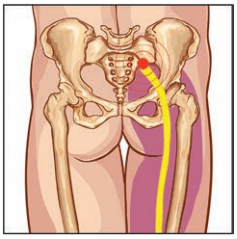
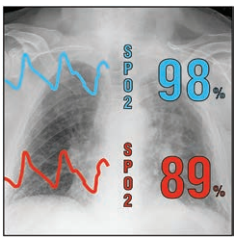
SCIENCE, MEDICINE, AND THE ANESTHESIOLOGIST
ANESTHESIOLOGY
Martin J. London, M.D., Editor
Key Papers from the Most Recent Literature Relevant to Anesthesiologists



Surgery versus conservative care for persistent sciatica lasting 4 to 12 months. N Engl J Med 2020; 382:1093–1102.

In contrast to studies demonstrating short-term symptom relief in patients with acute sciatica (less than 3 months) relative to conservative care, data on treatment of patients with chronic symptoms are limited. In this single-center, randomized trial, 128 adults with 4 to 12 months of symptomatic sciatica caused by disk herniation were randomized to either microdiskectomy or standardized nonoperative care followed by surgery, if necessary. The primary outcome was leg pain at 6 months using a visual analogue scale (0 to 10). Surgery occurred at a median of 3.1 weeks after randomization and the mean age of the study population was 38 yr (41% women). Mean baseline scores were 7.7 in the surgical group and 8.0 in the nonsurgical group. The 6-month scores were 2.8 and 5.2, respectively (adjusted mean difference, 2.4; 95% CI, 1.4 to 3.4; $P < 0.001$). Twenty-two patients (34%) from the nonsurgical group crossed over to surgical treatment at a median of 11 months. Adverse events occurred in 6% of the surgical group and 8% of the crossover patients. The most common adverse events were superficial wound infection and new onset neuropathic pain. Crossovers were more likely to be younger and less likely to have an asymmetrical decrease in reflexes. *(Article Selection: Martin J. London. Image: original image, Adobe Stock/image illustration, M. Lane-Fall.)*

Take home message: In patients with sciatica lasting 4 to 12 months caused by lumbar disk herniation, microdisketomy resulted in greater reduction in pain intensity than conservative treatment at 6-month follow-up.



Liberal or conservative oxygen therapy for acute respiratory distress syndrome. N Engl J Med 2020; 382:999–1008.

The potential hazards of hyperoxia on augmenting lung injury in acute respiratory distress syndrome (ARDS) has resulted in guideline-based recommendations for target Pao_2 between 55 and 80 mmHg. This multicenter (13 French intensive care units), randomized, nonblinded trial aimed to determine if conservative oxygen therapy would reduce 28-day all-cause mortality compared to liberal oxygenation in patients with ARDS. Patients receiving mechanical ventilation for less than 12 h for ARDS (Berlin Definition) were randomized to either conservative oxygen therapy (target Pao_2, 55 to 70 mmHg; oxygen saturation, measured by pulse oximetry [Spo_2], 88 to 92%) or liberal oxygen therapy (target Pao_2, 90 to 105 mmHg; Spo_2 greater than or equal to 96%) for 7 days. At day 28 there was no significant difference in mortality between groups; 34 of 99 (34.3%) patients in the conservative oxygen group died *versus* 27 of 102 (26.5%) patients in the liberal oxygen group (difference, 7.8 percentage points; 95% CI, –4.8 to 20.6). However, at day 90 mortality was higher in the conservative oxygen group (difference, 14.0 percentage points; 95% CI, 0.7 to 27.2) and five mesenteric events had occurred (*vs.* none). The trial was prematurely stopped by the safety monitoring board after enrollment of 205 patients, short of the projected sample size of 850 patients. *(Article Selection: Martin J. London. Image: M. Lane-Fall/J. P. Rathmell.)*

Take home message: Conservative oxygen therapy (target Pao_2 of 55 to 70 mmHg) did not increase survival rates at 28 days compared to liberal oxygen therapy and might be associated with severe adverse events, including death and mesenteric ischemia.

Perceptions on gender disparity in surgery and surgical leadership: A multicenter mixed methods study. Surgery 2020; 167:743–50.

Although the number of women entering medical school surpassed men for the first time in 2017, women still only represent 20% of leadership positions in academic surgery. This study aimed to identify reasons for this disparity as perceived by faculty surgeons and senior residents from four academic institutions. Thirty-six individuals (14 female and 22 male; 9 from each institution) were interviewed, and 100% of men and 86% of women reported perceiving a gender disparity in surgery. The respondents identified six contributing categories: varying definitions, mentoring gaps, family responsibility, disparity in leave, unequal pay, and professional advancement. Even though 94% of respondents identified gaps in mentoring, a higher percentage of women indicated it was difficult to find role models who had faced similar impediments. Both women and men responded that biases favoring individuals willing to sacrifice family existed and were system based. Although residents reported equal pay among themselves, the majority of respondents did report pay disparity in the field of surgery. Reasons for the disparity included system bias and women's lack of negotiation or self-advocacy in terms of higher salaries. A common barrier to advancement identified was the societal expectation that women act as primary family caretaker—a role from which female surgeons were not exempt. *(Article Selection: Beatrice Beck-Schimmer. Image: original image, Adobe Stock/image illustration, M. Lane-Fall.)*

Take home message: Even though more women than ever are entering the field of surgery, gender disparity is still hindering their career advancement.

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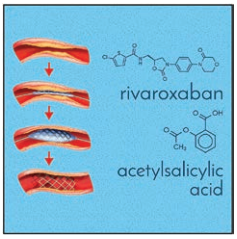


Rivaroxaban in peripheral artery disease after revascularization. N Engl J Med 2020; 382:1994–2004.

Patients with peripheral arterial disease and previous lower-extremity revascularization are at high risk of adverse limb and cardiovascular events. This large multinational trial evaluated the clinical effect and safety of rivaroxaban 2.5 mg twice daily added to aspirin *versus* aspirin plus placebo in 6,524 randomized patients. Median follow-up was 28 months. Primary composite outcome (acute limb ischemia, major amputation due to vascular causes, myocardial infarction, ischemic stroke, or cardiovascular death) and safety outcomes (fatal bleeding, intracranial hemorrhage, decrease in hemoglobin level of at least 5 g per deciliter, or hemotacrit of at least 15%) were evaluated. A secondary safety bleeding outcome (fatal bleeding, bleeding into a critical site, hemoglobin level of at least 2 g per deciliter, or transfusion of at least 2 units of packed erythrocytes or whole blood) was also evaluated. Three-year estimated incidence of the primary outcome for treatment *versus* placebo groups was 17.3% *versus* 19.9%, respectively (hazard ratio, 0.85; 95% CI, 0.76 to 0.96). Primary major bleeding was not significantly different: 2.65% *versus* 1.87% (hazard ratio, 1.43; 95% CI, 0.97 to 2.1). However, secondary bleeding was significantly higher in the treatment group (5.94% *vs.* 4.06% in the placebo group; hazard ratio, 1.42; 95% CI, 1.1 to 1.84). *(Article Selection: Martin J. London. Image: original image, Adobe Stock/image illustration, M. Lane-Fall.)*

Take home message: Adding rivaroxaban to aspirin may reduce limb and cardiovascular adverse events but may also be associated with major bleeding in patients with peripheral arterial disease and previous lower-extremity revascularization.

The effect of improving basic preventive measures in the perioperative arena on *Staphylococcus aureus* transmission and surgical site infections: A randomized clinical trial. JAMA Netw Open 2020; 3:e201934.

The Centers for Disease Control and Prevention has emphasized the need for improvements in preventive measures to stop bacterial spread and infection. Failure of single interventions indicated the need for a multifaceted approach to control perioperative *Staphylococcus aureus* transmission and surgical site infections. In this trial, 236 patients (mean age, 57 yr) undergoing total joint, spine, oncologic gynecological, thoracic, general, colorectal, open vascular, plastic, or open urological surgery were randomized to either usual care or the intervention group. Interventions included hand hygiene, organization of the anesthesia work area, disinfection of intravascular catheter and syringe tip, environmental cleaning, and patient decolonization with nasal povidone iodine. Patients were followed for 60 days. The intervention group had a reduced mean number of transmitted *S. aureus* isolates during surgery compared to the control group (0.47 *vs.* 1.25, $P = 0.002$), as well as a reduced incidence of *S. aureus* transmission (incidence risk ratio, 0.56; 95% CI, 0.37 to 0.86). Treatment reduced the risk of surgical site infection (hazard ratio, 0.12; 95% CI, 1.62 to 21.86; $P = 0.007$). *(Article Selection: Martin J. London. Image: original image, Adobe Stock/image illustration, M. Lane-Fall.)*

Take home message: A multi-intervention approach to improving basic intraoperative preventive measures may help reduce *S. aureus* transmission and perioperative surgical site infections.

Impact of a progressive mobility program on the functional status, respiratory and muscular systems of ICU patients: A randomized and controlled trial. Crit Care Med 2020; 48:491–7.

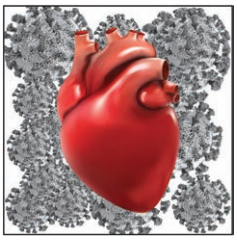
Patients hospitalized in intensive care units (ICUs) may incur immobility-related damage, especially in the cardiorespiratory and muscular systems, which can last months to years after discharge. In this single-center study, 90 ICU patients with previous functional independence were randomized to either a progressive mobility program including gait reeducation and cognitive components at levels appropriate for each patient or conventional treatment. Mobility sessions started within 48 h of ICU admission lasting an average of 40 min. At discharge, the intervention group had higher Barthel index scores (functional status) than the control group (97 *vs.* 76 [of 100], $P < 0.001$) and more independent patients (96 *vs.* 44, $P < 0.001$). Regarding muscular function, there were significant differences between the groups in the sit-and-stand ($P < 0.01$) and 2-min walk ($P < 0.001$) tests, but no significant differences in handgrip, timed up-and-go, or electromyographic tests. Maximal ventilatory ventilation scores differed significantly between groups (55 *vs.* 45 l/min, $P = 0.03$). At 3 months after discharge, the intervention group had more independent patients than the control group (97.5% *vs.* 74.4%, $P < 0.01$). *(Article Selection: Beatrice Beck-Schimmer. Image: original image, Adobe Stock/image illustration, M. Lane-Fall.)*

Take home message: Participating in progressive mobility programs may improve functionality in ICU patients at discharge and at 3 months posthospitalization.

Nonsedation or light sedation in critically ill, mechanically ventilated patients. N Engl J Med 2020; 382:1103–11.

The role of sedation protocols in treating mechanically ventilated patients in the intensive care unit (ICU) remains controversial. At eight Scandinavian centers, 710 mechanically ventilated adult patients were randomized to either no sedation or light sedation (patient arousable, with a Richmond Agitation and Sedation score of –2 to –3 [range: –5, unresponsive, to 4, combative]) with daily interruption. Bolus morphine was provided as necessary for analgesia. Sedated patients received propofol infusion for 48 h followed by midazolam thereafter. The primary outcome was 90-day mortality. Seven hundred patients had available data for the modified intention-to-treat analysis. By day 7, mean Richmond Agitation and Sedation score increased from day 1 in both groups: –1.3 to –0.8 in the nonsedation group and –2.3 to –1.8 in the sedation group. Mortality between nonsedation and sedation groups at 90 days was 42.4% *versus* 37.0% (difference, 5.4 percentage points; 95% CI, –2.2 to 12.2). Time on ventilation and length of ICU and hospital stay were not significantly different. *(Article Selection: Martin J. London. Image: J. P. Rathmell.)*

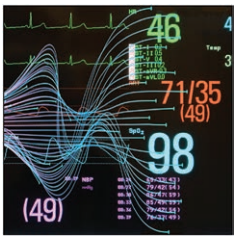
Take home message: Among mechanically ventilated patients in the ICU, no sedation compared to light sedation with daily interruption did not demonstrate significant differences in 90-day mortality, ventilation-free days, or length of either ICU or hospital stays.



Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020 Mar 27 [Epub ahead of print].

Coronavirus disease 2019 (COVID-19) is commonly associated with respiratory failure, but cardiovascular manifestations of the viral infection are a growing concern. This retrospective cohort study from Wuhan, China, evaluated the impact of underlying cardiovascular disease and myocardial injury on outcomes in hospitalized patients with COVID-19. Of the 187 patients (mean age, 58.5 yr), 66 (35.3%) had underlying cardiovascular disease (including hypertension, coronary heart disease, and cardiomyopathy) and 52 (27.8%) had myocardial injury (indicated by elevated troponin T levels). Patients with elevated troponin T levels had higher mortality rates than those with normal levels (59.6% *vs.* 8.9%). Median duration from illness onset to death in the group with elevated troponin T levels was 23 days. Patients with underlying cardiovascular disease and elevated troponin T levels had the highest mortality rate (69.9%). Notably, patients with cardiovascular disease but with normal troponin T levels had a more favorable prognosis, compared to those with elevated troponin T levels but without cardiovascular disease (13.3% *vs.* 37.5% mortality). Plasma troponin T levels showed a high and significantly positive linear association with N-terminal pro-brain natriuretic peptide levels ($\beta = 0.613$, $P < 0.001$). Among patients who died, plasma troponin T levels and N-terminal pro-brain natriuretic peptide levels increased significantly during hospitalization and with impending death, compared to admission values. No significant change in troponin T or N-terminal pro-brain natriuretic peptide levels was observed among survivors. *(Article Selection: Martin J. London. Image: original image, Adobe Stock/image illustration, M. Lane-Fall.)*

Take home message: Myocardial injury was significantly associated with fatal outcome in COVID-19 patients. Patients with underlying cardiovascular disease without myocardial injury had a more favorable prognosis.



Effect of a machine learning–derived early warning system for intraoperative hypotension vs standard care on depth and duration of intraoperative hypotension during elective noncardiac surgery: The HYPE randomized clinical trial. JAMA 2020; 323:1052–60.

Hypotension during surgery is associated with increased morbidity and mortality. This preliminary randomized trial evaluated whether a machine learning–derived early warning system, combined with hemodynamic diagnostic guidance and treatment protocol, could reduce intraoperative hypotension. The early warning system had been previously validated, with sensitivity of 88% and specificity of 87%. Sixty-eight patients (median age 64 yr) undergoing elective noncardiac surgery, with general anesthesia and continuous invasive blood pressure monitoring, were assigned to either the early warning system or standard care. Median length of surgery was 256 min. Median time-weighted average of hypotension was significantly less in the intervention group (0.10 mmHg) *versus* the control group (0.44 mmHg; median difference, 0.38 mmHg; 95% CI, 0.14 to 0.43; $P = 0.001$). The intervention group also had a reduced median time of hypotension per patient, compared to the control group (8 *vs.* 37 min; median difference, 17 min; 95% CI, 7.7 to 31; $P < 0.001$). There were no adverse events in the intervention group, and 2 (7%) in the control group. *(Article Selection: Martin J. London. Image: M. Lane-Fall.)*

Take home message: In patients undergoing elective noncardiac surgery, use of a machine learning–derived early warning system resulted in less intraoperative hypotension compared to standard care.

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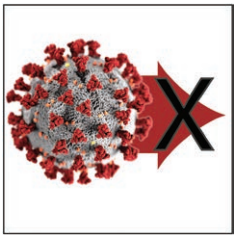
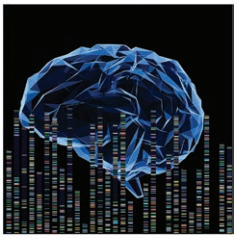


SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020; 181:271–280.e8.

The novel coronavirus now known as SARS-CoV-2 has been detected in people infected with coronavirus disease 19 (COVID-19) and is related to the severe acute respiratory syndrome coronavirus (SARS-CoV) that emerged in 2002. This study aimed to determine what base pair sequence similarities between the two viruses exist and if elucidation of their cellular activity could translate to a therapeutic intervention. The SARS-CoV-2 spike (S) protein (generic to all coronaviruses) has been shown to bind to angiotensin-converting enzyme 2 (ACE2), which acts as the entry receptor. It then uses the cellular serine protease TMPRSS2 for S protein priming. This process facilitates entry of coronaviruses into target cells. Using a human cell line (293T), investigators demonstrated that SARS-CoV-2 does in fact use ACE2 for entry and TMPRSS2 for binding. As TMPRSS2 is dispensable for development and homeostasis, it is an attractive drug target. The serine protease inhibitor camostat mesylate, a TMPRSS2 inhibitor, was able to block entry of SARS-CoV-2 into lung cells. A neutralizing antibody response directed at the coronavirus S protein in convalescent SARS patients was able to reduce SARS-CoV-2 cell entry. *(Article Selection: Martin J. London. Image: original image, Centers for Disease Control and Prevention/image illustration, M. Lane-Fall.)*

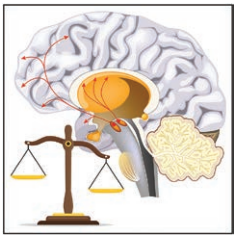
Take home message: Similar to SARS, COVID-19 uses ACE2 and TMPRSS2 for cell binding and priming, respectively. A serine protease inhibit was able to block the virus's entry into lung cells, suggesting a potential treatment option. Furthermore, antibodies raised against SARS during infection or vaccination may also provide protection against COVID-19.



The genetic architecture of the human cerebral cortex. Science 2020; 367(6484):eaay6690.

Variations in surface area and thickness of the cerebral cortex are associated with neurologic, psychologic, and behavioral characteristics. In this study, genetic variants that may affect cortical structure were investigated. In a discovery sample of 33,992 participants of European origin, 306 nominally genome-wide significant ($P < 5 \times 10^{-8}$) loci associated with cortical structure were identified. Ultimately, 199 loci passed multiple testing correction ($P < 8.3 \times 10^{-10}$), of which 187 affected surface area and 12 affected thickness. Common genetic variants explained 34% of variation in surface area and 26% in average thickness. Negative genetic correlation ($rG = -0.32$, $P = 6.5 \times 10^{-12}$) between surface area and thickness suggested that genetic influences have opposing effects on them. Variants that alter gene regulatory activity in neural progenitor cells during fetal development were found to affect total surface area. Conversely, active regulatory elements in adult brain samples influenced thickness, potentially indicating processes occurring after mid-fetal development. Positive genetic correlations and evidence of bidirectional causation were seen between total surface area and general cognitive functioning and educational attainment. Further positive genetic correlations, but not evidence of causation, were observed with total surface area and Parkinson disease. Negative genetic correlations were seen with total surface area and insomnia, attention deficit hyperactivity disorder, depressive symptoms, major depressive disorder, and neuroticism. *(Article Selection: Martin J. London. Image: original image, Adobe Stock/image illustration, M. Lane-Fall.)*

Take home message: Distinct genes appear to influence the development of specific cortical areas. Brain structure is a key phenotype along the causal pathway leading from genetic variation to differences in general cognitive function.



Dopamine promotes cognitive effort by biasing the benefits versus costs of cognitive work. Science 2020; 367(6484):1362–6.

Striatal dopamine has been shown to invigorate physical action by mediating cost-benefit trade-offs. In this study, the authors hypothesized that methylphenidate, a dopamine and noradrenaline reuptake blocker, would boost cognitive control by increasing striatal dopamine and, consequently, sensitivity to benefits of cognitive effort instead of its costs. Fifty healthy, young adults (age range 18 to 43 yr, equal sex) who underwent functional magnetic resonance imaging with administration of placebo, sulpiride, or methylphenidate, completed a cognitive effort-discounting model that quantified subjective effort costs as the amount of money needed to make participants equally willing to perform a hard *versus* easier task. Methylphenidate did change the benefit-to-cost ratio of cognitive work resulting in increased willingness to exert cognitive effort. Individuals with higher striatal dopamine synthesis by functional magnetic resonance imaging capacity had greater willingness to expend cognitive effort. Methylphenidate and the selective D2 receptor agonist sulpiride together increased motivation in participants with lower synthesis capacity. A sequential sampling model based on momentary gaze showed that decisions to expend effort were associated with amplified benefit-to-cost information occurring early in the decision process. The effect of benefits was strengthened with higher synthesis capacity and with methylphenidate. *(Article Selection: J. David Clark. Image: original image, Adobe Stock/image illustration, M. Lane-Fall.)*

Take home message: In humans, methylphenidate may boost perceived benefits of cognitive effort over costs by modulating striatal dopamine signaling on functional magnetic resonance imaging.