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

Bag-valve-mask ventilation and survival from out-of-hospital cardiac arrest: A multicenter study. Circulation 2023; 148:1847–56. PMID: 37952192.

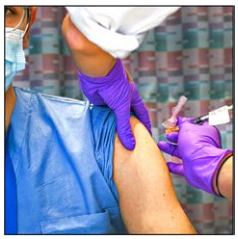
Cardiac arrest represents the most extreme example of a complicated, time-dependent condition where survival drops by 10% for every 60 s of pulselessness with favorable outcomes varying fivefold between providers of cardiopulmonary resuscitation (CPR). In 2010, the American Heart Association reordered the guidelines for advanced cardiac life support from Airway-Breathing-Circulation (ABC) to Circulation-Airway-Breathing (CAB), prioritizing circulation with prompt cardiopulmonary resuscitation over airway/breathing. This study used data from 1,976 patients who underwent 30:2 CPR (30 chest compressions followed by two bag mask ventilations) collected during the ROC CCC trial (Trial of Continuous Compressions versus Standard CPR [before placement of advanced airway] in Patients with Out-of-Hospital Cardiac Arrest) and a novel method of measuring ventilation that exploits the thoracic bioimpedance channel recordings used by some defibrillators. Detectable ventilation occurred in only 40% of compression pauses in a minority of patients receiving mask ventilation. When mask ventilation was more adequate than not (50% or more chest compression pauses with at least 250 ml), victims were twice as likely to have return of spontaneous circulation, three times more likely to survive to hospital discharge, and fourfold more likely to survive with favorable neurologic outcome (10.6% *vs.* 2.4%; $P < 0.0001$). *(Article Selection: Michael Zaugg, M.D., M.B.A. Image: Adobe Stock.)*

Take home message: While mask ventilation is often ineffective during cardiopulmonary resuscitation, improving ventilation may lead to favorable clinical outcomes.

A therapeutic strategy to target distinct sources of IgE and durably reverse allergy. Sci Transl Med 2023; 15:eadf9561 [Epub December 13]. PMID: 38091405.

Allergen crosslinking of immunoglobulin E (IgE) plays a crucial role in allergic and anaphylactic disorders. Clinically used monoclonal antibodies that target IgE-producing B cells have only modestly reduced circulating IgE. Identifying the additional source of IgE, which persists long after allergen exposure, could present a complementary therapeutic strategy to more thoroughly eliminate IgE in allergic diseases. In a 4-week acute mouse model of allergy, pretreatment with an interleukin-4 receptor (IL-4Rα) antibody prevented an increase in IgE. In contrast, in a 12-week chronic model of allergy, the later introduction of the IL-4Rα antibody only partially impaired the increase in IgE, which is consistent with a prior establishment of allergen-specific bone marrow plasma cells as the additional source of IgE. In an attempt to eliminate residual IgE, a bispecific antibody was used that links a receptor on plasma cells to the CD3 receptor on T cells resulting in plasma cell killing. This combination therapy with the IL4-Rα antibody and the bispecific antibody linking plasma cells to T cells during the 12-week chronic model of allergy eliminated detectable IgE. Similar findings of IgE depletion with combination therapy occurred in nonsensitized cynomolgus monkeys and the bispecific antibody reduced IgE production in patients with multiple myeloma. *(Article Selection: Charles Emala, M.D. Image: Adobe Stock.)*

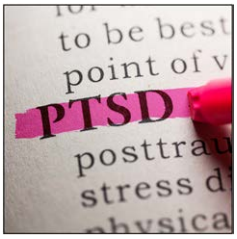
Take home message: While antibodies directed against the IL-4 receptor can partially attenuate IgE levels in allergic diseases, complete attenuation of IgE levels can be achieved by combination therapy with an antibody against the IL-4 receptor and an antibody that crosslinks IgE-producing plasma cells with T cells, resulting in plasma cell killing. This dual approach holds promise for more effectively and chronically mitigating allergic inflammatory diseases mediated by persistent IgE.



Association between coronavirus disease 2019 vaccination and mortality after major operations. Ann Surg 2024; 279:58–64. PMID: 37497640.

An American Society of Anesthesiologists–Anesthesia Patient Safety Foundation joint statement recommends postponing elective surgery for at least 7 weeks after a COVID-19 infection in unvaccinated patients. The benefits of vaccination are unclear. This national U.S. multicenter retrospective, matched cohort study using Veterans Health Administration data sources analyzed patients undergoing high-risk general, vascular, orthopedic, neurosurgery, or genitourinary surgeries from July 2021 to October 2022. The primary outcome was all-cause mortality within 90 days of the index surgery. Within 8 weeks of surgery, 437 (12.9%) of 3,401 fully vaccinated patients (receiving at least two doses of vaccine; those with fewer were considered unvaccinated) were found to be COVID-19 positive on preoperative testing (or by symptoms in the medical record). Unadjusted mortality rates were not significantly different between vaccinated patients with COVID-19 and vaccinated patients without COVID-19 (5% *vs.* 3.3%, respectively; $P = 0.07$). After inverse probability treatment-weighted adjustment, mortality risk was not significantly different between vaccinated COVID-19–positive patients compared to vaccinated patients without COVID-19 (adjusted odds ratio, 1.38; 95% CI, 0.70 to 2.72). The timing of COVID-19 diagnosis to the index surgery did not affect mortality risk in either cohort. *(Article Selection: BobbieJean Sweitzer, M.D. Image: J. P. Rathmell.)*

Take home message: In this large, retrospective cohort study from the Veterans Administration, postoperative mortality did not differ among vaccinated patients with and without COVID-19 undergoing high-risk surgery within 8 weeks of infection.



Neural patterns differentiate traumatic from sad autobiographical memories in PTSD. Nat Neurosci 2023; 26:2226–36. PMID: 38036701.

It is unclear whether pathologic traumatic memories are simply stronger manifestations of nontraumatic negative memories, or whether completely different neural mechanisms are involved. Twenty-eight patients with posttraumatic stress disorder listened to audio narratives of their personal traumatic memory, and their functional magnetic resonance imaging responses were compared with those from narratives of nontraumatic sad events and from calm positive memories. It was hypothesized that traumatic and sad memories would have different semantic-to-neural activation patterns in the brain areas necessary for episodic memory (hippocampus) and internal re-experiencing of memory (posterior cingulate cortex). Semantic similarity was estimated by word-embedding and compared with the brain imaging using intersubject representational similarity analysis. Semantic similarity and neural patterns in the hippocampus were positively correlated for sad memories ($r = 0.177$, $P = 0.005$), but not for posttraumatic stress disorder (PTSD) memories ($r = -0.117$, $P = 0.104$). These differences in semantic-to-neural representation between traumatic and sad memories were more marked in the posterior hippocampus but absent in the posterior cingulate cortex and amygdala. Patients with more severe symptoms had stronger representation in the posterior cingulate cortex ($P = 0.001$), but there was no correlation in the amygdala. *(Article Selection: Jamie Sleigh, M.D. Image: Adobe Stock.)*

Take home message: These results suggest that the neural basis for hippocampal encoding of traumatic memories is different from that of sad memories.

Prone positioning during extracorporeal membrane oxygenation in patients with severe ARDS: The PRONECMO randomized clinical trial. JAMA 2023; 330:2343–53. PMID: 38038395.

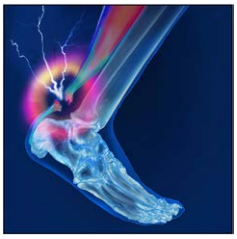
While it has been shown that prone ventilation in acute respiratory distress syndrome (ARDS) patients reduces 90-day mortality, there is a lack of evidence for prone positioning during venovenous extracorporeal membrane oxygenation (ECMO). This randomized controlled trial was performed in 14 French intensive care units (ICUs) between March and December 2021 to define the effect of prone positioning with at least four sessions of 16 h during venovenous ECMO on ECMO weaning time in patients with severe ARDS. The primary outcome was time to successful ECMO weaning within 60 days. Secondary outcomes included ECMO and mechanical ventilation-free days, ICU and hospital length of stay, and all-cause mortality at 90 days. A total of 170 patients were randomized (median age, 51 y [interquartile range, 43 to 59 y], 35% female). No significant differences were noted in the primary outcome (44% *vs.* 44%; risk difference, 0.1% [95% CI, –14.9 to 15.2%]). Likewise, no significant differences were noted for secondary outcomes: ECMO duration within 90 days, ICU and hospital length of stay, or 90-day all-cause mortality (51% *vs.* 48%; risk difference, 2.4% [95% CI, –13.9 to 18.6%]; $P = 0.62$). *(Article Selection: Beatrice Beck-Schimmer, M.D. Image: Adobe Stock.)*

Take home message: This randomized clinical trial assessing the effect of prone positioning on successful weaning from venovenous ECMO in patients with severe ARDS does not report a shorter weaning time with a prone positioning intervention.

Preoperative midazolam and patient-centered outcomes of older patients: The I-PROMOTE randomized clinical trial. JAMA Surg 2023; e236479. PMID: 38117527.

While a recent large randomized clinical trial showed that oral premedication with midazolam did not affect patient satisfaction, data evaluating its effect in an aged patient population is missing. This is a double-blind, parallel-group, placebo-controlled randomized clinical trial performed in patients between 65 and 80 yr, undergoing elective surgery (longer than 30 min) under general anesthesia with an intervention of oral midazolam (3.75 mg) 30 to 45 min before anesthesia induction. The primary outcome was global patient satisfaction on the first postoperative day using the self-reported Evaluation du Vécu de l'Anesthésie Generale (EVAN-G) questionnaire. Secondary outcomes included adverse events, serious complications, and cognitive and functional recovery up to 30 days after surgery. This study conducted at nine German hospitals (2017 to 2019) analyzed 607 patients (62% male, mean ± SD age, 72 ± 4.4 yr). No difference in the global index of patient satisfaction was found between the intervention (n = 304) and placebo arm (n = 303) (69.5 ± 10.7 *vs.* 69.6 ± 10.8; mean difference, –0.2; 95% CI, –1.9 to 1.6; $P = 0.85$). Except for a higher systolic blood pressure (greater than 160 mmHg) in the control group at anesthesia induction, secondary outcomes were comparable. *(Article Selection: Beatrice Beck-Schimmer, M.D. Image: Adobe Stock.)*

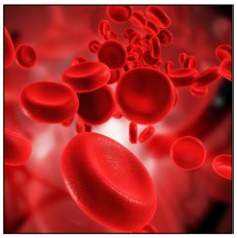
Take home message: In this randomized trial of senior patients undergoing elective surgery with general anesthesia, oral midazolam premedication administered shortly before anesthesia induction had no impact on global patient satisfaction up to 30 days postoperatively relative to placebo.



TrkA-mediated sensory innervation of injured mouse tendon supports tendon sheath progenitor cell expansion and tendon repair. Sci Transl Med 2023; 15:eade4619 [Epub December 20]. PMID: 38117901.

Nerve growth factor (NGF) has long been recognized for its role to promote the growth of nociceptive nerves *via* its high-affinity receptor tropomyosin receptor kinase A (TrkA). Clinical trials using anti-NGF monoclonal antibodies have shown significant efficacy in alleviating pain in osteoarthritis patients, but with noticeable side effects such as joint damage. This study explored the role of NGF in a mouse model of Achilles tendon injury, revealing new nerve growth near tendon cells expressing NGF. It was found that NGF production not only played a critical role in nerve regeneration but also contributed to the improvement of tendon repair indicators. Neurovascular ingrowth was observed as an early response to Achilles tendon injury. Mechanistically, TrkA is required for NGF's beneficial actions in tendon repair. Treatment of tendon-injured mice with a small-molecule partial agonist of TrkA resulted in multiple benefits for tendon tissue repair. This treatment increased anti-inflammatory and pro-regenerative signaling of TGF-β, enhanced neurovascular response, and expanded tendon sheath progenitor cells. The study's findings were further supported by analyses of injured human tendon biopsy samples. *(Article Selection: Ru-Rong Ji, Ph.D. Image: Adobe Stock.)*

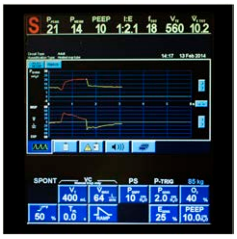
Take home message: In a mouse model of tendon injury, nerve innervation promotes tendon repair through NGF and TrkA receptor signaling.



Apixaban for stroke prevention in subclinical atrial fibrillation. N Engl J Med 2024; 390:107–17. PMID: 37952132.

Subclinical atrial fibrillation is increasingly recognized given the widespread use of personal electrocardiogram monitoring devices as well as pacemakers or defibrillators. Although it is associated with an increased risk of stroke, the impact of treatment with oral anticoagulation is unclear. Patients with subclinical atrial fibrillation lasting 6 min to 24 h and a CHA_2DS_2-VASc score of 3 or more were enrolled at 247 sites in 16 European and North American countries and randomized to either apixaban (5 or 2.5 mg twice daily) or aspirin (81 mg daily). The primary efficacy outcome, stroke, or systemic embolism was assessed by intention-to-treat; the primary safety outcome, major bleeding, was assessed per-protocol. Four thousand twelve patients (mean ± SD age, 76.8 ± 7.6 yr; CHA_2DS_2-VASc score 3.9 ± 1.1; 36.1% female) were enrolled. At a mean follow-up of 3.5 ± 1.8 yr, the primary efficacy outcome occurred in 55 patients in the apixaban group (0.78% per patient-year) *versus* 86 patients in the aspirin group (1.24% per patient-year) (hazard ratio, 0.63; 95% CI, 0.45 to 0.88; $P = 0.007$). The safety outcome occurred in 1.71% per patient-year in the apixaban group *versus* 0.94% per patient-year in the aspirin group (hazard ratio, 1.80; 95% CI, 1.26 to 2.57; $P = 0.001$), although fatal bleeding occurred in five *versus* eight patients, respectively. *(Article Selection: Martin J. London, M.D. Image: Adobe Stock.)*

Take home message: This multicenter, randomized, double-blind trial demonstrated a significant reduction in the primary efficacy outcome of stroke or systemic embolism with apixaban *versus* aspirins, although the primary safety outcome of major bleeding was higher.



Sigh ventilation in patients with trauma: The SiVent randomized clinical trial. JAMA 2023; 330:1982–90. PMID: 37877609.

Mechanical ventilation with constant tidal volumes may lead to ventilator-induced lung injury from alteration or depletion of surfactant. This pragmatic, parallel-group randomized control trial conducted at 15 U.S. academic trauma centers tested whether the addition of a sigh breath (plateau pressure raised to 35 cm H_2O, or to 40 cm H_2O for patients with body mass index greater than 35 kg/m^2) every 6 min increased ventilator-free days (primary outcome) compared to usual care for mechanically ventilated adult trauma patients at risk for acute respiratory distress syndrome. Between April 2016 and September 2022, 524 adult patients were randomized to usual care (n = 263) or sigh breathing (n = 261). Median ventilator-free days was 18.4 (interquartile range, 7.0 to 25.2) in patients with sigh breathing compared to 16.1 (interquartile range, 1.1 to 24.4) for usual care ($P = 0.080$); adjusted mean difference was 1.4 days (95% CI, –0.2 to 3.0). The prespecified secondary outcome of 28-day morality was 11.6% for sigh breathing *versus* 17.6% for usual care ($P = 0.050$). No differences in adverse event rates were observed with sigh breathing (30.9%) *versus* usual care (30.7%). *(Article Selection: William Tharp, M.D., Ph.D. Image: J. P. Rathmell.)*

Take home message: This randomized trial of sigh breathing did not increase the number of ventilator-free days compared to usual care in adult trauma patients at risk for acute respiratory distress syndrome.