods such as milliseconds and longer periods such as minutes remains unclear. Abrupt changes in brain connectivity may indicate brain phase transition, which indicates loss of criticality. As a follow-up to a previously reported study, Dr. Rebecca Pullon of the University of Auckland, New Zealand, and colleagues explored brain criticality. They administered propofol to 16 adult volunteers in gradually increasing doses, to achieve a brain phase transition. They measured brain network connectivity using 31-channel electroencephalogram data. Brain connectivity metrics for short time scales of less than 5 seconds included coherence and weighted phase lag indexes; metrics for medium and long time scales were calculated using mutual information. During the transition to anesthesia, for long time scales of tens of seconds, global network efficiency of 2Hz slowed and then abruptly decreased. At the same time, however, the global network efficiency for 10-Hz connectivity increased significantly for the short time scale metric of weighted phase lag index. The brain network complexity for both 2 Hz asynchronous and 10 Hz hypersynchronous network states decreased significantly, also at the time of loss of behavioral responsiveness. The authors used a model of a network of phase-coupled oscillators illustrative of order-disorder phase transition to interpret the findings. The results suggest a network phase transition around the loss and return of behavioral responsiveness associated with propofol anesthesia. The authors noted that their study of network dynamics may explain the diversity in brain connectivity over different frequencies and time scales when propofol is used. An editorial by Drs. George Mashour, Robert Sanders, and UnCheol Lee accompanies this article. The editorial authors compared the use of EEG data and activity of different electrodes to singers in three-part harmony. The singers' activity is functionally connected even if they are not directly influencing each other because all are reading from the same musical score. The evidence of phase transition reflects the dynamics of a larger system beyond micro-level events, and suggests the brain does not slide down to general anesthesia in a linear way, the authors emphasized. You can access this article for free in this month's issue.

Our next study evaluates the effect of anesthesia type on outcomes potentially related to cancer. Current experimental studies conducted alongside clinical trials have shown conflicting results for the anti-tumor effects of different modes of anesthesia. However, some data suggest that propofol may have an advantage. This was a prospective, randomized trial to assess the potential effect of propofol versus sevoflurane on the expression profiles of circulating anti-tumor immune cells during colorectal cancer surgery. Dr. Chung-Sik Oh of Konkuk University Medical Center in Seoul, Korea, and colleagues used flow cytometric analysis to evaluate immune cells. The primary outcome was changes in the fractions of circulating natural killer cells, circulating T lymphocytes, and related circulating immune cells for 153 colorectal cancer patients, 76 given propofol and 77 given sevoflurane during surgery. The result was that overall, the fraction of circulating natural killer cells was not significantly different between the propofol and sevoflurane groups up to 24 hours after surgery. There were also no significant differences in the apoptosis rate of circulating natural killer cells, or the fractions of circulating type 1 and type 17 helper cells, or the fraction of circulating cytotoxic T cells, or the fractions of CD39+ and CD73+ circulating regulatory T cells. The authors did note limitations to their study, including the lack of data on cancer outcomes, and the evaluation of immune cells only up to 24 hours postoperatively. They concluded that propofol and sevoflurane effects on immune cells are not different, and the effects of anesthetics on perioperative immune status are minimal. Check out this article for free in this month's issue.

We move next to another study of anesthesia and cancer. This was a retrospective cohort study of epidural analgesia and recurrence after colorectal cancer surgery. Although surgery is the primary treatment for colorectal cancer, recurrence is common and is often the primary cause of death in these patients. The immune system stress associated with surgery might contribute to cancer progression, according to Dr. Rune Hasselager of the Center for Surgical Science, Zealand University Hospital, Denmark, and colleagues. Given the ability of epidural anesthesia to mitigate stress response, the authors tested the hypothesis that epidural use might result in less cancer recurrence. They identified more than 11,000 patients from a Danish cancer database who underwent surgery for colorectal cancer between 2004 and 2018. Of these, approximately 30 percent had an epidural catheter inserted before surgery. Colorectal cancer recurrence was the primary outcome. Over a median follow-up of 58 months, cancer recurred in 19% of patients who had epidurals and 20% of those who did not have epidurals, which was not different. Mortality was approximately 32% in

both groups. The authors noted that the findings were strengthened by the large sample size, but limitations included a lack of data on the exact timing, duration, and dosing of the epidural anesthesia. Their findings contrasted with other studies in which survival was greater and recurrence was less among patients with who received epidurals. However, the authors also cited other studies showing no difference in recurrence based on regional anesthesia. The authors concluded that in colorectal cancer surgery, epidural analgesia was not significantly associated with less cancer recurrence. This article is available for free in this month's issue.

Next, we have a retrospective case-control study of the use of end-tidal CO2 for diagnosing anaphylaxis in patients with post-induction hypotension. Anaphylaxis is often suspected when severe hypotension occurs soon after the induction of anesthesia, but such hypotension can have several causes. Previous research suggested that a rapid decrease in end tidal CO2 might signal anaphylaxis and allow for prompt treatment. However the ability of end-tidal CO2 to distinguish between anaphylaxis and non-hypersensitivity reactions in hypotensive patients is unknown. Dr. Clémence Erlich of the University of Lille, in France, and colleagues tested this hypothesis and compared end-tidal CO2 in patients with allergic or non-allergic anaphylaxis to end tidal CO2 in patients with severe hypotension from any other cause following induction of anesthesia. They identified patients aged 18 years and older who underwent surgery between 2010 and 2018 in a single center. Of these, 49 experienced a perioperative immediate hypersensitivity reaction and 555 experienced post-induction hypotension. Overall, the authors found that both ETCO2 and systolic blood pressure were significantly lower in the anaphylaxis group compared to hypotension group. The authors added that cardiac output measures were relatively unaffected in the hypotension group, but decreased in the anaphylaxis group. The findings were limited in part by the retrospective design and an inability to draw conclusions about confounding factors. However, the authors concluded that ETCO2 was a sensitive, specific, and independent marker of anaphylaxis that could be used in clinical practice. Check out this article for free in this month's issue.

Our first review article this month addresses the postoperative management of lung transplant patients. The number of lung transplants is increasing worldwide, and outcomes continue to improve. Five-year survival rates are approximately 60%. However, the review does identify factors associated with increased perioperative risk, including risk factors and characteristics of both donors and recipients. Dr. Matteo Di Nardo of the Bambino Gesù Children's Hospital in Rome, and colleagues provided an update of the postoperative management of lung transplant patients in the intensive care unit. The authors addressed six main areas: management of mechanical ventilation; fluid and hemodynamic management; immunosuppressive therapies; prevention and management of neurologic complications; antimicrobial therapy; and management of nutritional support and abdominal complications. They reviewed the main potential postoperative complications that occur in lung transplant patients in the ICU. Of these, primary graft dysfunction is the most relevant, they explained. This form of respiratory distress is associated with both short- and long-term morbidity and mortality. If you want to delve deeper into the risk factors for primary graft dysfunction, the authors included a useful illustration of donor factors, recipient factors, and the risk factors associated with donor/recipient interaction. Examples of donor factors include bronchial circulation, type of organ donation, and demographics. Examples of recipient risk factors include recipient comorbidities and pulmonary diagnosis. Donor-recipient interaction risk factors included ischemia-reperfusion injury, size mismatch, and immune match and sensitization. Other common complications in lung transplant patients include heart failure, supraventricular tachyarrhythmias and pericarditis, delirium, and gastric content aspiration. The review includes a detailed table outlining strategies for mechanical ventilation, and an illustration of lung allograft function monitoring. The authors based their review primarily on published research from the past 10 years. They emphasized that perioperative and postoperative management of lung transplant patients requires integrated care from intensivists, thoracic surgeons, pneumologists, infectious disease specialists, nurses, clinical pharmacists, physiotherapists, social workers, and psychologists. You can access this review for free in this month's issue.

We close this month with a second review article, this one on the relationship between anesthesia and the developing brain. Animal models show disrupted neurodevelopment in response to anesthetics, but any evidence for this in humans is inconsistent. Dr. Caleb Ing of Columbia University led a team in reviewing the latest consensus and disagreements among experts. The authors noted that brief or single early anesthetic exposure in children is not associated with neurodevelopmental deficits. They also explain that identifying a phenotype for injury is an ongoing challenge. The authors presented several possible research approaches to address the question of whether anesthesia causes any long-term neurodevelopmental problems in children. Notably, the T-REX trial, currently underway, compares children exposed to low dose sevoflurane plus remifentanil and dexmedetomidine to children exposed to a traditional higher dose of sevoflurane. The research hypothesis is that the sevoflurane combination will have less effect on study outcomes than the higher dose of sevoflurane alone. Full scale intelligence quotient is the primary outcome, and other aspects of neurodevelopment will be measured as secondary outcomes. The authors note other areas of research including the use of biomarkers such as brain imaging studies and serum-based assays, the attempts to identify which if any children are vulnerable to any neurodevelopmental effects of anesthesia, and the possible effects of prenatal anesthesia exposure. Despite the challenges of conducting neurotoxicity studies in children, more research is needed to inform clinical decision-making for children undergoing surgery and anesthesia.

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As always, thank you for listening to this podcast and thank you for your support of Anesthesiology. I hope you find the information presented helps to guide and improve your clinical practice. I look forward to sharing more important research with you next month.