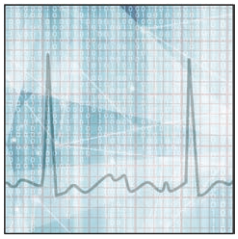
SCIENCE, MEDICINE, AND THE ANESTHESIOLOGIST

ANESTHESIOLOGY

Martin J. London, M.D., Editor

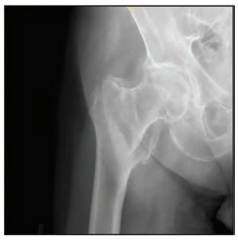
Key Papers from the Most Recent Literature Relevant to Anesthesiologists



Deep neural network-estimated electrocardiographic age as a mortality predictor. Nat Commun 2021; 12:5117. PMID: 34433816.

Cardiovascular diseases are often screened using the 12-lead electrocardiogram utilizing signal processing techniques based on preconfigured parameters. To improve prediction, deep neural networks were employed in which the raw signal was evaluated without interpretation based on pre-existing electrocardiogram knowledge. A model to predict the patient's age from the raw electrocardiogram signal using a large population-based cohort (more than 1.5 million subjects; CODE cohort) was constructed. The model was evaluated using three additional large cohorts. The primary outcome was the risk of death based on the difference between the electrocardiogram predicted and the subject's actual chronological age. An estimated electrocardiogram age of more than 8 yr over the chronological age significantly predicted mortality (hazard ratio, 1.79 [95% CI, 1.69 to 1.90]; $P < 0.001$). Patients with an electrocardiogram age less than 8 yr over chronological age had lower risk of death (hazard ratio, 0.78 [95% CI, 0.74 to 0.83]; $P < 0.001$). Cardiovascular risk factors (hypertension, diabetes, and smoking) were associated with a predicted electrocardiogram age of more than 8 yr. Reviews by three cardiologists were unable to discriminate between higher electrocardiogram predicted age; analysis suggests that low-frequency components (P and T waves, components between 8 and 15 Hz) were most likely to contribute to model prediction. *(Article Selection: Beatrice Beck-Schimmer, M.D. Image: J. P. Rathmell/Thinkstock.)*

Take home message: A predicted age derived from deep neural network analysis of the raw 12-lead electrocardiogram is able to predict cardiovascular mortality and may offer advantages over classical signal extraction methods.



Spinal anesthesia or general anesthesia for hip surgery in older adults. N Engl J Med 2021; 385:2025–35. PMID: 34623788.

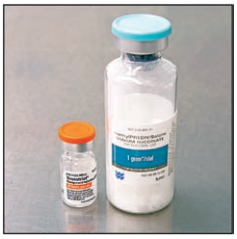
Potential advantages of spinal anesthesia over general anesthesia in surgery for hip fracture have not been systematically evaluated in a large trial. A pragmatic, randomized superiority trial comparing spinal anesthesia with general anesthesia was performed in patients 50 yr of age or older undergoing surgery for hip fracture at 46 U.S. and Canadian hospitals. The primary outcome was a composite of death, or an inability to walk 10 feet independently, or with a walker or cane at 60 days postrandomization. Secondary outcomes included death within 60 days, delirium, time to discharge, and ambulation at 60 days. A total of 1,600 patients were enrolled; 795 were assigned to receive spinal anesthesia and 805 to receive general anesthesia (mean age 78 yr; 67% women). Using a modified intention-to-treat analysis, the composite primary outcome was not different between groups (composite relative risk, 1.03 [95% CI, 0.84 to 1.27], $P = 0.83$; inability to walk independently at 60 days, relative risk, 1.06 [95% CI, 0.82 to 1.36]; death within 60 days, relative risk, 0.97 [95% CI, 0.59 to 1.57]). The incidence of delirium was not different between groups (relative risk, 1.04 [95% CI, 0.84 to 1.30]). *(Article Selection: Martin J. London, M.D. Image: J. P. Rathmell.)*

Take home message: Spinal anesthesia for previously ambulatory hip fracture surgery in older adults without contraindications was not superior to general anesthesia with respect to survival and recovery of ambulation at 60 days.

Awake prone positioning for COVID-19 acute hypoxaemic respiratory failure: A randomised, controlled, multinational, open-label meta-trial. Lancet Respir Med 2021 Aug 20 [Epub ahead of print]. PMID: 34425070.

Awake prone positioning has been reported to improve oxygenation for patients with COVID-19 in retrospective and observational studies, although its effects on longer-term outcomes is uncertain. A prospective, meta-trial of six randomized controlled open-label superiority trials of adults requiring respiratory support with high-flow nasal cannula for acute hypoxemic respiratory failure due to COVID-19 randomly assigned to awake prone positioning (n = 567) or standard care (n = 559) between April 2020 and January 2021 was performed. The primary composite outcome was treatment failure (proportion of patients intubated or 28-day postenrollment mortality). By intention-to-treat analysis, the primary outcome was significantly less in the prone group (relative risk, 0.86 [95% CI, 0.75 to 0.98]; hazard ratio for intubation, 0.75 [95% CI, 0.62 to 0.91]; for mortality 0.87 [95% CI, 0.68 to 1.11]). Prespecified adverse events were similar in both groups. *(Article Selection: Martin J. London, M.D. Image: J. P. Rathmell.)*

Take home message: Awake prone positioning for patients with COVID-19–associated hypoxemic respiratory failure results in a lesser incidence of intubation or 28-day postenrollment mortality.



Effect of vasopressin and methylprednisolone vs placebo on return of spontaneous circulation in patients with in-hospital cardiac arrest: A randomized clinical trial. JAMA 2021; 326:1586–94. PMID: 34587236.

Epinephrine, amiodarone, or lidocaine are drugs currently used for in-hospital cardiac arrest. There are limited data on the use of vasopressin and glucocorticoids in this setting. This randomized double-blind placebo-controlled trial conducted in 10 Danish hospitals compared a combined intervention of intravenous methylprednisolone (40 mg) and vasopressin (20 IU) *versus* placebo after the first dose of epinephrine. Additional doses of vasopressin could be given after subsequent doses of epinephrine to a maximum of 4 doses (80 IU). The primary outcome was return of spontaneous circulation; secondary outcomes included survival and favorable neurologic outcome at 30 and 90 days. A total of 501 patients were randomized and analyzed: 245 in the intervention and 267 in the control arm. A significant difference in the primary outcome was noted with intervention (risk ratio, 1.3 [95% CI, 1.03 to 1.63]; risk difference, 10% [95% CI, 1.1 to 18.0%]; $P = 0.03$). No significant differences were noted in the secondary outcomes (survival at 30 days risk ratio, 0.83 [95% CI, 0.50 to 1.37], risk difference, –2.0% [95% CI, –7.5 to 3.5%], $P = 0.48$; favorable neurologic 30-day outcome risk ratio, 1.00 [95% CI, 0.55 to 1.83], risk difference, 0.0% [95% CI, –4.7 to 4.9%], $P > 0.99$). Similar findings were noted at 90 days. *(Article Selection: Beatrice Beck-Schimmer, M.D. Image: J. P. Rathmell.)*

Take home message: Return of spontaneous circulation was significantly greater with the addition of vasopressin and methylprednisolone during resuscitation for in-hospital cardiac arrest. Exploratory longer-term secondary outcomes were not improved.

Association of epidural analgesia during labor and delivery with autism spectrum disorder in offspring. JAMA 2021; 326:1178–85. PMID: 34581736.

An association between epidural analgesia during labor and delivery and the diagnosis of autism spectrum disorder has been suggested in a few cohort studies, but the evidence remains controversial. In this population-based retrospective cohort study including term singleton children born in British Columbia (Canada), the association between autism spectrum disorder and epidural analgesia after adjustment for maternal sociodemographics, maternal conditions during pregnancy, labor, delivery, antenatal care characteristics, infant sex, gestational age, and status of small or large for gestational age was reviewed. Of the 388,254 children included in the cohort, 5,192 were diagnosed with autism spectrum disorder (1%) and 111,480 (29%) were exposed to epidural analgesia. The proportion of children diagnosed with autism spectrum disorder was 2% in the group that were exposed to epidural analgesia and 1% in the unexposed group. A statistically significant association was found for the 3 adjusted models (adjusted hazard ratio for model 1, 1.30 [95% CI, 1.22 to 1.38]; adjusted hazard ratio for model 2, 1.12 [95% CI, 1.05 to 1.20]; and adjusted hazard ratio for model 3, 1.09 [95% CI, 1.00 to 1.15]), although not confirmed in the within-woman matched conditional logistic regression (839 of 1,659 [51%] in the exposed group *vs.* 1,905 of 4,587 [42%] in the unexposed group; fully adjusted hazard ratio, 1.07 [95% CI, 0.87 to 1.30]). *(Article Selection: David Faraoni, M.D., Ph.D. Image: J. P. Rathmell.)*

Take home message: In this population-based study, maternal epidural analgesia during labor and delivery was associated with an increase in the risk of autism spectrum disorder, although the risk of residual confounding is high.

Association of labor epidural analgesia with autism spectrum disorder in children. JAMA 2021; 326:1170–7. PMID: 34581738.

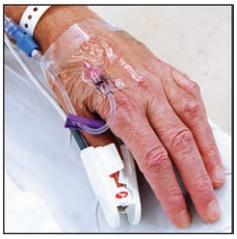
Given recent data suggesting an association between epidural analgesia use and the incidence of autism spectrum disorder, a nationwide retrospective cohort study in Denmark including all live-born children between January 2006 and December 2013 to investigate an association between labor epidural and the risk of autism in offspring was performed. The cohort included 479,178 children; of these, 92,900 (19%) were exposed to epidural analgesia during labor. Median follow-up was 7 yr (interquartile range, 5 to 9 yr), and by the end of follow-up, 6,428 children (1%) had been diagnosed with autism spectrum disorder. Hazard ratios were estimated using Cox regression, adjusted for maternal comorbidity, sociodemographic factors, lifestyle, pregnancy, psychiatric illness, psychotropic medication, medical-seeking behavior, and family history of autism. Exposed children had an autism diagnosis incidence rate of 23% per 10,000 person-years compared with 19% per 10,000 person-years in the unexposed group (crude hazard ratio, 1.29 [95% CI, 1.21 to 1.37]; adjusted hazard ratio, 1.05 [95% CI, 0.98 to 1.11]). A secondary within-mother analysis including 59,154 children (12%) estimated an autism diagnosis incidence rate of 21% per 10,000 person-years in the exposed group and 17% per 10,000 person-years in the unexposed group (adjusted hazard ratio, 1.05 [95% CI, 0.90 to 1.21]). *(Article Selection: David Faraoni, M.D., Ph.D. Image: J. P. Rathmell.)*

Take home message: This nationwide cohort study of Danish children did not find a significant association between maternal exposure to epidural analgesia during labor and autism spectrum disorder in offspring.

Metoprolol in critically ill patients with COVID-19. J Am Coll Cardiol 2021; 78:1001–11. PMID: 34474731.

Pleiotropic effects of the beta-blocker metoprolol may include anti-inflammatory effects in the setting of myocardial infarction. Potentially beneficial effects on alveolar inflammation and respiratory function in patients with COVID-19–associated ARDS were postulated. Twenty COVID-19 mechanically ventilated patients with ARDS were randomized to intravenous metoprolol (n = 12; 3 x 5 mg doses 2 min apart daily for 3 days) or control (n = 8; no treatment). All patients underwent bronchoalveolar lavage before and after completion of treatment or control on day 4. All patients received concurrent corticosteroid therapy. Metoprolol administration was well tolerated hemodynamically. Neutrophil content at baseline did not differ between groups. On day 4, metoprolol patients had significantly fewer neutrophils (metoprolol median: 14.3 neutrophils/ml *vs.* control 397 neutrophils/ml; $P < 0.016$). Neutrophil extracellular trap content and other markers of lung inflammation were reduced. Oxygenation (Pao_2:Fio_2 ratio) significantly improved after 3 days of metoprolol treatment (median: 130 *vs.* 267 at baseline and day 4, respectively; $P < 0.003$), but remained unchanged in control subjects. Differences in ventilator days, length of ICU stay, and mortality (one in each group) did not differ. *(Article Selection: Martin J. London, M.D. Image: J. P. Rathmell.)*

Take home message: In a small pilot trial, intravenous metoprolol administration to patients with COVID-19–associated ARDS for 3 days was safe with reduced exacerbated lung inflammation and improved oxygenation relative to control patients.



Comparison of routine replacement with clinically indicated replacement of peripheral intravenous catheters. JAMA Intern Med 2021; 181:1471–8. PMID: 34533191.

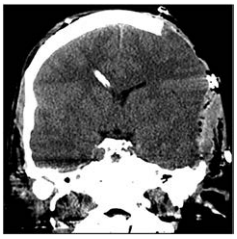
Infections from peripheral intravenous catheters are rare, but potentially severe and usually preventable. A retrospective observational cohort study using a prospective infection control surveillance database of all patients with an intravenous catheter while hospitalized at a large tertiary Swiss hospital (2016 to 2020) was conducted. The primary outcome was the incidence of catheter-related blood stream infections during a period when catheters were routinely replaced every 96 h (baseline period) compared to a subsequent period when they were only replaced if clinically indicated (intervention period) followed by a period when they were again replaced every 96 h (reversion period). There were 241,432 placements in the baseline period, 130,779 during the intervention, and 40,420 during the reversion period. The number of catheters in place more than 7 days was higher during the intervention period. Although the incidence of infection was very low (11 baseline, 46 interventions, and 4 reversion), a significantly greater incidence rate ratio was observed for the intervention period (incidence rate ratio, 7.20; 95% CI, 3.65 to 14.22; $P < 0.001$) compared with the baseline period, whereas during the reversion period there was no significant difference (incidence rate ratio, 1.35 [95% CI, 0.30 to 6.17]; $P = 0.69$). *(Article Selection: BobbieJean Sweitzer, M.D. Image: J. P. Rathmell.)*

Take home message: In a large observational cohort analysis, routine replacement of peripheral intravenous catheters every 96 h was associated with a lower risk of blood stream infection compared with replacement when clinically indicated.

Comparison of long-term clinical outcomes of skeletonized vs pedicled internal thoracic artery harvesting techniques in the Arterial Revascularization Trial. JAMA Cardiol 2021 Sep 29 [Epub ahead of print]. PMID: 34586338.

Controversy exists regarding long-term safety of skeletonized internal thoracic artery grafts *versus* use of a pedicled internal thoracic artery in patients undergoing coronary artery bypass surgery (CABG). A *post hoc* analysis of data from the Arterial Revascularization Trial, a multicenter trial randomizing CABG patients to either bilateral internal thoracic artery or a single internal thoracic artery with saphenous vein grafts, which has followed patients for 10 yr, was completed. Subjects were stratified by internal thoracic artery harvesting technique comparing 10-yr clinical outcomes. The primary outcome was all-cause mortality, secondary outcomes were major adverse cardiac events (MACE; including all-cause mortality, myocardial infarction, and repeat revascularization) and a composite of MACE and sternal wound complication. A total of 2,161 subjects were analyzed (14% female), median age 65 yr. All-cause mortality was not significantly different between groups at 10 yr (hazard ratio, 1.12 [95% CI, 0.92 to 1.36]; $P = 0.27$). Secondary outcomes were significantly higher in the skeletonized group compared with the pedicled group (MACE: hazard ratio, 1.25 [95% CI, 1.06 to 1.47]; $P = 0.01$; MACE and sternal wound infection: hazard ratio, 1.22 [95% CI, 1.05 to 1.43]; $P = 0.01$). A significant effect of surgeon experience was noted as the effect was not observed in surgeons enrolling more than 51 patients in the original trial. *(Article Selection: Martin J. London, M.D. Image: J. P. Rathmell.)*

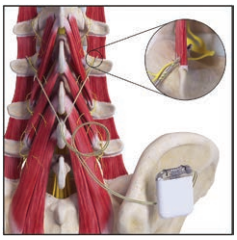
Take home message: *Post hoc* analysis of a large, randomized trial investigating use of internal thoracic artery grafting in which surgical technique was not controlled suggests that although long-term survival was not different, the rate of adverse cardiovascular events was significantly greater in the skeletonized group and the difference was associated with surgeon experience.



Axonal marker neurofilament light predicts long-term outcomes and progressive neurodegeneration after traumatic brain injury. Sci Transl Med 2021; 13:eabg9922. PMID: 34586833.

Traumatic brain injury can cause axonal injury, which often results in long-term functional impairment. A simple blood biomarker of the severity of axonal injury might improve clinical outcome prediction. In this prospective study of 197 moderate to severe traumatic brain injury patients, markers of axonal injury (the cytoskeletal protein, neurofilament light) and grey matter atrophy (the microtubule associated protein, tau) were collected from plasma and, in a small subset, cerebral extracellular fluid (microdialysis, n = 18), and were correlated with neuroimaging (n = 146) and clinical outcomes (Glasgow Outcome Scale Extended). Plasma neurofilament light concentrations peaked around 20 days after the injury (median = 507 pg/ml; interquartile range, 728) but were still elevated after a year (52% had concentrations greater than 2 SD above healthy control mean). These concentrations correlated with diffusion magnetic resonance imaging evidence of axonal injury ($r = -0.44$, $P < 0.001$), brain extracellular concentrations of neurofilament light ($P = 0.001$), and predicted functional outcomes after 1 yr ($P < 0.001$). Tau correlated with grey matter atrophy ($R^2 = 0.34$, $P < 0.001$). *(Article Selection: Jamie Sleigh, M.D. Image: J. P. Rathmell.)*

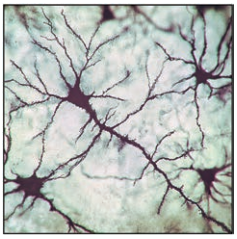
Take home message: Measurement of plasma neurofilament light concentrations are a sensitive measure of axonal injury after traumatic brain injury and may have a role in predicting long-term functional recovery.



An implantable restorative-neurostimulator for refractory mechanical chronic low back pain: A randomized sham-controlled clinical trial. Pain 2021; 162:2486–98. PMID: 34534176.

Chronic low back pain is a leading cause of disability worldwide. Loss of motor control and degeneration of the multifidus muscles, crucial for providing lumbar spine stability, may be contributing factors. By electrically stimulating the medial branch of the dorsal ramus nerve using an implanted stimulator, investigators hypothesized that low back pain would be improved. A total of 204 participants from 26 pain centers were randomized to active *versus* sham stimulation 30 min twice daily for 120 days. The primary endpoint, 30% or more pain reduction without an increase in analgesic use, was not statistically significant at this timepoint (57% *vs.* 47% [95% CI, 23 to 24%], $P = 0.138$). Several secondary outcomes including pain intensity, global impression of change, quality of life, and others showed modest improvements in favor of active stimulation. Serious adverse events, mostly device pocket infections, occurred in 4% of the participants. After 120 days, all participants had their stimulators activated, and outcomes were followed over 1 yr. Improvements in all outcome measures continued to accrue during this phase. *(Article Selection: J. David Clark, M.D, Ph.D. Image: Courtesy of Mainstay Medical.)*

Take home message: In patients with chronic low back pain, multifidus muscle stimulation was not associated with a reduction in pain at 120 days after implantation compared to sham stimulation.



Early-life midazolam exposure persistently changes chromatin accessibility to impair adult hippocampal neurogenesis and cognition. Proc Natl Acad Sci USA 2021; 118:e2107596118. PMID: 34526402.

Repeated early-life exposure to anesthetics is associated with higher risk of learning disability and attention deficit hyperactivity disorder. However, it remains elusive how transient exposure to anesthetics may cause long-term neuronal dysfunction. Midazolam (10 mg/kg), a γ-aminobutyric acid type A ($GABA_A$) receptor agonist and commonly used drug in pediatric anesthesia, was administered transiently to 7-day-old mice for three consecutive days, and its long-term effects on neuronal stem cells, the principal contributors to hippocampus-related memory processing, were explored after 8 weeks (adult state). Midazolam suppressed the proliferation of neuronal stem cells shortly after exposure and induced long-lasting dormancy, resulting in sustained impaired neurogenesis until adulthood. Cognitive decline was confirmed in midazolam-treated mice when compared with control mice using behavioral tests. Transcriptomics of neuronal stem cells collected 10 days after initiation of midazolam exposure revealed a molecular signature of quiescence, which was maintained for 8 weeks. Specifically, midazolam increased the chromatin accessibility of transcription factors, namely neurofibromatosis type I family members and early growth response 1 (Egr1), to their target sites within chromatin insulator proteins. Cell experiments further showed that Egr1 expression activates genes (Id4, Notch2) that reinforced neuronal stem cell dormancy. Voluntary exercise in a running wheel reversed these epigenetic changes and memory dysfunction, even when started as late as 3 weeks after exposure. *(Article Selection: Michael Zaugg, M.D. Image: Adobe Stock.)*

Take home message: Early-life midazolam exposure in mice induces transcriptional alterations in neuronal stem cells causing long-lasting dormancy with impaired neurogenesis, which can be fully offset by physical activity.