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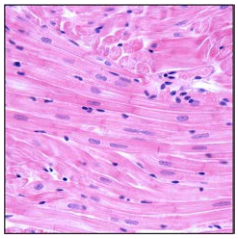
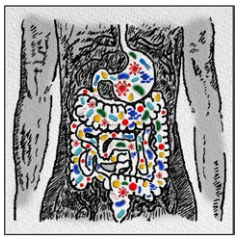
Martin J. London, M.D., Editor
Key Papers from the Most Recent Literature Relevant to Anesthesiologists



Fueling the heartbeat: Dynamic regulation of intracellular ATP during excitation-contraction coupling in ventricular myocytes. Proc Natl Acad Sci USA 2024; 121:e2318535121. PMID: 38865270.

The human cardiac muscle requires a vast amount of adenosine triphosphate (ATP) for the approximately 100,000 beats/day. This study investigated the impact of excitation-contraction coupling on the intracellular ATP concentration ([ATP]i) in cardiac myocytes. Using mouse myocytes with a genetically encoded ATP fluorescent reporter, beat-to-beat real-time [ATP]i was recorded. The experiments revealed the following findings, some at odds with long-standing concepts. First, [ATP]i showed rapid beat-to-beat fluctuations. Diastolic [ATP]i varied between 200 and 800 μM, *i.e.*, it was 10-fold lower than previously measured by nuclear magnetic resonance. Time-resolved measurements showed that diastolic ATP consumption by homeostatic cellular processes was significant, but the majority of ATP was used for excitation-contraction coupling. Due to the lower [ATP]i, 6 to 10% of the sarcolemmal K_{ATP} channels were open, reducing cellular Ca^{2+} influx and stabilizing the diastolic membrane potential. Increases in [ATP]i were closely associated with sarcoplasmic reticulum Ca^{2+} release and mediated by mitochondrial Ca^{2+} influx *via* the formation of mitochondrial-sarcoplasmic reticulum junctions, activating oxidative phosphorylation. Myocytes with selectively reduced mitochondrial mitofusin-2, which regulates inter-organelle Ca^{2+} cross talk and has been found reduced in heart failure patients, showed much smaller fluctuations of [ATP]i during excitation-contraction coupling. Activation of β-adrenergic receptors using isoproterenol lowered [ATP]i, emphasizing its heavy toll on cardiac energetics. *(Article Selection: Michael Zaugg, M.D., M.B.A. Image: Adobe Stock.)*

Take home message: These studies highlight the fluctuations of [ATP]i in cardiac myocytes during the excitation-contraction coupling, which has potential implications in myocardial health and disease.



Mining human microbiomes reveals an untapped source of peptide antibiotics. Cell 2024; 187:5453–67. PMID: 39163860.

Microbial resistance to antibiotics is an ever-present challenge in the management of infections and has traditionally been addressed by the reiterative synthesis of novel synthetic antibiotics. Antimicrobial peptide antibiotics are produced naturally by many microbial organisms and are an ancient form of host defense allowing microorganisms to compete for survival in their niche. Currently, a limited number of naturally occurring peptide antibiotics are in clinical use, including bacitracin, colistin, and polymyxin B. The human microbiome provides an untapped resource for identifying small peptides (less than 50 amino acids) with antimicrobial activities. The authors conducted a computational analysis of 1,773 previously assembled human metagenomes for small genetic open reading frames encoding small peptides. They identified 323 candidates with predicted antimicrobial properties predicted by software (AmPEP) based on distribution patterns of amino acid properties along the sequence. Seventy-eight of these peptide candidates were synthesized to test for toxicity against human cells and antibiotic activity in preclinical murine models of skin abscesses and deep thigh infections. More than half of the candidate peptides displayed antimicrobial activity at concentrations that were not toxic to human cells. Five of the most promising candidates were derived from diverse phyla from human oral, skin, and gut locations. *(Article Selection: Charles Emala, M.D. Image: Adobe Stock.)*

Take home message: The human microbiome is replete with microorganisms that naturally produce small peptide antibiotics to compete and survive within their niche. High-throughput computational modeling of these metagenomes allows for the identification of novel peptide antibiotics that have potential in clinical medicine, joining the small group of microbial peptides currently in clinical use (*i.e.*, bacitracin, colistin, and polymyxin B).

Intraoperative oxygen treatment, oxidative stress, and organ injury following cardiac surgery: A randomized clinical trial. JAMA Surg 2024; 159:1106–16. PMID: 39110454.

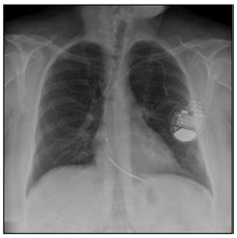
Liberal administration of oxygen (hyperoxia) is commonly used intraoperatively ostensibly to enhance patient safety, particularly during cardiac surgery, despite potential adverse effects on perioperative organ function related to oxidative stress. This assessor- and participant-blinded clinical trial at a single tertiary U.S. center randomized stable adult patients undergoing elective open cardiac surgery with cardiopulmonary bypass to either hyperoxia (1.00 fraction of inspired oxygen [F_{IO_2}]) or normoxia (minimum F_{IO_2} to maintain oxygen saturation 95 to 97%) (N = 100 in each group following exclusions; median [interquartile range] age, 66 [59 to 72] yr; 70% male). The primary mechanistic endpoint was oxidative damage (the sum of plasma concentrations of F2- isoprostanes and isofurans collected during and after surgery), and the primary clinical endpoint was change in serum creatinine concentration from baseline to postoperative day 2. Secondary outcomes included kidney, myocardial, and brain and respiratory injury markers and safety outcomes; 1-yr follow-up was performed. The primary mechanistic outcome was significantly higher in the hyperoxia group by 9.2 pg/ml (95% CI, 1.0 to 17.4; $P = 0.03$), whereas there was no difference in the clinical endpoint (median difference, 0.03; 95% CI, −0.04 to 0.10; $P = 0.45$). There were no differences in secondary outcomes and at 1 yr. *(Article Selection: Martin J. London, M.D. Image: J. P. Rathmell.)*

Take home message: This randomized blinded trial of hyperoxia *versus* normoxia in stable patients undergoing cardiac surgery with cardiopulmonary bypass noted increased intraoperative oxidative stress, which did not appear to influence a battery of clinical or 1-yr outcomes.

Povidone iodine vs chlorhexidine gluconate in alcohol for preoperative skin antisepsis: A randomized clinical trial. JAMA 2024; 332:541–9. PMID: 38884982.

The World Health Organization recommends chlorhexidine solutions over povidone iodine solutions for surgical skin preparation. This advice is based on meta-analyses suggesting that chlorhexidine achieves better skin antisepsis than does povidone iodine. However, there is a concerning emergence of resistance to chlorhexidine. A noninferiority multicenter cluster-randomized trial was done in which 3,360 surgical patients were enrolled (cardiac, n = 2,187 [65%]; abdominal, n = 1,173 [35%]). The primary outcome was surgical site infection within 30 days for abdominal surgery and within 1 yr for cardiac surgery. The assessors were blinded. Noninferiority was predefined if the lower Wald 95% CI limit lay within a margin of −2.5%. The chlorhexidine and povidone iodine groups were alike with regard to demographic data, type and duration of surgery, and timing of prophylactic antibiotics. There was no difference in the rate of surgical site infections between the chlorhexidine group (n = 97, 5.5%) and the povidone iodine group (n = 80, 5.1%). The 95% CI of the difference (−1.1 to 2.0%) did not include the prespecified margin. Thus, when used to prevent surgical site infections in cardiac and abdominal surgery patients, a solution of povidone iodine in alcohol was noninferior to a solution of chlorhexidine gluconate in alcohol. *(Article Selection: Jamie Sleigh, M.D. Image: Adobe Stock.)*

Take home message: This large, randomized study suggests that the purported superiority of chlorhexidine over povidone iodine for skin preparation may be overstated.



Periprocedural management and multidisciplinary care pathways for patients with cardiac implantable electronic devices: A scientific statement from the American Heart Association. Circulation 2024; 150:e183–96. PMID: 38984417.

Periprocedural management of cardiac implantable electric devices (CIEDs) is challenging given the variety of devices currently in use. The American Heart Association's guideline recommends preoperative practices, including identifying the type of device (transvenous or leadless pacemaker; transvenous, subcutaneous, or extravascular defibrillator; cardiac resynchronization device; or implantable cardiac monitor); location of the device (right or left infraclavicular, intracardiac, abdominal, or midaxillary region); indication for placement (sick sinus syndrome, atrioventricular block, prevention of sudden death, ventricular tachycardia or fibrillation); pertinent history (heart failure, cause of cardiomyopathy); and whether electromagnetic interference is a possibility. Key information that needs to be obtained preoperatively are battery life, programmed pacing mode, magnet response, magnetic resonance imaging (MRI) compatibility, underlying rhythm, and pacing dependency. The guideline highlights intraoperative risk mitigation strategies such as keeping the current path away from the CIED by placing the return electrode on the contralateral lower limb; using bipolar electrosurgery whenever possible; minimizing monopolar electrosurgery to 5-s bursts or shorter; and avoiding whole-body return electrodes. The guideline provides specific information on the magnet response of various devices by type, manufacturer, and models. Different strategies and workflows for successful periprocedural management of CIEDs are presented. The guideline includes user-friendly graphics. *(Article Selection: BobbieJean Sweitzer, M.D. Image: J. P. Rathmell.)*

Take home message: Periprocedural management of CIEDs includes patient-specific factors such as pacemaker dependency and device location; device-specific factors such as device type, settings, and function; and procedure-specific factors including the planned surgery, electrocautery, and positioning.

Neural circuit basis of placebo pain relief. Nature 2024; 632:1092–100. PMID: 39048016.

The placebo effect exerts an enormous role for pain, being greater than the intrinsic effects of most therapies. Yet, the neural basis remains unclear. A 7-day placebo analgesia conditioning (PAC) assay was developed, resulting in anticipatory pain-relief expectations in mice. In the conditioning phase, the floor of one chamber was set to a painful 48°C while in the other it was 30°C, conditioning animals to expect pain relief when leaving chamber 1 and entering chamber 2. Conditioned but not unconditioned mice developed a preference for chamber 2 even when both floor temperatures were 30°C. When subjected to multifarious painful stimuli, conditioned but not unconditioned mice displayed less-nocifensive behaviors inside but not outside the PAC apparatus. The analgesic effect during posttesting, but not conditioning, was abolished by naloxone, simulating the placebo effect in humans. Using an adeno-associated virus injected into the rostral anterior cingulate cortex (rACC), *in vivo* calcium imaging of neural activity, and electrophysiologic recordings, this study shows that expectations of analgesia boosted the activity of rACC→pontine nuclei neural pathways while disruption of this pathway abolished placebo analgesia. Based on Purkinje cell activity patterns resembling rACC→pontine nucleus neurons, the results suggest a role for the cerebellum in cognitively reflexive pain inhibition. *(Article Selection: Steven P. Cohen, M.D. Image: Adobe Stock.)*

Take home message: Given the outsized role that the placebo effect plays in pain and co-existing psychiatric conditions, understanding the physiologic basis may provide targets for future drugs and therapies such as neurostimulation in order to improve pain relief by placebo and nonplacebo mechanisms.

Continuation vs discontinuation of renin-angiotensin system inhibitors before major noncardiac surgery: The Stop-or-Not randomized clinical trial. JAMA 2024; 332:970–8. PMID: 39212270.

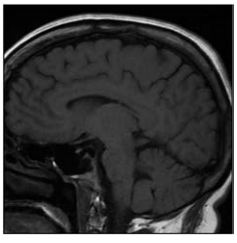
The impact of preoperative administration of renin-angiotensin system inhibitors (RASIs; angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) on intra- and postoperative outcomes remains a controversial topic given a lack of large-scale randomized studies. This large clinical trial (40 French centers; 2018 to 2023) randomized patients treated with a RASI for at least 3 months scheduled for major noncardiac surgery to either continuation until the day of surgery (n = 1,107) or to discontinuation 48 h before surgery (n = 1,115). The primary outcome was a composite of all-cause mortality and major postoperative complications by 28 days after surgery. Secondary outcomes included intraoperative, acute kidney injury; postoperative organ failure; and hospital/intensive care unit lengths of stay by 28 days after surgery. Of 2,222 patients (mean ± SD age, 67 ± 10 yr; 65% male), 46% were receiving angiotensin-converting enzyme inhibitors and 54% angiotensin receptor blockers. There was no significant difference in the primary outcome between the continuation and discontinuation groups (22% in each; risk ratio, 1.02 [95% CI, 0.87 to 1.19]; $P = 0.85$) nor in the prevalence of intraoperative hypotension (41% discontinuation *vs.* 54% continuation; risk ratio, 1.31 [95% CI, 1.19 to 1.44]). Likewise, no differences occurred in other study outcomes. *(Article Selection: Martin J. London, M.D. Image: Adobe Stock.)*

Take home message: This large, multicenter, randomized trial of continuation *versus* discontinuation of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in patients undergoing major noncardiac surgery did not demonstrate significant differences between groups in either mortality, major postoperative complications by 28 days, or intraoperative hypotension.

Inhibition of IL-11 signalling extends mammalian healthspan and lifespan. Nature 2024; 632:157–65. PMID: 39020175.

The cell signaling pathways ERK, AMPK, and mTORC1 are well-known lifespan regulators in different species. In aging animals, these pathways play a crucial role in terms of activating hallmarks of aging such as, for example, mitochondrial dysfunction or cellular senescence. Conversely, interference with these pathways such as inhibition of mTOR is known to increase lifespan in rodents. An important aspect of aging is immunosenescence with increased activation of interleukin (IL)-6 and therefore increased inflammation, known as a hallmark of aging. This study tested the hypothesis of whether IL-11, a proinflammatory and also profibrotic cytokine of the IL-6 family, promotes age-associated pathologies and reduces lifespan in mice. In aging mice, IL-11 was upregulated in various tissues (liver, visceral gonadal white adipose tissue, and skeletal muscle), propagating thereby aging pathologies through the ERK-AMPK-mTORC1 axis interaction. Deletion of IL-11 or its receptor IL-11ra1 provided protection against metabolic decline, frailty, and multi-morbidity in aging animals, thereby increasing lifespan; genetic deletion of IL-11 led to an extension of life by 25% on average in both sexes. In anti-IL-11, blocking studies in 75-week-old mice metabolism and muscle function were improved, with a reduction of frailty and an overall extension of the median lifespan of 22.5% and 25% in male and female animals, respectively. *(Article Selection: Beatrice Beck-Schimmer, M.D. Image: Adobe Stock.)*

Take home message: This murine study shows promising results of blocking the proinflammatory cytokine IL-11 in older mice, positively affecting age-related decline and increasing lifespan in both male and female animals. The role of an anti-IL-11 therapy currently being tested in clinical trials for the treatment of fibrotic lung disease on aging in humans is not yet known.



Molecular mechanism of ligand gating and opening of NMDA receptor. Nature 2024; 632:209–17. PMID: 39085540.

Glutamate-induced excitatory synaptic transmission, vital for brain function, is partly mediated by *N*-methyl-D-aspartate receptors (NMDARs), which are critical in synaptic plasticity and learning and memory. NMDARs are ligand-gated ion channels composed of GluN1 and GluN2 (2A-2D) subunits. Their dysfunction is linked to diseases like dementia, stroke, and chronic pain. GluN2B is upregulated in chronic pain and contributes to its pathology. Unlike other glutamate receptors, NMDARs require both ligand binding and membrane depolarization to remove the Mg^{2+} block and open the channel. The authors used electron cryomicroscopy to reveal the structure of the GluN1-GluN2B NMDAR in its open state, bound to a positive allosteric modulator. This interaction alters the symmetry of the transmembrane domain. Interestingly, binding glycine or glutamate alone induces distinct GluN1-GluN2B dimer arrangements but does not trigger channel opening. The research also sheds light on the unique dual-agonist requirement of NMDAR, explaining why glycine or D-serine is necessary to prime the receptor as positive allosteric modulator for glutamate-induced activation. This mechanism distinguishes NMDAR from other ionotropic glutamate receptors. The study also explains how ketamine binds to NMDAR. *(Article Selection: Ru-Rong Ji, Ph.D. Image: J. P. Rathmell.)*

Take home message: The study uncovers a key mechanism in NMDAR gating, offering insights for developing pharmacological strategies to manage chronic pain.