SCIENCE, MEDICINE, AND THE ANESTHESIOLOGIST
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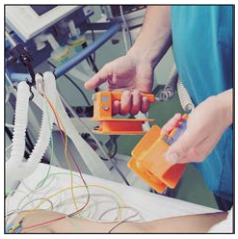
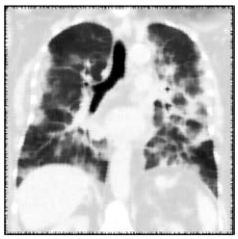
Martin J. London, M.D., Editor
Key Papers from the Most Recent Literature Relevant to Anesthesiologists



Dual vs single cardioversion of atrial fibrillation in patients with obesity: A randomized clinical trial. JAMA Cardiol 2024; 9:641–8. PMID: 38776097.

Atrial fibrillation and obesity are common, and both are increasing in prevalence. Obesity is associated with failure of cardioversion of atrial fibrillation using a standard single set of defibrillator pads, even at high output. Optimal management of obese patients with atrial fibrillation requiring elective cardioversion is controversial. The use of dual direct-current cardioversion (DCCV) using two sets of pads, with each pair simultaneously delivering 200 J, has traditionally been reserved for salvage therapy after failure of traditional single 200-J DCCV using one set of pads. This randomized, prospective trial at three U.S. hospitals compared the use of either approach as a primary therapy in clinically stable adult subjects undergoing nonemergent electrical cardioversion for atrial fibrillation with body mass index of 35 or higher. The primary outcome was return to sinus rhythm, regardless of duration, immediately after the first cardioversion attempt. Secondary outcomes included adverse cardiovascular events and chest discomfort after the procedure. Two hundred patients (median [interquartile range] age, 67.6 [60.1 to 72.4] yr; 63.5% male; mean ± SD BMI, 41.2 ± 6.5) were analyzed. The primary outcome was significantly increased in the dual DCCV group (98% *vs.* 86%, odds ratio, 6.7; 95% CI, 3.3 to 13.6; $P = 0.01$). No significant difference was noted in the secondary outcomes. *(Article Selection: Martin J. London, M.D. Image: Adobe Stock.)*

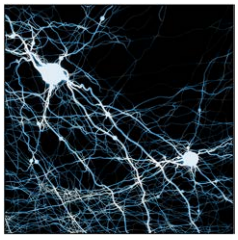
Take home message: In this randomized study of obese patients requiring cardioversion for atrial fibrillation, dual DCCV resulted in enhanced achievement of sinus rhythm compared with single DCCV, without any increase in complications or patient discomfort.



Longitudinal analysis of the lung proteome reveals persistent repair months after mild to moderate COVID-19. Cell Rep Med 2024; 5:101642. PMID: 38981485.

The inflammatory and immunologic environment of the lung during COVID-19 infections has been extensively characterized; however, the resolution of proteins involved in these responses after the resolution of clinical and radiographic disease is unknown. This study investigated the lung lavage proteome in 45 patients with mild to moderate COVID-19 at 1 to 40 days after symptom onset, between 6 and 12 weeks after symptom recovery, and during convalescence phases at 3 to 13 months. They utilized three complementary methods of protein analysis of lung lavages: mass spectrometry, proximal extension assays, and targeted enzyme-linked immunosorbent assay immunoassays of lung lavage and plasma. Despite resolution of clinical symptoms, the lung lavage proteome did not normalize at the latest time point analyzed, suggesting an unrecognized prolonged period of lung repair. The proteome revealed tissue repair and host defense processes during the acute phase, with resolution of inflammatory and fibrogenic proteins during recovery, but persistent activation of cellular repair processes with depression of renin-kallikrein-kinin, coagulation, and complement proteins into the late convalescent phases despite radiographic and symptomatic resolution of disease. While clinical symptoms of long COVID have been described in multiple organ systems, this is the first demonstration of prolonged protein changes in the lungs after the resolution of overt clinical symptoms. *(Article Selection: Charles Emala, M.D. Image: J. P. Rathmell.)*

Take home message: Proteins involved in lung cellular repair and host defenses remain activated long after the resolution of radiographic and clinical symptoms of COVID-19. It remains unknown whether there are later clinical sequelae of these persistent changes and whether similar proteomic changes may persist after other viral pulmonary infections.



Chromatin plasticity predetermines neuronal eligibility for memory trace formation. Science 2024; 385:eadg9982. PMID: 39052786.

Memory formation involves a cascade of cellular processes linking neuronal activity to long-term alterations in protein expression and synaptic connectivity. However, it is clear that these changes occur in only small subsets of the total number of neurons receiving learning inputs. It is not known whether there is some underlying epigenetic plasticity that precedes the memory encoding process and defines which neurons are preferentially selected for memory formation. A suite of experiments was conducted, focusing on the mouse lateral amygdala, a region of the brain necessary for fear conditioning memory. It was observed that the learning-activated neurons had more hyperacetylated histones—a sign of epigenetic modification. When histone acetylation was experimentally manipulated by insertion of histone acetyltransferases to increase epigenetic plasticity, there was increased propensity for these neurons to be involved in the memory allocation. This pattern of differentially altered gene expression specifically involved genes associated with increased synaptic plasticity (such as protein kinase C) and increased intrinsic neuronal excitability (such as calcium voltage-gated channels). Behaviorally, these memories were retained up to 8 days, and were lost if the neurons were optogenetically silenced. The level of histone acetylation correlated with intrinsic excitability at a single cell level in neuronal cell cultures. *(Article Selection: Jamie Sleigh, M.D. Image: Adobe Stock.)*

Take home message: The epigenetic state of a neuron, prior to the learning exposure, determines the ease with which it becomes incorporated in a subsequent memory trace, thus implicating epigenomic heterogeneity as part of long-term memory mechanisms.

A μ-opioid receptor modulator that works cooperatively with naloxone. Nature 2024; 631:686–93. PMID: 38961287.

Agonists and antagonists of the μ-opioid receptor (μOR) bind at an overlapping (orthosteric) site in the extracellular vestibule of the 7-transmembrane receptor. Motivated by the current opioid crisis with so many overdoses and deaths caused by highly potent synthetic opioids, recent research is aimed at developing μOR antagonists with prolonged blocking and opioid-reversing actions through allosteric modulation, *i.e.*, by binding at a site on the μOR other than the orthosteric site. In this study, a large DNA-encoded chemical library (4.4 billion compounds) was screened to identify compounds strongly binding to the inactive μOR saturated with naloxone, but minimally binding to fully active μORs bound to met-encephalin or Gi. A potent negative allosteric modulator of the μOR (compound 368) was discovered that caps naloxone bound to the μOR, boosting its inhibition by stabilizing the vestibule, as evidenced by cryogenic electron microscopy. A bioluminescence resonance energy transfer-base assay in μOR-expressing cells for measuring naloxone's potency to block the agonist-induced signaling revealed a 7.6-fold increase in the presence of compound 368. Using an *in vivo* mouse model, compound 368 enhanced the potency and duration of actions by naloxone to inhibit the effects of morphine and fentanyl in tests for pain, withdrawal symptoms, and respiratory depression. *(Article Selection: Michael Zaugg, M.D., M.B.A. Image: Adobe Stock.)*

Take home message: Allosteric cooperation of a newly discovered compound with the μOR antagonist naloxone opens promising approaches to more efficiently treat morphine- and fentanyl-induced adverse effects.

Bisoprolol in patients with chronic obstructive pulmonary disease at high risk of exacerbation: The BICS randomized clinical trial. JAMA 2024; 332:462–70. PMID: 38762800.

Previous observational data suggest that β-blocker use may be associated with reduced risk of chronic obstructive pulmonary disease (COPD) exacerbations. Yet, a recent randomized trial of metoprolol found that it increased COPD exacerbations. The role of increased beta1 selectivity using bisoprolol has not been reported. The Bisoprolol in COPD Study (BICS) multicenter United Kingdom double-blind placebo-controlled trial randomized patients with COPD (moderate airflow obstruction on spirometry [ratio of forced expiratory volume in the first second of expiration (FEV_1)] to forced vital capacity less than 0.7; FEV_1 < 80% predicted and at least two prior COPD exacerbations in the prior 12 months) to either bisoprolol (1.25 mg orally daily titrated as tolerated during four sessions to a maximum of 5 mg/d; n = 261) or placebo (n = 258). The primary outcome was the number of COPD exacerbations treated with oral corticosteroids, antibiotics, or both over 1 yr. Although the plan was to enroll 1,574 patients, due to the COVID-19 pandemic, only 515 patients (mean ± SD age, 68 ± 7.9 yr; 274 men [53%]; mean FEV_1, 50.1%) were enrolled. No difference was noted in the primary outcome between groups (mean exacerbation rate of 2.03/yr, *vs.* 2.01/yr; adjusted incidence rate ratio was 0.97 [95% CI, 0.84 to 1.13]; $P = 0.72$). No difference was noted in serious adverse events (14.5% *vs.* 14.3%; relative risk, 1.01; 95% CI, 0.62 to 1.66; $P = 0.96$). *(Article Selection: Martin J. London, M.D. Image: Adobe Stock.)*

Take home message: This multicenter United Kingdom randomized trial of bisoprolol *versus* placebo in patients with high-risk COPD found no difference in patient-reported episodes of COPD exacerbations requiring treatment with oral corticosteroids, antibiotics, or both.

Stress ulcer prophylaxis during invasive mechanical ventilation. N Engl J Med 2024; 391:9–20. PMID: 38875111.

Proton-pump inhibitors are commonly administered for stress ulcer prophylaxis in critically ill patients receiving mechanical ventilation, but increased mortality in recent clinical trials necessitated higher-quality evidence to support this practice. The Reevaluating the Inhibition of Stress Erosions (REVISE) trial enrolled critically ill adults undergoing mechanical ventilation in an international, randomized, placebo-controlled trial of pantoprazole for prevention of significant upper gastrointestinal bleeding within 90 days in 68 intensive care units worldwide. The primary outcome was clinically important upper gastrointestinal bleeding defined by hemodynamic compromise or need for therapeutic intervention (transfusion, vasopressors, diagnostic imaging, or procedural intervention) assessed by proportional hazards modeling. Mortality was the primary safety outcome; secondary outcomes included ventilator-associated pneumonia and *Clostridioides difficile* infection. Between July 2019 and October 2023, the study randomized 4,821 patients (64% male; mean age, 58.2 ± 16.4 yr) to pantoprazole (n = 2,417) or placebo (n = 2,404). Pantoprazole treatment reduced clinically important upper gastrointestinal bleeding (hazard ratio, 0.30; 95% CI, 0.19 to 0.48; $P < 0.001$) at 90 days but had no effect on 90-day mortality (hazard ratio, 0.94; 95% CI, 0.85 to 1.04; $P = 0.25$) or secondary outcomes. *(Article Selection: William G. Tharp, M.D., Ph.D. Image: Adobe Stock.)*

Take home message: The large, multinational, multicenter REVISE trial found that treatment of critically ill adults receiving mechanical ventilation with pantoprazole reduced the risk of clinically important upper gastrointestinal bleeding but had no effect on 90-day mortality.

Sleep loss diminishes hippocampal reactivation and replay. Nature 630; 935–42. PMID: 38867049.

Sleep plays a crucial role for memory consolidation with the hippocampus as an important structure for sleep-dependent memories. Sharp-wave ripples (SWRs) from the hippocampus featuring sharp waves in CA1 pyramidal cells coupled with ripple oscillations near cell bodies are considered critical for the sleep-dependent memory process. During SWRs, activities initially expressed during learning and behavior can be replayed and reactivated. Therefore, this process is considered to play a key role in memory consolidation. The mechanisms by which sleep deprivation affects memory consolidation, however, is not clear. Neuronal activities during maze exploration, sleep, sleep loss, and recovery sleep were tested in a rat model. Compared to sleep, SWRs during sleep deprivation presented with higher rates, but with lower power and higher frequency ripples. Firing in pyramidal cells was reduced during sleep, while it continued during sleep loss. While overall firing-rate dynamics were still present during sleep loss, specific content of SWRs was affected. Sleep loss decreased replay and reactivation of neuronal firing patterns. In addition, upon recovery of sleep deprivation, reactivation partially rebounded but without reaching the levels of natural sleep. *(Article Selection: Beatrice Beck-Schimmer, M.D. Image: Adobe Stock.)*

Take home message: This rat study suggests that sleep deprivation leads to a dissociation at the hippocampus with sustained SWRs, but a low number of replays and reactivations, and therefore reduced memory consolidation.

Automated CT analysis of body composition as a frailty biomarker in abdominal surgery. JAMA Surg 2024; 159:766–74. PMID: 38598191.

Low skeletal muscle mass assessed on computerized tomography scans is now considered an "imaging biomarker." It can assist in phenotyping frailty and is associated with surgical morbidity and mortality. This retrospective cohort study correlated body size, muscle quantity and quality, and distribution of adiposity measurements obtained from preoperative computerized tomography scans with electronic health record data from a random sample of adults having abdominal surgeries at 20 Kaiser Permanente Northern California medical centers over a 10-yr period. The primary outcomes were all-cause 30-day mortality or postdischarge readmissions. The secondary outcome was 30-day morbidity. The mean ± SD age of the 48,444 adults was 61 ± 17 yr, and 51% were female. Higher muscle quantity and quality scores were inversely correlated ($r = -0.42$; 95% CI, −0.43 to −0.41) with Hospital Frailty Risk Scores and associated with lower 30-day readmissions and mortality (quartile 4 *vs.* quartile 1: relative risk, 0.61; 95% CI, 0.56 to 0.67) and 30-day morbidity (quartile 4 *vs.* quartile 1: relative risk, 0.59; 95% CI, 0.52to 0.67). These findings were independent of sex, age, comorbidities, body mass index, type of surgery, and the Hospital Frailty Risk Scores. Body size and greater subcutaneous and intermuscular *versus* visceral adiposity scores were inconsistently associated with outcomes, and only associated with 30-day morbidity after adjustment for the Hospital Frailty Risk Scores. *(Article Selection: BobbieJean Sweitzer, M.D. Image: Adobe Stock.)*

Take home message: This large, retrospective cohort study suggests that computed tomography assessment of muscle quantity and quality can provide an objective measure of patient frailty that may identify surgical patients at high risk of mortality or readmissions.

Liberal or restrictive transfusion strategy in patients with traumatic brain injury. N Engl J Med 2024; 391:722–35. PMID: 38869931.

Anemia in traumatic brain injury might correlate with decreased oxygen delivery to a vulnerable brain. This large, randomized trial was designed to assess superiority of a liberal *versus* restrictive transfusion strategy with a primary outcome defined as unfavorable 6-month outcome with the Glasgow Outcome Scale-Extended (GOS-E) ranging from 1 (death) to 8 (full return to normal life). A sliding dichotomy of the GOS-E was used for the prognosis of each patient at baseline defining unfavorable outcome with a score of less than or equal to 3, 4, or 5. Secondary outcomes included, among others, 6-month mortality and depression. Adult patients from 34 centers from Canada, the United Kingdom, France, and Brazil with a Glasgow Coma Scale of 3 to 12 with anemia (hemoglobin 10 g/dl or less) were randomized between September 2017 and April 2023 to a liberal transfusion strategy arm with a hemoglobin trigger level of 10 g/dl or less while 7 g/dl or less for the restrictive-strategy group. In the liberal-strategy group, 68% of 364 patients (24% female, median hemoglobin of 10.8 g/dl) had an unfavorable outcome *versus* 74% of 358 patients in the restrictive-strategy group (30% female, median hemoglobin of 8.8 g/dl; adjusted absolute difference, 5.4% points; 95% CI, –2.9 to 13.7). Secondary outcomes were comparable. *(Article Selection: Beatrice Beck-Schimmer, M.D. Image: J. P. Rathmell.)*

Take home message: This multicenter randomized trial comparing liberal *versus* restrictive transfusion strategy in critically ill patients with traumatic brain injury and anemia did not demonstrate superiority of a liberal strategy on neurologic outcome at 6 months after injury.