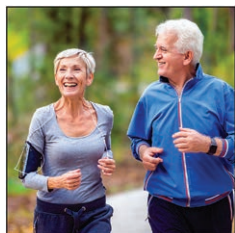


# SCIENCE, MEDICINE, AND THE ANESTHESIOLOGIST

# ANESTHESIOLOGY

Deborah J. Culley, M.D., Editor

Key Papers from the Most Recent Literature Relevant to Anesthesiologists



## Physical activity trajectories and mortality: Population based cohort study. *BMJ* 2019; 365:l2323.

Relatively few studies have quantified the long-term effects of physical activity on population health. This study examined baseline and long-term trajectories of physical activity on mortality from cardiovascular disease, cancer, and all causes. The study followed 14,599 adults in the United Kingdom for lifestyle factors for up to 11 yr, then for mortality for a median of 13 yr. The authors used questionnaires to measure physical activity energy expenditure, calibrated against combined movement and heart rate monitoring. They found that 3,148 deaths occurred during 171,277 person years of follow-up and that long-term increases in physical activity were inversely associated with mortality, regardless of baseline activity levels. Being inactive at

baseline and working up to 150 min per week of moderate intensity physical activity over 5 yr was associated with a decrease in the risk of all-cause mortality (hazard ratio 0.76; 95% CI, 0.71 to 0.82), cardiovascular disease mortality (hazard ratio 0.71; 95% CI, 0.62 to 0.82), and cancer mortality (hazard ratio 0.89; 95% CI, 0.79 to 0.99). The authors concluded that adhering to minimum physical activity recommendations would potentially prevent 46% of deaths associated with physical inactivity at the population level. (Article Selection: Beatrice Beck-Schimmer. Image: ©gettyimages.)

**Take home message:** Older adults can gain substantial longevity benefits by becoming more physically active during mid- to late life, irrespective of past physical activity levels and established risk factors.

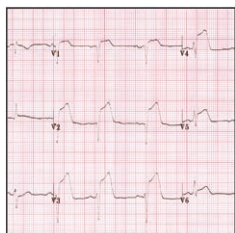


## Cluster-randomized trial of opiate-sparing analgesia after discharge from elective hip surgery. *J Am Coll Surg* 2019 Jun 5 [Epub ahead of print].

Postoperative pain relief with opioids after hip replacement is common. This study examined whether multimodal analgesia and conservative opiate prescribing postdischarge were effective for pain management. Patients undergoing hip replacement (N = 235) were randomized to receive one of three discharge pain regimens: (1) scheduled-dose multimodal analgesia with a minimal opiate supply (acetaminophen, meloxicam, and gabapentin); (2) scheduled-dose multimodal analgesia with a traditional opiate supply; or (3) a traditional opiate regimen alone. Five participating surgeons alternated in a randomized sequence between interventions. Primary outcomes were daily Visual Analogue Scale pain scores and opiate utilization for

30 days. Patients in group A (Coeff  $-0.81$ ,  $P = 0.003$ ) and group B (Coeff  $-0.61$ ,  $P = 0.021$ ) had less pain than those in group C. Duration of opiate use was significantly shorter for group A (1.1 weeks) and group B (1.4 weeks) compared with group C (2.6 weeks). The authors concluded that both multimodal regimens improved satisfaction and sleep without harming hip function or increasing adverse events. (Article Selection: J. David Clark. Image: J. P. Rathmell.)

**Take home message:** Multimodal analgesia with minimal opioids improved pain control while significantly decreasing opiate utilization and opioid-related side effects.

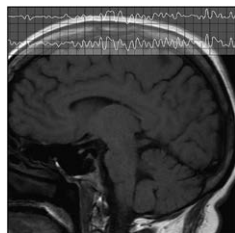


## Examining risk: A systematic review of perioperative cardiac risk prediction indices. *Mayo Clin Proc* 2019 Jun 13 [Epub ahead of print].

Risk indices are used to assist clinicians in identifying the risk of cardiac events in the perioperative period. However, the different indices can yield divergent risk estimates, causing uncertainty about the advice provided to patients and colleagues. This systematic review evaluated 11 cardiac risk indices in 2,910,297 adult patients. The authors found that studies varied in factors including size, population, quality, accuracy, and clinical usefulness. They also found that congestive heart failure, type of surgery, creatinine, diabetes, history of stroke or transient ischemic attack, and emergency surgery were the risk factors most likely to be highly predictive of adverse cardiac events as was American Society of Anesthesiologists physical status clas-

sification. The authors recommend using a National Surgery Quality Improvement Program–based risk index to estimate the risk of the most drastic cardiac outcomes in conjunction with an index that predicts a broader range of cardiac outcomes, even if its accuracy is lower. (Article Selection: Martin J. London. Image: J. P. Rathmell.)

**Take home message:** Cardiac risk indices often have either high accuracy for predicting a narrow range of cardiac outcomes or lower accuracy for predicting a broader range of cardiac outcomes. It may be most useful to use one index of each type to accurately identify cardiac risk.



### A common neuroendocrine substrate for diverse general anesthetics and sleep. *Neuron* 2019; 102:1053–65.

It remains unclear whether anesthetic agents and sleep share any common neural pathways. This study used Fos staining, *ex vivo* brain slice recording, and *in vivo* multichannel electrophysiology in mice to discover a core group of hypothalamic neurons in and near the supraoptic nucleus that may be related to sleep and anesthesia. These neurons consisted primarily of neuroendocrine cells, which are known to be affected by multiple general anesthetic agents. The authors found that chemogenetic or brief optogenetic activations of these anesthesia-activated neurons strongly promoted slow-wave sleep and potentiated general anesthesia and that conditional ablation or inhibition of these anesthesia-activated neurons led to shorter bouts of slow-wave sleep but did not affect the number of slow-wave sleep sessions. In contrast, conditional ablation or inhibition of anesthesia-activated neurons decreased the number but not the length of random eye movement sleep sessions suggesting differential effects of these neurons on slow wave and random eye movement sleep. (Article Selection: Evan D. Kharasch. Image: J. P. Rathmell.)

**Take home message:** These findings identify a common neural substrate underlying diverse drugs and natural sleep and reveal a crucial role of the neuroendocrine system in regulating global brain states.



### GINA 2019: A fundamental change in asthma management: Treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents. *Eur Respir J* 2019; 53:1901046.

Each year, the Global Initiative for Asthma publishes guidelines for asthma prevention and management through a coordinated worldwide effort. The 2019 update, published in April, was perhaps the most fundamental change in asthma management in 30 yr. The new guideline states that, for safety, "[Global Initiative for Asthma] no longer recommends treatment of asthma in adolescents and adults with short-acting  $\beta_2$ -agonists alone. Instead, to reduce their risk of serious exacerbations, all adults and adolescents with asthma should receive either symptom-driven (in mild asthma) or daily inhaled corticosteroid-containing treatment." The update follows a decade-long effort by the Global Initiative for Asthma to explore the risks and consequences of the widespread use of short-acting  $\beta_2$ -agonists only as an initial management strategy. The Global Initiative for Asthma wanted to obtain evidence about effective treatment options for mild asthma while providing consistent messaging for patients and clinicians across the spectrum of asthma severity. This article provides the evidence and rationale for these changes. (Article Selection: Beatrice Beck-Schimmer. Image: J. P. Rathmell.)

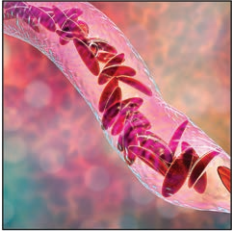
**Take home message:** This article explains the new Global Initiative for Asthma recommendations and summarizes the evidence and rationale for the changes.



### Drug-eluting or bare-metal stents for percutaneous coronary intervention: A systematic review and individual patient data meta-analysis of randomised clinical trials. *Lancet* 2019; 393:2503–10.

In head-to-head noninferiority trials, new-generation drug-eluting stents have generally had similar efficacy and safety when compared to early-generation drug-eluting stents. What's less clear is the safety profile of these stents when compared to bare-metal stents. This meta-analysis compared postimplantation outcomes of drug-eluting and bare-metal stents in patients undergoing percutaneous coronary intervention. The primary outcome was the composite of cardiac death or myocardial infarction. The authors analyzed 20 randomized trials including 26,616 patients. They found that patients with drug-eluting stents were less likely to experience the primary outcome of composite cardiac death or myocardial infarction (hazard ratio 0.84; 95% CI, 0.78 to 0.90;  $P < 0.001$ ). This was primarily due to a reduced risk of myocardial infarction (hazard ratio 0.79; 95% CI, 0.71 to 0.88;  $P < 0.001$ ) and a possible but nonsignificant decrease in cardiac mortality (hazard ratio 0.89; 95% CI, 0.78 to 1.01;  $P = 0.075$ ). There was no effect on all-cause death rates. (Article Selection: Martin J. London. Image: J. P. Rathmell.)

**Take home message:** Drug-eluting stents are associated with a lower risk of myocardial infarction and death in the first year after implantation when compared to bare metal stents.



### Management of chronic pain in adults living with sickle cell disease in the era of the opioid epidemic: A qualitative study. *JAMA Netw Open* 2019; 2:e194410.

Sickle cell disease is marked by acute and episodic vasoocclusive pain that can progress to chronic pain with disabling exacerbations that have traditionally been managed with opioids. This study explored how the current opioid epidemic and the Centers for Disease Control and Prevention opioid prescribing guidelines have affected pain management in patients with sickle cell disease. This qualitative study was based on hour-long semistructured phone interviews with adult sickle cell patients. Interviews focused on patient perspectives of whether their pain management regimen has changed since the introduction of the new guidelines. All of the 15 participants were African American and most ( $n = 13$ ) were female, with a median age of 32 yr. Participants reported increased challenges with obtaining opioids, including more restrictive prescribing and monitoring, and reduced opioid availability in pharmacies. The participants also sensed greater stigma and believed that the intense focus on reducing opioid use hampered their medical care and led to an associated interest in alternative pain management therapies including cannabis. (Article Selection: J. David Clark. Image: ©gettyimages.)

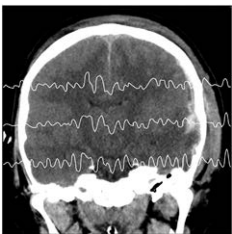
**Take home message:** Restrictive opioid prescribing resulting from the opioid epidemic may have negatively affected patients with sickle cell disease.



### Association of nonmedical prescription opioid use with subsequent heroin use initiation in adolescents. *JAMA Pediatr* 2019 Jul 8 [Epub ahead of print].

Nonmedical prescription opioid use among teens is known to occur but whether it is associated with subsequent heroin use is unclear. This prospective longitudinal cohort study administered eight surveys to students in the ninth through twelfth grade in 10 high schools in Los Angeles, California, to assess nonmedical prescription opioid and heroin use among adolescents that had not previously used heroin. The main outcome was self-reported heroin use at any point after the first survey. Among the 3,298 participants, the prevalence of new nonmedical prescription opioid use was 2 to 3%. Seventy of the 3,298 students (2%) initiated heroin use. Among those students, multivariate analysis identified that nonmedical prescription opioid use (hazard ratio 2.09; 95% CI, 1.14 to 3.83;  $P = 0.02$ ), alcohol use (hazard ratio 1.76; 95% CI, 1.04 to 2.98;  $P = 0.04$ ), and other substance use (hazard ratio 2.20; 95% CI, 1.45 to 3.33;  $P < 0.001$ ) within the previous 6 months was associated with subsequent heroin use initiation. Similarly, nonmedical prescription opioid use (hazard ratio 3.18; 95% CI, 1.68 to 6.02;  $P < 0.001$ ), cannabis use (hazard ratio 1.68; 95% CI, 1.02 to 2.82;  $P = 0.04$ ), and alcohol use (hazard ratio 2.04; 95% CI, 1.10 to 3.92;  $P = 0.03$ ) within the previous 30 days was associated with subsequent heroin use initiation. (Article Selection: Laszlo Vutskits. Image: J. P. Rathmell.)

**Take home message:** Nonmedical prescription opioid use in adolescents may lead to subsequent heroin use. Further research is needed to determine whether this association is causal.



### Detection of brain activation in unresponsive patients with acute brain injury. *N Engl J Med* 2019; 380:2497–505.

Electroencephalography can detect brain activation in response to spoken motor commands in clinically unresponsive patients. However, it is not known how common this phenomenon is, nor whether it is prognostic. This single-center study prospectively followed patients with acute brain injury who were unresponsive to spoken commands, some of whom could localize painful stimuli or track visual stimuli. The investigators applied machine learning to electroencephalography recordings to detect brain activation when patients were told to move their hands. The authors found that 15% of patients (16 of 104) had detectable brain activation at a median of 4 days after injury. Eight of these patients and 23 of the remaining 88

patients (26%) without brain activation were ultimately able to follow commands before discharge. At 12 months, nearly half of the patients with brain activation (7 of 16, 44%) had a Glasgow Outcome Scale of 4 or higher and thus were able to function independently. Only 14% of patients without brain activation (12 of 84 patients) were able to do so (odds ratio 5; 95% CI, 1 to 17). (Article Selection: Martin J. London. Image: J. P. Rathmell.)

**Take home message:** Brain activation in response to a request to follow a command may be predictive of long-term neurologic outcomes in patients that do not physically respond to a request to follow a command.

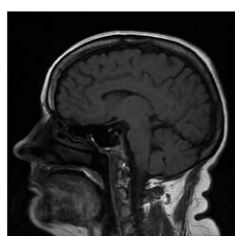


### Intraosseous basivertebral nerve ablation for the treatment of chronic low back pain: A prospective randomized double-blind sham-controlled multicenter study. *Eur Spine J* 2018; 27:1146–56.

Degenerated or damaged vertebral endplates are a frequent cause of chronic low back pain that is often inadequately addressed by routine care. This prospective randomized trial compared the effectiveness of intraosseous radiofrequency ablation of the basivertebral nerve to routine care in patients whose symptoms were suspected to be vertebrogenic. Investigators randomized 140 patients with low back pain to receive either intraosseous radiofrequency ablation or routine care.

The primary outcome measure was the Oswestry Disability Index at 3, 6, 9, and 12 months. An interim analysis demonstrated clear statistical superiority for both the primary and secondary outcome measures among patients randomized to the ablation arm at the 3-month timepoint. The mean changes in the Oswestry Disability Index at 3 months were –25 (95% CI, –30 to –21) points in the ablation group and –4 (95% CI, –8 to 0) points in the standard care arm ( $P < 0.001$ ). In the ablation arm, 75% of patients achieved more than a 10-point improvement compared with 33% in the standard care arm ( $P < 0.001$ ). (Article Selection: J. David Clark. Image: J. P. Rathmell.)

**Take home message:** Minimally invasive intraosseous radiofrequency ablation of the basivertebral nerve is associated with significant improvement of pain at 3 months in patients with chronic vertebrogenic-related low back pain.

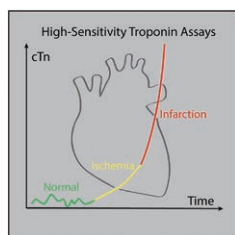


### Associations of amyloid, tau, and neurodegeneration biomarker profiles with rates of memory decline among individuals without dementia. *JAMA* 2019; 321:2316–25.

A National Institute on Aging and Alzheimer's Association workgroup proposed a research framework for Alzheimer disease in which biomarker classification of research participants is labeled as AT(N) for amyloid, tau, and neurodegeneration biomarkers. This study set out to determine the associations between amyloid, tau, and neurodegeneration biomarker profiles and memory decline in a cohort of 408 older adults without dementia at baseline and whether the biomarkers added incremental prognostic value. They used amyloid and tau positron emission tomography scanning and magnetic resonance

imaging cortical thickness as markers for amyloid, tau, and neurodegeneration markers, respectively, with a median follow-up of 4.8 yr. The addition of these biomarkers enhanced prediction of memory performance when compared to a clinical model ( $P < 0.001$ ). Memory declined fastest in the amyloid positive, tau positive, neurodegenerative positive; amyloid positive, tau positive, neurodegeneration negative; and the amyloid positive, tau negative, neurodegeneration positive groups when compared to the other five classifications ( $P = 0.002$ ). Estimated rates of decline these groups were –0.13 (95% CI, –0.17 to –0.09), –0.10 (95% CI, –0.16 to –0.05), and –0.10 (95% CI, –0.13 to –0.06) z score units per year, respectively, for an 85-yr-old that does not carry an APOE ε4 allele. (Article Selection: Martin J. London. Image: J. P. Rathmell.)

**Take home message:** The addition of amyloid positron emission tomography, tau positron emission tomography, and magnetic resonance imaging cortical thickness may enhance the ability to predict memory decline in older patients when compared to readily available clinical and genetic variables.



### Application of high-sensitivity troponin in suspected myocardial infarction. *N Engl J Med* 2019; 380:2529–40.

There is uncertainty about whether high-sensitivity troponin concentrations in patients with suspected myocardial infarction are predictive of myocardial infarction and subsequent 30-day outcomes. This study examined high-sensitivity troponin I or high-sensitivity troponin T at presentation and after serial sampling in 22,651 patients from 15 international cohorts. The authors used a derivation ( $n = 9,604$ ) and validation ( $n = 13,047$ ) study design to assess the diagnostic and prognostic performance of multiple high-sensitivity troponin cutoff combinations. The overall prevalence of myocardial infarction was 15%. The authors identified that initial lower high-sensitivity troponin concentrations and smaller absolute changes during

serial sampling suggested that myocardial infarction and cardiovascular events were less likely. Using this system, more than 50% of patients presenting to the emergency departments would be classified as low risk of myocardial infarction or cardiovascular events. (Article Selection: Martin J. London. Image: J. P. Rathmell.)

**Take home message:** High-sensitivity troponin I or troponin T concentration at emergency department presentation and changes during serial sampling can be used to estimate the probability of myocardial infarction or cardiac events.