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

Restrictive or liberal transfusion strategy in myocardial infarction and anemia. N Engl J Med 2023 Nov 11 [Epub ahead of print]. PMID: 37952133.

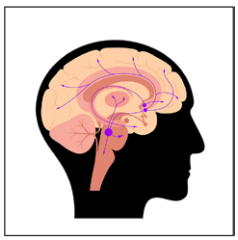
It is widely recommended to restrict transfusions only when hemoglobin concentrations are less than 7 to 8 g/dL. This has been questioned with acute myocardial infarction (MI). In this multicenter trial (144 sites internationally, 2017 to 2023), patients with MI and hemoglobin less than 10 g/dL were randomized to a restrictive transfusion strategy (hemoglobin less than 7 to 8 g/dL cutoff for transfusion) or a liberal transfusion strategy (hemoglobin less than 10 g/dL cutoff for transfusion). The primary outcome was recurrent MI or death at 30 days. In 3,504 randomized patients, the mean ± SD of red cell units transfused was 0.7 ± 1.6 in the restrictive group and 2.5 ± 2.3 in the liberal group. Mean hemoglobin was 1.3 to 1.6 g/dL lower in the restrictive group than in the liberal group 1 to 3 days after randomization. A primary-outcome event occurred in 17% of the restrictive group *versus* 15% of the liberal group (risk ratio modeled with multiple imputation for incomplete follow-up, 1.15; 95% CI, 0.99 to 1.34; $P = 0.07$). Death occurred in 10% of the restrictive group *versus* 8% in the liberal group (risk ratio, 1.19; 95% CI, 0.96 to 1.47). MI occurred in 9% *versus* 7% of patients, respectively (risk ratio, 1.19; 95% CI, 0.94 to 1.49). *(Article Selection: BobbieJean Sweitzer, M.D. Image: J. P. Rathmell.)*

Take home message: In this international multicenter randomized trial, the risk of recurrent MI or death at 30 days was not significantly reduced with a liberal *versus* restrictive transfusion strategy in patients with acute MI and anemia.

Primary care physician follow-up and 30-day readmission after emergency general surgery admissions. JAMA Surg 2023: e234534. PMID: 37755816.

Although evidence suggests that primary care physician follow-up may reduce readmissions in hospitalized patients for medical conditions, its implication for patients undergoing an emergency general surgery condition is uncertain. This cohort study evaluated the association between primary care physician follow-up and 30-day readmission rates after hospital discharge for an emergency general surgery condition. Data from the Centers for Medicare & Medicaid Services Beneficiary for 345,360 Medicare beneficiaries (mean ± SD age, 74.4 ± 12.0 yr; females 54%) hospitalized with an emergency general surgery condition managed operatively or nonoperatively (2016 to 2018) was used to evaluate follow-up within 30 days after hospital discharge and the primary outcome of readmission within 30 days using an inverse probability weighted regression model. The secondary outcome was readmission within 30 days after discharge stratified by treatment type (operative *vs.* nonoperative treatment). Forty-five percent had a follow-up primary care physician visit, 31% received operative treatment, and 69% received nonoperative treatment; 18% were readmitted within 30 days after discharge. Patients with primary care physician follow-up had 67% lower odds of readmission (adjusted odds ratio, 0.33; 95% CI, 0.31 to 0.36) compared to those without. Patients treated operatively and having follow-up had similar associations with reduced odds of readmission than those treated nonoperatively (adjusted odds ratio, 0.21; 95% CI, 0.18 to 0.25 *vs.* 0.36; 95% CI, 0.34 to 0.39). *(Article Selection: Martin J. London, M.D. Image: Adobe Stock.)*

Take home message: This cohort study suggests that primary care follow-up within 30 days after discharge for an emergency general surgery condition is associated with a significant reduction in the adjusted odds of 30-day readmission for patients undergoing either surgical or nonsurgical intervention.



A cholinergic circuit that relieves pain despite opioid tolerance. Neuron 2023; 111:3414–34.e15. PMID: 37734381

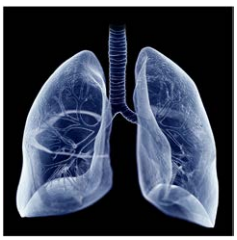
The descending pain pathways originating from the ventrolateral periaqueductal gray (vlPAG) control pain transmission through the endogenous opioid system. Cholinergic terminals have also been described in the vlPAG, but their function is still unknown. This study evaluated the role of those cholinergic terminals in pain regulation. Using innovative molecular, biochemical, and behavioral approaches, by unraveling the cholinergic circuitry and receptor mechanisms that alleviate pain despite opioid tolerance reporting, it was found that acetylcholine release decreased during acute and chronic inflammatory pain. Acetylcholine in the vlPAG was sourced from projections from the pedunculopontine tegmental nucleus (PPTg), and its stimulation produced thermal analgesia in laboratory animals implicating α7 nicotinic acetylcholine receptors (α7 nAChR). In animals with chronic inflammatory, this stimulation opposed hyperalgesia and cold allodynia. Inhibiting μ opioid receptor–expressing vlPAG neuron or stimulating PPTg-vlPAG projections produced analgesia in both opioid-naive and opioid-tolerant animals, demonstrating conserved analgesic potency of the cholinergic circuitry even after opioid tolerance. In addition, α7 nAChR activation inhibited GABA interneurons leading to the disinhibition of descending pain pathway and pain relief. The results were recapitulated by administering the α7 nAChR agonist, EVP-6,124 without producing tolerance, rewarding effects, or withdrawal symptoms. *(Article Selection: Cyril Rivat, Ph.D. Image: Adobe Stock.)*

Take home message: Cholinergic circuitry-expressing α7 nAChR controls descending pain inhibitory pathways to promote analgesia. Targeting α7 nAChR may represent an innovative strategy for the management of chronic pain with limited side effects.

Remote ischemic conditioning for acute stroke: The RESIST randomized clinical trial. JAMA 2023; 330:1236–46. PMID: 37787796.

This randomized clinical trial was performed between March 2018 and November 2022 to investigate whether remote ischemic conditioning combined in the preclinical and in-hospital setting provides protection in acute stroke. The primary outcome was defined as improved functionality at 90 days, assessed with the modified Rankin Scale score ranging from 0 (no symptoms) to 6 (death). Patients from four Danish stroke centers were included in the study with prehospital stroke symptoms for less than 4 h. In the intervention arm, remote ischemic conditioning was performed on one upper extremity (cuff pressure at least 200 mmHg; sham group: 20 mmHg) with five cycles of 5 min cuff inflation/5 min deflation for the first time in the ambulance and 6 h later in the hospital. The median age of the enrolled 1,433 patients with consent was 71 yr (591 women, 41%). Seven hundred thirty-seven (82%) patients were diagnosed with an ischemic condition and 165 (18%) with a hemorrhagic stroke. No significant difference in functional outcome was found in the remote ischemic conditioning group (n = 436) with a median modified Rankin Scale score at 90 days of 2 (interquartile range, 1 to 3) in remote ischemic conditioning and 1 (interquartile range, 1 to 3) in sham patients (n = 466) (odds ratio, 0.95; 95% CI, 0.75 to 1.20, $P = 0.67$). The number of serious adverse events in both groups was comparable. *(Article Selection: Beatrice Beck-Schimmer, M.D. Image: Adobe Stock.)*

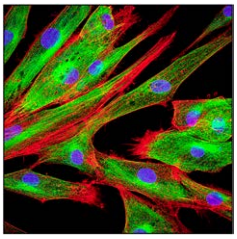
Take home message: This multicenter randomized clinical trial found no significant difference in functional outcome at 90 days after ischemic or hemorrhagic stroke with a remote ischemic conditioning intervention performed in the preclinical as well as in the in-hospital setting.



Lung microbiome on admission in critically ill patients with acute bacterial and viral pneumonia. Sci Rep 2023; 13: 17724. PMID: 37853062.

The lung microbiome is composed of the bacterial, viral, and fungal populations found in the lower respiratory tract and is the therapeutic target for pneumonia, but reliable sampling often impedes diagnosis of the pathogenic agent by standard microbiologic methods. In this single-center (Donostia University Hospital, Spain), cross-sectional study, metagenomic next-generation sequencing of 16S rRNA was applied to protected mini-bronchoalveolar lavages collected between 2019 and 2021 from 31 intubated intensive care unit patients with severe community-acquired bacterial (n = 14) or viral (n = 17) pneumonia and six healthy surgical patients to delineate the composition and diversity of the lung bacterial microbiome. The lung microbiomes from the surgical controls were diverse, composed of 21 genera from 6 to 13 phyla, including species of Microbacterium (3%), Propionobacterium (5%), Corynebacterium (5%), Streptococcus (4%), Staphylococcus (3%), and Enterococcus (6%). Lung microbiomes from patients with viral pneumonia had similar diversity and composition to controls, whereas those from patients with pneumococcal pneumonia were less diverse, composed primarily of Streptococcus (44%) and Haemophilus (18%). Those from patients with non-pneumococcal pneumonia showed predominance of the primary pathogenic bacteria identified by standard microbiologic methods. *(Article Selection: William G. Tharp, M.D., Ph.D. Image: Adobe Stock.)*

Take home message: Metagenomic sequencing of the lung microbiome is an emerging diagnostic tool for bacterial pneumonia.



Fibroblasts in heart scar tissue directly regulate cardiac excitability and arrhythmogenesis. Science 2023; 381:1480–7. PMID: 37769108.

While cardiac fibroblasts are recognized to be important in extracellular matrix production and cardiac remodeling, electrical coupling between fibroblasts, and cardiac myocytes has been also reported recently, definitive *in vivo* evidence has been lacking. In this study, an optogenetic transgenic mouse was engineered that selectively expressed the light-sensitive channelrhodopsin 2 (a nonselective cationic channel), which enabled the researchers to depolarize fibroblast membranes by illumination with blue light. Blue light illumination of scar fibroblasts in mice subjected to coronary occlusion and myocardial infarction demonstrated electrical coupling increasing the heart rate from 360 beats/min to 420 beats/min with 1:1 concordance. When optical pacing ceased, 40% of the hearts (10 days after myocardial infarction) did not return to sinus rhythm and exhibited ectopic beats and atrioventricular blocks, suggesting that fibroblast-myocyte coupling promotes arrhythmia *in vivo*. Mechanistic *in vitro* experiments using fibroblasts deficient in connexins (CX40, CX43, CX45, pannexin 1) cocultured with myocytes suggest that these membrane channel proteins are not necessary for this heterocellular coupling, which could be corroborated by computational simulations showing that cell-to-cell transfer of electrical activity is also possible through the extracellular space by rapid changes of ionic channels in a junctional cleft ("ephaptic or electrical field coupling"). *(Article Selection: Michael Zaugg, M.D., M.B.A. Image: Adobe Stock.)*

Take home message: These experimental findings have potential clinical implications, suggesting that infarct-related fibroblast accumulation and remodeling may create fresh coupling foci with the potential of life-threatening arrhythmogenesis.

Behavioral and brain responses to verbal stimuli reveal transient periods of cognitive integration of the external world during sleep. Nat Neurosci 2023; 26:1981–93. PMID:37828228.

It is widely believed that a characteristic of the state of sleep is perceptual disconnection from the environment. Although there is some electrophysiologic evidence for high-level semantic sensory processing during sleep, it is unclear whether this involves consciousness. Twenty-seven narcoleptic patients (in whom lucid dreaming is common) and 21 healthy volunteers were studied. Participants were instructed to frown or smile three times in response to different stimuli (real words *versus* pseudo-words), presented while they were having daytime naps. To reduce the obfuscating factor of sleep hypotonia, the responses were detected with facial electromyography. Except during deep slow-wave (N3) sleep in the healthy volunteer group, motor responses to the auditory stimuli—*versus* no stimuli periods—were seen in all sleep stages (N2 sleep: healthy volunteers [5% *vs.* 2%, $P < 0.0001$]; narcoleptic patients [20% *vs.* 2%, $P < 0.0001$]). Responses were not associated with any electroencephalographic (EEG) signs of waking. The probability of an accurate response was increased if the prestimulus EEG showed increased complexity and faster oscillations, which are signs of higher cognitive state. *(Article Selection: Jamie Sleigh, M.D. Image: Adobe Stock.)*

Take home message: Except during deep slow-wave sleep, sleeping humans have transient periods when they can comprehend and respond to sensory input from the external world.

Early and empirical high-dose cryoprecipitate for hemorrhage after traumatic injury: The CRYOSTAT-2 randomized clinical trial. JAMA 2023; 330:1882–91. PMID: 37824155.

Fibrinogen depletion is present in many patients sustaining major trauma. The timing, type, and dosing of fibrinogen repletion in this setting is controversial, with most being given relatively late following hemorrhage. This randomized, open-label, international, multicenter trial (26 U.K. and U.S. centers; 2017 to 2021) analyzed 1,531 injured adults who required activation of the center's major transfusion protocol and who had at least one systolic blood pressure less than 90 mmHg and had received at least 1 unit of blood component to either standard care (local center protocol; N = 771) or administration of cryoprecipitate (6 g fibrinogen) within 90 min of randomization and 3 h of injury (in addition to standard care; N = 760). The primary outcome was all-cause mortality at 28 days by intention-to-treat. The median (interquartile range) age of participants was 39 (26 to 55) yr, 1,251 (79%) were male, median (interquartile range) Injury Severity Score was 29 (18 to 43), 36% had penetrating injury, and 33% had systolic blood pressure less than 90 mm Hg at hospital arrival. There was no difference between groups in the primary outcome (26.1% standard *vs.* 25.3% cryoprecipitate; odds ratio, 0.96 [95% CI, 0.75 to 1.23]; $P = 0.74$). Likewise, no differences were noted in safety or thrombotic outcomes (13% *vs.* 13%). *(Article Selection: Martin J. London, M.D. Image: J. P. Rathmell.)*

Take home message: This multicenter, randomized trial failed to show any difference in all-cause mortality at 28 days in trauma patients receiving early cryoprecipitate in addition to standard care *versus* standard care alone.

Short-chain fatty acid, butyrate prevents morphine- and paclitaxel-induced nociceptive hypersensitivity. Sci Rep 2023; 13:17805. PMID: 37853033.

Nociceptive hypersensitivity is a side effect of chronic administration of opioids and some chemotherapeutic agents such as paclitaxel, but the mechanisms are poorly understood. Previous studies suggest that the gut microbiome plays a role in the physiologic and pharmacologic effects of repeated morphine administration and chemotherapeutic-induced mechanical hyperalgesia. Short-chain fatty acids, including butyrate, are products of gut bacteria and have diverse physiologic effects outside of the intestinal tract. In the current mouse studies, oral butyrate reduced thermal hyperalgesia induced by chronic morphine and reduced cold allodynia induced by paclitaxel. Enhanced neuronal excitability in dorsal root ganglia isolated from mice chronically treated with morphine or paclitaxel was reduced compared to isolated dorsal root ganglia of mice concurrently treated with butyrate. To investigate the role for gut microbiota in these findings, colonic segments were incubated *ex vivo* overnight with morphine and the resulting conditioned media was used to treat naive dorsal root ganglia from control mice. These naive dorsal root ganglia demonstrated enhanced neuronal activity not seen in dorsal root ganglia treated with conditioned media from colonic segments from mice concurrently treated with morphine and butyrate. In contrast, dorsal root ganglia incubated *ex vivo* with morphine demonstrated enhanced neuronal excitability not attenuated by concurrent *ex vivo* butyrate. *(Article Selection: Charles Emala, M.D. Image: Adobe Stock.)*

Take home message: Oral butyrate reduces chronic morphine- or paclitaxel-induced neuronal hypersensitivity through an indirect mechanism involving the gut microbiome, suggesting potential prophylactic therapeutic value of oral butyrate in the nociceptive hypersensitivity induced by their chronic use.