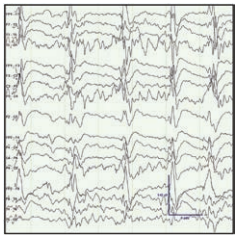
SCIENCE, MEDICINE, AND THE ANESTHESIOLOGIST

ANESTHESIOLOGY

Martin J. London, M.D., Editor

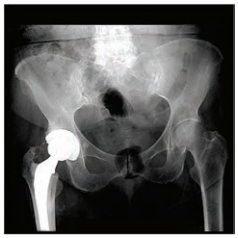
Key Papers from the Most Recent Literature Relevant to Anesthesiologists



Treating rhythmic and periodic EEG patterns in comatose survivors of cardiac arrest. N Engl J Med 2022; 386:724–34. PMID: 35196426.

Pharmacologic suppression of rhythmic and periodic electroencephalographic (EEG) patterns in comatose survivors of cardiac arrest remains controversial. This study reports a randomized trial (11 European intensive care units [ICUs]) of rhythm and periodic EEG pattern suppression (on continuous EEG monitoring) in this setting. A stepwise strategy of antiseizure suppressive medications for 48 h (antiseizure drugs plus sedation within 3 h of detection) plus standard care or standard care alone (targeted temperature management) were compared. The primary outcome was neurologic outcome dichotomized as either good or poor outcome using the Cerebral Performance Category scale at 3 months postrandomization. One hundred seventy-two patients were randomized. Abnormal EEG activity were detected at a median of 35 h after arrest. Complete suppression occurred in 56% of the treated group *versus* 2% of control. At 3 months, no differences were noted: 90% of the antiseizure-treatment group *versus* 92% of the control group had a poor outcome (difference, 2 percentage points; 95% CI, –7 to 11; $P = 0.68$). Mortality at 3 months was 80% in the treatment group *versus* 82% in the control group. The mean length of stay in the ICU and duration of mechanical ventilation were slightly longer in the treatment group than in the control group. *(Article Selection: Martin J. London, M.D. Image: Jong Woo Lee, M.D., Ph.D.)*

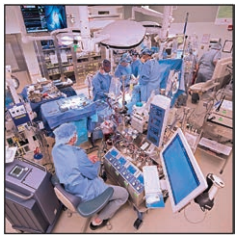
Take home message: In comatose survivors of cardiac arrest, the incidence of a poor neurologic outcome at 3 months did not differ significantly between a strategy of suppressing rhythmic and periodic EEG activity with the use of antiseizure medication for at least 48 h plus standard care and standard care alone.



Cemented or uncemented hemiarthroplasty for intracapsular hip fracture. N Engl J Med 2022; 386:521–30. PMID: 35139272.

Given limited available postoperative quality-of-life data, equipoise exists regarding the need for bone cement in hip fractures treated with hemiarthroplasty. This study reports a randomized controlled trial of cemented *versus* uncemented hemiarthroplasty in patients with an intracapsular fracture aged 60 yr or older at 14 UK centers. Perioperative process variables were all dictated by local center policies. The primary outcome (health-related quality of life) was assessed with utility scores on the EuroQol Group 5-Dimension (EQ-5D) questionnaire *via* telephone 4 months after randomization (range of scores, –0.594 to 1, with higher scores reflecting better quality of life; minimal clinically important difference, 0.050 to 0.075). Primary outcome data were available for 72% of randomized patients (610 cemented, 615 uncemented). A modest but statistically significant improvement in quality of life was noted in the cemented group: mean EQ-5D utility score 0.371 *versus* 0.315 (adjusted difference, 0.055; 95% CI, 0.009 to 0.101; $P = 0.02$). Periprosthetic fracture was lower in the cemented group (0.5% *vs.* 2.1%; odds ratio [uncemented *vs.* cemented], 4.37; 95% CI, 1.19 to 24.00). Other complications were similar in the two groups. *(Article Selection: Martin J. London, M.D. Image: J. P. Rathmell.)*

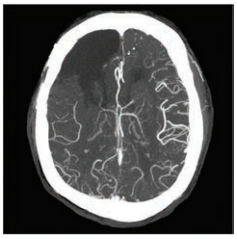
Take home message: In a large randomized trial, quality of life was better and periprosthetic fracture was lower in patients with cemented hemiarthroplasty after intracapsular hip fracture.



Ten-year outcomes of off-pump vs on-pump coronary artery bypass grafting in the Department of Veterans Affairs: A randomized clinical trial. JAMA Surg 2022; 157:303–10. PMID: 35171210.

From February 2002 to May 2007, a randomized controlled trial (Randomized On/Off Bypass trial [ROOBY]) was performed including more than 2,000 veterans. Patients were randomized to on-pump or off-pump coronary artery bypass grafting (CABG) procedures in 18 Veterans Affairs (VA) medical centers. Results have previously been published at 1 and 5 yr of follow-up. The 10-yr co–primary endpoints included all-cause mortality or a composite of subsequent revascularization (percutaneous coronary intervention [PCI] or repeat CABG) or death, assessed dichotomously and as time-to-events. Secondary outcomes included PCIs, repeat CABG, cardiac symptoms, and estimated costs. Outcome information was collected *via* electronic medical records in combination with VA and non-VA databases. Intention-to treat analysis revealed no difference in 10-yr mortality: 31% on-pump in 1,099 patients (mean age, 62.5 yr) *versus* 34% off-pump in 1,104 patients (mean age, 62.3 yr) (relative risk, 1.05; 95% CI, 0.99 to 1.11; $P = 0.12$). The median time to reach the composite endpoint in the on-pump was significantly shorter in the off-pump group, 4.6 yr (interquartile range, 1.4 to 7.5 yr) *versus* 5.0 yr (interquartile range, 1.8 to 7.9 yr) on-pump; $P = 0.03$. All other endpoints were comparable between the two groups. Results were also confirmed in sensitivity analyses. *(Article Selection: Beatrice Beck-Schimmer, M.D. Image: J. P. Rathmell.)*

Take home message: In this large, selected cohort of veteran patients enrolled in the landmark ROOBY trial, no long-term advantages were found for off-pump CABG.



Endovascular therapy for acute stroke with a large ischemic region. N Engl J Med 2022; 386:1303–13. PMID: 35138767.

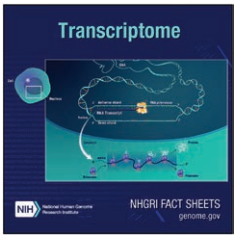
The role of endovascular therapy *versus* medical care alone for large acute ischemic strokes (which is generally avoided due to risk of postreperfusion bleeding) has not been well studied. This is a multicenter, randomized trial in Japan of patients with large strokes on imaging, as indicated by an Alberta Stroke Program Early Computed Tomographic Score (ASPECTS) value of 3 to 5 (scale, 0 to 10; lower values indicate larger infarction). Patients were randomized to receive endovascular therapy with medical care or medical care alone within 6 h after symptom onset or within 24 h if there was no early change on imaging. One hundred one patients were randomized to endovascular therapy and 102 to the medical care group; 27% in each group received alteplase (0.6 mg/kg). The primary outcome was the percentage of patients with a modified Rankin scale score of 0 to 3 (scale, 0 to 6; higher scores indicate greater disability) at 90 days. The primary outcome was better in the endovascular therapy group relative to medical therapy alone (31% *vs.* 13%; relative risk, 2.43; 95% CI, 1.35 to 4.37; $P = 0.002$). Any intracranial hemorrhage occurred in 58% and 31%, respectively ($P < 0.001$). *(Article Selection: David Faraoni, M.D., Ph.D. Image: J. P. Rathmell.)*

Take home message: Patients with large cerebral infarctions had better functional outcomes with endovascular therapy compared to medical care alone, albeit with more intracranial hemorrhages.

Regular acetaminophen use and blood pressure in people with hypertension: The PATH-BP Trial. Circulation 2022; 145:416–23. PMID: 35130054.

Observational studies suggest that acetaminophen may increase blood pressure, but clinical trials are lacking. This single-center, double-blind, randomized, investigator-initiated crossover study enrolled 110 individuals with a history of hypertension to receive 4 g acetaminophen daily in divided doses or matched placebo for 2 weeks. Patients crossed over to the alternate treatment after a 2-week washout period. At the beginning and end of each treatment period, 24-hr ambulatory blood pressure readings were measured. The primary outcome was the change in mean daytime systolic blood pressure from baseline to end of treatment between the placebo and acetaminophen arms. One-hundred three patients completed both arms of the study. Those taking acetaminophen, compared with placebo, had significantly greater mean daytime systolic blood pressure (133 ± 10 to 136 ± 10 mmHg [acetaminophen] *vs.* 134 ± 10 to 132 ± 10 mmHg [placebo]; $P < 0.0001$) with a placebo-corrected rise of 4.7 mmHg (95% CI, 2.9 to 6.6). Mean daytime diastolic blood pressure was also greater in patients taking acetaminophen (81 ± 8 to 82 ± 8 mmHg in the acetaminophen group *vs.* 82 ± 8 to 81 ± 8 mmHg in the placebo patients; $P = 0.005$) with a placebo-corrected rise of 1.6 mmHg (95% CI, 0.5 to 2.7). Similar findings were seen for 24-hr ambulatory and clinic blood pressure readings. *(Article Selection: BobbieJean Sweitzer, M.D. Image: J. P. Rathmell.)*

Take home message: Individuals with hypertension taking 4 g acetaminophen daily had greater systolic blood pressure by approximately 5 mmHg when compared with placebo, raising concerns about safety in those with cardiovascular risk factors.



System-wide transcriptome damage and tissue identity loss in COVID-19 patients. Cell Rep Med 2022; 3:100522. PMID: 35233546.

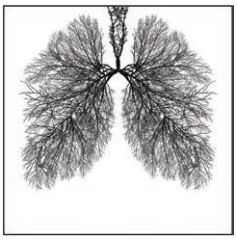
The molecular mechanisms underpinning the clinical presentation of patients with SARS-CoV-2 infection are poorly characterized. Body-wide and tissue-compartment-specific transcriptional profiling, combined with imaging, were applied to nasopharyngeal swabs and autopsy tissue from 39 patients who died from SARS-CoV-2 infection and compared with 22 healthy organ donor samples and non–COVID-19 acute lung injury samples. Duration of illness was inversely proportional to viral load. There was loss of tissue type identity. The COVID-19 samples were marked by a ubiquitous increase in fibroblasts and immune cells but a loss of organ-specific major cell types, such as alveolar epithelial cells in the lung and cardiomyocytes in the heart. Interferon- and cytokine-related pathways increased in large airway tissues, while complement activation was found in vascular tissues. The differentially expressed genes in the nasopharyngeal swabs correlated to tissue-specific gene expression in the early stages of infection but not in later infection. There was enrichment of macrophage, neutrophil, and T-cell pathways in SARS-CoV-2 samples compared to the non–COVID-19 acute lung injury samples. *(Article Selection: Jamie Sleigh, M.D. Image: Public domain, available at https://www.genome.gov/about-genomics/fact-sheets/Transcriptome-Fact-Sheet.)*

Take home message: The map of SARS-CoV-2 molecular pathophysiology is complex but dominated by transcriptional dysregulation of immune responses and loss of tissue identity.

Chronic paternal morphine exposure increases sensitivity to morphine-derived pain relief in male progeny. Sci Adv 2022; 8:eabk2425. PMID: 35171664.

Preclinical investigations report that prenatal morphine exposure may produce changes in the nervous system regarding morphine-induced antinociception in the offspring. However, previous approaches limit relevance of the results. This study evaluated consequences of prenatal morphine exposure (in the male parent) using novel approaches to assess nociception in rats validating a "rat pain scale" in both sexes using high-speed imaging of pain-like behaviors such as orbital tightening, paw shake, jumping, and paw guarding, combined with statistical approaches and machine learning. Analyses of behaviors obtained with von Frey filaments (commonly used to assess mechanical thresholds assumed to relate to nociception thresholds) did not produce pain-like behaviors. Offspring of morphine-exposed sires displayed morphine-induced antinociception that was detected with the rat pain scale but not with the latter. RNA sequencing in the periaqueductal gray indicated that morphine-sired male progeny had alterations in the expression of genes related to regulation of the G protein–signaling family of proteins with down-regulation in Rgs4, Rgs14, and Rgs16 and up-regulation in Rgs8. These proteins are known to regulate the opioid receptor, thus providing mechanisms in the alteration of morphine-induced antinociception in males prenatally exposed to morphine. *(Article Selection: Cyril Rivat, Ph.D. Image: J. P. Rathmell.)*

Take home message: This study demonstrates the need to develop more sensitive behavioral approach to accurately assess pain-like behaviors in animal studies. It also shows the effects of prenatal parental morphine exposure on offspring response to morphine-induced antinociception.



Ex vivo enzymatic treatment converts blood type A donor lungs into universal blood type lungs. Sci Transl Med 2022; 14:eabm7190. PMID: 35171649.

Successful lung transplantation depends on using donor organs that have protein or carbohydrate antigens on their cell surface that are immunologically compatible with the recipient. This results in some recipients (*e.g.*, ABO-O recipients) having to wait longer for compatible organs, increasing their risk of death due to lack of suitable donors. A strategy to create universally compatible ABO organs would improve fair access to donor organs. In the current study, human lungs were treated enzymatically to remove the A antigen during 1 to 3 h of *ex vivo* lung perfusion. After treatment, lungs were perfused with plasma samples from ABO-O individuals for 4 h to serve as a surrogate recipient circulation to mimic an *in vivo* reperfusion phase. Circulating anti-A antibodies were not depleted in the plasma, indicative of limited binding of antibodies to enzymatically ABO-A antigen-depleted cell surfaces. Inflammatory cytokines and complement C4d deposition were reduced in the enzymatically treated lungs compared to control lungs not devoid of ABO-A antigens. *(Article Selection: Charles Emala, M.D. Image: Adobe Stock.)*

Take home message: These preliminary findings suggest that enzymatic reduction of ABO-A antigens prevented hyperacute antibody-mediated injuries in simulated human lung transplantation; however, endogenous glycosyltransferases would be expected to regenerate cleaved A antigens such that longer-term compatibility requires further study.

Whole blood versus red cell concentrates for children with severe anaemia: A secondary analysis of the Transfusion and Treatment of African Children (TRACT) trial. Lancet Glob Health 2022; 10:e360–8. PMID: 35180419.

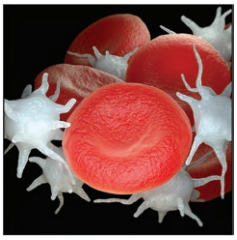
In sub-Saharan Africa, whole blood remains the first-line transfusion option for children with severe anemia although the use of components (*e.g.*, packed or settled red blood cells) is increasing. The Transfusion and Treatment of African Children (TRACT) trial was a factorial, randomized trial of children (2 months to 12 yr) with hemoglobin less than 6 g/dl conducted in Uganda and Malawi. Children received either 20 to 30 ml/kg whole blood or red cell concentrates *versus* no immediate transfusion (control group; unless hemoglobin was less than 4 g/dl). This secondary analysis examined the effects of whole blood *versus* red cell concentrates on outcomes in 3,188 children. Whole blood was the first component provided in 41% of the 3,992 transfusions. Hemoglobin recovery at 8 h was significantly lower in those who received component therapy than in those receiving whole blood (means ranging from –1.0 to –1.5 g/dl varying with packed *vs.* settled cells and dose [overall $P < 0.0001$]). Children receiving packed or settled cells had higher odds of a second transfusion (odds ratio, 2.32 [95% CI, 1.30 to 4.12] for packed cells and 2.97 [2.18 to 4.05] for settled cells; $P < 0.001$). There was no association between component type and mortality at 28 days or 180 days, or readmission to hospital. *(Article Selection: David Faraoni, M.D., Ph.D. Image: J. P. Rathmell.)*

Take home message: In anemic children in sub-Saharan Africa, transfusion with packed or settled red cells led to a slower rise in hemoglobin and greater odds of a second transfusion relative to whole blood transfusion.

A three-step support strategy for relatives of patients dying in the intensive care unit: A cluster randomised trial. The Lancet 2022; 399:656–64. PMID: 35065008.

One in five Americans are admitted to the intensive care unit (ICU) at or near the time of their death. This is a major stressor for caregivers, who experience high rates of depression, anxiety, and posttraumatic stress disorder during and after their relative's time in the ICU. This multi-center, cluster-randomized controlled trial conducted from 2017 to 2018 in 34 ICUs across France evaluated whether a physician-driven and nurse-aided three-step support strategy for caregivers who have decided to withdraw or withhold life support would improve caregiver outcomes. The intervention comprised three meetings of the attending physician and bedside nurse with the caregiver, at the time of the decision to withdraw, during the dying process, and after the patient's death. Staff were trained to emphasize attentive listening, empathy, and caregiver well-being. The primary outcome was the proportion of caregivers with prolonged grief (as measured with the Prolonged Grief-13 questionnaire, score 30 or above), measured 6 months after the patient's death. The study enrolled and randomized 875 caregivers, and 379 (78%) in the intervention group *versus* 309 (79%) completed 6-month follow-up. Caregivers in the intervention group were less likely to have prolonged grief (21% *vs.* 15%; $P = 0.035$) and had lower median Prolonged Grief-13 scores (19 *vs.* 21; mean difference, 2.5; 95% CI, 1.04 to 3.95). *(Article Selection: Meghan Prin, M.D., M.S. Image: J. P. Rathmell.)*

Take home message: A physician-led and nurse-supported three-step support strategy for caregivers who decide to withdraw life support for a dying relative resulted in less prolonged grief among caregivers.



Platelet-mimicking procoagulant nanoparticles augment hemostasis in animal models of bleeding. Sci Transl Med 2022; 14:eabb8975. PMID: 35080915.

The use of platelets for the treatment of bleeding disorders faces challenges, including bacterial contamination, donor availability, short shelf life, and high costs. Hence, the availability of a platelet-mimicking procoagulant for the management of bleeding would be beneficial. This study developed a hybrid liposomal nanoparticle system (platelet-mimicking procoagulant nanoparticles) in which the liposomal membrane contained distearoylated phosphatidylserine, the procoagulant anionic phospholipid found on the surface of activated platelets, in combination with other lipopeptide components, namely cholesterol-tethered polyethylene glycol, which is cleaved at the site of injury by plasmin, allowing site-specific activation of the clotting cascade. *In vitro* experiments with platelet-mimicking procoagulant nanoparticles immobilized on glass slides showed rescue of thrombin generation and clot formation in thrombocytopenic plasma. Addition of platelet-mimicking procoagulant nanoparticles to human plasma depleted of platelets amplified thrombin and fibrin generation and reduced clot lysis. *In vivo* experiments testing hemostatic effect of platelet-mimicking procoagulant nanoparticles in a tail transection mouse model where mice were rendered thrombocytopenic showed that 2 mg/kg platelet-mimicking procoagulant nanoparticles administered 2 h before tail transection reduced bleeding times from 1,071 to 404 s ($P < 0.001$), reaching bleeding times similar to those in conditions with platelet substitution (355 s). Platelet-mimicking procoagulant nanoparticles also enhanced hemostasis and survival in rodent traumatic hemorrhage models. *(Article Selection: Michael Zaugg, M.D., M.B.A. Image: J. P. Rathmell.)*

Take home message: Platelet-mimicking procoagulant nanoparticles foster hemostasis without off-target thrombotic risks in rodent models of bleeding.

Activity-dependent spinal cord neuromodulation rapidly restores trunk and leg motor functions after complete paralysis. Nat Med 2022; 28:260–71. PMID: 35132264.

Each year, nearly half a million people suffer from spinal cord injury, which can lead to severe disability and poor quality of life and is associated with a high mortality rate, even after surviving the initial injury. In this setting, epidural electrical stimulation—commonly termed *spinal cord stimulation*—recruits large-diameter afferent fibers entering the spinal cord *via* the dorsal roots, which in well-selected patients can improve motor function in incomplete injury to facilitate ambulation. This study demonstrates a redesigned paddle electrode to target dorsal roots involved in lower trunk and leg movements. A computational framework was created using structural and functional imaging to optimize lead placement with software enabling the rapid configuration of biomimetic stimulation programs that deliver concurrent stimulation waveforms that are switched on and off with precision. The device and software were tested in three individuals with complete sensorimotor paralysis and quiescent muscles during any attempt to walk. Within 1 day, these individuals regained the ability to control motor movements so that they could independently step on a treadmill, although extension motions were limited. Within 3 days, all could ambulate independently and cycle or swim. *(Article Selection: Steven Cohen, M.D. Image: Adobe Stock.)*

Take home message: Building on advances in neuromodulation in patients with incomplete spinal cord injury, spinal cord stimulation provides hope for clinically meaningful improvement in patients with complete injury and possibly a wide range of neurodegenerative conditions.