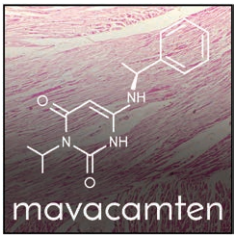
SCIENCE, MEDICINE, AND THE ANESTHESIOLOGIST
ANESTHESIOLOGY
Martin J. London, M.D., Editor
Key Papers from the Most Recent Literature Relevant to Anesthesiologists

Blood–brain barrier crossing renin-angiotensin drugs and cognition in the elderly: A meta-analysis. Hypertension 2021; 78:629–43. PMID: 34148364.

Hypertension is associated with an accelerated rate of cognitive decline and dementia in elderly subjects. Renin-angiotensin system drugs (AT1-receptor blockers or angiotensin-converting enzyme inhibitors) may show cognitive benefits beyond those related to blood pressure control, particularly those that penetrate the blood–brain barrier. This meta-analysis compared the potential cognitive benefits of blood–brain barrier penetrating agents *versus* nonpenetrant agents. Data from 14 heterogeneous studies (one randomized trial, ten prospective and one retrospective longitudinal cohort studies) were included. A multivariable model was constructed for decline from baseline in seven cognitive domains (attention, executive function, language, verbal memory learning, recall, mental status, and processing speed). After 3 yr of follow-up, those taking blood–brain barrier penetrating drugs had slightly better memory recall despite a relatively higher vascular risk burden (four studies, effect size = 0.07 [95% CI, 0.01 to 0.12]; $P = 0.03$), but worse attention (two studies, effect size = –0.17 [95% CI, –0.23 to –0.10]; $P = 0.02$), than the group who had been taking the peripherally acting drugs. *(Article Selection: Jamie Sleigh, M.D. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: These data suggest some link between blood–brain barrier crossing renin-angiotensin system drugs and a slower rate of memory decline in elderly subjects. Better attention in those taking peripherally acting drugs might be explained by a lower vascular risk burden.



Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): Health status analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2021; 397:2467–75. PMID: 34004177.

Mavacamten is a first-in-class cardiac myosin inhibitor for the treatment of hypertrophic obstructive cardiomyopathy. EXPLORER-HCM, a randomized, placebo-controlled, double-blind phase 3 trial previously demonstrated that patients with symptomatic hypertrophic obstructive cardiomyopathy dosed orally once per day for 30 weeks had significantly lower-post-exercise left ventricular outflow tract gradients, peak oxygen consumption, and improved New York Heart Association class rating compared to placebo. In this health status analysis of that trial, the Kansas City Cardiomyopathy questionnaire, a validated 100-point patient-reported scale, was used to assess heart failure symptom frequency and severity, functional capacity, and quality of life. Changes of 20 or more points correlate with large changes in clinical status from the patient and provider perspective. Of 251 enrolled patients, 75% of treated subjects completed the 30-week questionnaire *versus* 69% of placebo. At 30 weeks, treated patients had an overall score difference of 9 points (95% CI, 6 to 13; $P < 0.0001$) compared to placebo, with 36% treated reporting a large increase (greater than 20 points) *versus* 15% of placebo (number needed to treat of 5 [95% CI, 3 to 11]). After an 8-week drug washout period, health scores returned to baseline in the treated group. *(Article Selection: Marilyn Michelow, M.D. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: This health status analysis of a randomized treatment trial of mavacemten for symptomatic obstructive hypertrophic cardiomyopathy reports significantly better health status associated with its use.

MDMA-assisted therapy for severe PTSD: A randomized, double-blind, placebo-controlled phase 3 study. Nat Med 2021; 27:1025–33. PMID: 33972795.

Post-traumatic stress disorder (PTSD) is a common and sometimes severe psychiatric condition caused by experiencing or witnessing a traumatic event. The use of psychotropic drugs for the treatment of psychological conditions is of growing interest. MDMA (3,4-methylenedioxymethamphetamine) is one such drug that inhibits serotonin reuptake by binding to transporters. In this two-arm, randomized, blinded phase 3 trial, a series of three sessions involving psychotherapy with concomitant MDMA or placebo infusion was carried out on a total of 90 participants. The Clinician-Administered PTSD Scale-5 administered at 18 weeks was the primary endpoint. A mean decrease (improvement) of 24 points (mean ± SD, –24 ± 12) in the MDMA plus psychotherapy group compared to a mean decrease of 14 ± 12 in the placebo with psychotherapy group was observed ($P < 0.001$). Clinically important (greater than or equal to 10 points reduction) in symptoms was observed in 67% of those receiving MDMA, but only 32% of those receiving placebo. Importantly, the MDMA-assisted therapy was effective for groups known to be resistant to therapy, including those with substance use disorders, dissociative-type PTSD, and in patients with childhood trauma. Side effects were more common with MDMA and included mild to moderate muscle tightness, decreased appetite, nausea, hyperhidrosis, and feeling cold. *(Article Selection: J. David Clark, M.D., Ph.D. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: MDMA use was associated with a significant improvement in subjects with post-traumatic stress disorder relative to placebo, although minor side effects were more common.

Obstructive sleep apnea and cardiovascular disease: A scientific statement from the American Heart Association. Circulation 2021; 144:e56–e67. PMID: 34148375.

Obstructive sleep apnea (OSA) may occur in 40 to 80% of men and women with hypertension, heart failure, atrial fibrillation, coronary artery disease, stroke, and pulmonary hypertension. Severe obstructive sleep apnea is associated with greater cardiovascular and all-cause mortality. This scientific statement from the American Heart Association provides a comprehensive recent review of literature on the pathophysiology, clinical manifestations, screening, diagnostic evaluation, treatments, and areas for future research for OSA in patients with a variety of cardiovascular diseases. Screening is recommended for patients with resistant systemic hypertension, pulmonary hypertension, and recurrent atrial fibrillation. In patients with New York Heart Association class II or greater heart failure, tachy-brady syndrome, a history of ventricular tachycardia, or survivors of sudden cardiac death, formal assessment should be considered. After stroke, there is clinical equipoise with respect to the benefit of sleep apnea screening and treatment. Continuous positive airway pressure therapy has been associated with decreased daytime sleepiness and improved quality of sleep, modest systemic and pulmonary blood pressure reduction, improved atrial fibrillation burden, and possibly lesser long-term mortality in heart failure. For mild to moderate obstructive sleep apnea, oral appliances may be helpful. Interventions should be followed by repeat sleep testing to confirm effectiveness. *(Article Selection: Marilyn Michelow, M.D. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: A scientific statement from the American Heart Association provides a comprehensive updated review of obstructive sleep apnea in patients with cardiovascular disease.

Effect of platelet-rich plasma injection vs sham injection on tendon dysfunction in patients with chronic midportion achilles tendinopathy: A randomized clinical trial. JAMA 2021; 326:137–44. PMID: 34255009.

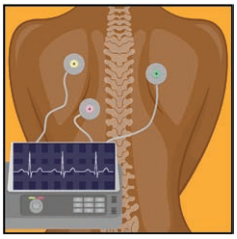
Platelet-rich plasma injections are commonly used for chronic midportion Achilles tendinopathy despite limited evidence for a treatment effect. In a participant-blinded, multicenter randomized clinical trial of 240 people at 24 United Kingdom National Health Service sites, the effects of a single platelet-rich plasma injection (n = 121) *versus* sham injection (n = 119) were assessed using the Victorian Institute of Sport Assessment-Achilles (VISA-A) score (a composite measure of tendinopathy severity, range 0 to 100; 12-point difference considered clinically important) measured 6 months after treatment allocation. Subjects had Achilles tendon pain for more than 3 months and findings confirmed by either ultrasound or magnetic resonance imaging. The primary analysis was adjusted for laterality, age, sex, and baseline VISA-A score. The mean age of subjects was 52 yr (58% women) and 92% completed the trial. At 6-month follow-up, mean VISA-A scores were not significantly different between groups: platelet-rich plasma 54 *versus* placebo 53 (adjusted mean difference, –2.7 [95% CI, –8.8 to 3.3]). Adverse events included injection site discomfort (97 *vs.* 73 patients), swelling (56 *vs.* 52 patients) and bruising (48 *vs.* 49 patients). *(Article Selection: Martin J. London, M.D. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: Achilles tendon dysfunction at 6 months was not different between patients who received a single injection of intratendinous platelet-rich plasma compared to a sham injection.

Association of intravenous tranexamic acid with thromboembolic events and mortality: A systematic review, meta-analysis, and meta-regression. JAMA Surg 2021; 156:e210884. PMID: 33851983.

Tranexamic acid, a synthetic derivative of lysine with antifibrinolytic activity, has been advocated to reduce perioperative blood loss and transfusion requirements, but concerns about associated thromboembolic complications persist. The authors evaluated randomized controlled trials (1976 to 2020) comparing intravenous tranexamic acid to placebo to evaluate the association of intravenous tranexamic acid with thromboembolic events (venous or hepatic artery thrombosis, pulmonary embolism, venous thromboembolism, myocardial or cerebral ischemia or infarction, and limb or mesenteric ischemia) and mortality in patients of all ages and medical/surgical disciplines. This meta-analysis considered 216 trials of 125,550 patients with outcome data. Thromboembolic events occurred in 1,020 (2%) patients receiving tranexamic acid *versus* 900 (2%) control patients (risk difference, 0.001 [95% CI, –0.001 to 0.002]; $P = 0.49$). Thromboembolic complications were not more common in studies that included patients with a previous history of vascular occlusive events. Meta-regression of 143 tranexamic acid intervention groups found no dose-effect association (risk difference, –0.005 [95% CI, –0.021 to 0.011]; $P = 0.53$). Intravenous tranexamic acid was associated with less overall mortality (risk difference, –0.011 [95% CI, –0.015 to –0.007]; $P < -0.001$) and bleeding mortality (risk difference, –0.008 [95% CI, –0.011 to –0.005]; $P < 0.001$), but not nonbleeding mortality (risk difference, –0.002 [95% CI, –0.006 to 0.002]; $P = 0.29$). *(Article Selection: Meghan Prin, M.D., M.S. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: Intravenous tranexamic acid is not associated with a greater risk of thromboembolic complications regardless of the dose or previous history of vascular occlusive events. Intravenous tranexamic acid reduces overall and bleeding mortality.



Prone and supine 12-lead ECG comparisons: Implications for cardiac assessment during prone ventilation for COVID-19. JACC Clin Electrophysiol 2021 Jun 22 [Epub ahead of print]. PMID: 34217662.

Prone positioning may improve oxygenation in patients with COVID-19 pneumonia. Relocating precordial leads to the dorsal thorax during proning has been advocated to avoid moving the patient in the event of a complication, but its impact on electrocardiogram (ECG) morphology is unclear. This prospective, observational cohort study included 100 spontaneously ventilating non-COVID-19 patients recruited from cardiology units who underwent sequential evaluation of three 12-lead ECG configurations: supine front; prone position with frontal precordial leads; and prone with mirror image precordial leads. Prone positioning was associated with a small but statistically significant degree of QTc prolongation (prone front: 437 ± 32 ms *vs.* supine front 432 ± 31 ms; $P < 0.01$; prone back 436 ± 34 ms *vs.* supine front 432 ± 31 ms; $P < 0.02$). With prone back positioning leads V1 to V3 demonstrated a qR morphology in 90% along with changes in T-wave polarity in 84%. Diagnostic signs of anterior ischemia (V1 – V3) were not detected and were replaced by an R wave in V1. Left bundle branch block appeared as right bundle branch block in 71%; QRS narrowing with a qR in V1 occurred in 83% of patients with right bundle branch block. ST-segment/T-wave changes in limb leads and arrhythmia detection were largely unaffected. *(Article Selection: Martin J. London, M.D. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: Although useful for ST-segment/T-wave evaluation in limb leads, bundle branch detection, and rhythm monitoring, prone ECG monitoring with dorsal precordial leads is insensitive for detecting anterior ischemia.

The Lancet Women and Cardiovascular Disease Commission: Reducing the global burden by 2030. Lancet 2021; 397:2385–438. PMID: 34010613.

Despite efforts to reduce cardiovascular disease burden in women, it remains a global problem. This Lancet Commission, *via* an extensive didactic review, provides a pathophysiologic and epidemiologic framework to identify knowledge gaps in the prevention, diagnosis, treatment, and research in this arena with the goal to reduce its burden by 2030. Concrete strategies are provided to improve outcomes in women, including the following priorities: direct funding for data acquisition on prevalence and outcomes of cardiovascular disease in women globally; development of educational programs on cardiovascular disease in women for researchers, healthcare providers and communities; prioritization of sex-specific research; development of strategies improving participation of women in clinical trials; prioritization of funding in health organizations for cardiovascular disease health programs in women from socioeconomically deprived regions; education of healthcare providers and patients regarding early detection and prevention of cardiovascular disease in young women; launching of policy-based initiatives and cardiovascular disease risk factor programs in settings frequented by women; research investigating sex-specific, psychosocial, and socioeconomic risk factors on cardiovascular disease in women; promotion and increase of healthy heart programs in highly populated and progressively industrialized regions; and establishment of public–private partnerships to develop large-scale programs for women with cardiovascular disease. *(Article Selection: Beatrice Beck-Schimmer, M.D. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: This Lancet Commission report provides an extensive didactic review of the pathophysiology and epidemiology of cardiovascular disease in women with the express goal for its reduction by 2030.

Aspirin versus clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention (HOST-EXAM): An investigator-initiated, prospective, randomised, open-label, multicentre trial. Lancet 2021; 397:2487–96. PMID: 34010616.

Current guidelines recommend 6 to 12 months of dual antiplatelet therapy after percutaneous coronary intervention with drug eluting stents, but it is unknown whether clopidogrel or aspirin is superior for subsequent indefinite single antiplatelet therapy. In a prospective, randomized, open-label, multicenter trial including 37 study sites in South Korea (HOST-EXAM), 5,530 patients (75% male) were randomized to receive either clopidogrel 75 mg or aspirin 100 mg once daily for 24 months after intervention after an event-free period of 6 to 18 months of dual antiplatelet therapy. The primary outcome included all-cause death, nonfatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and major bleeding assessed by clinical follow-up at 12 and 24 months, and it occurred in 6% of patients with clopidogrel *versus* 8% of patients with aspirin monotherapy (hazard ratio, 0.73 [95% CI, 0.59 to 0.90]; $P = 0.0035$), with an absolute risk reduction of 2% and a number needed to treat of 51. Clopidogrel treatment caused less major bleeding (2.3 *vs.* 3.3%, $P = 0.036$) and fewer hemorrhagic strokes (0.2 *vs.* 0.6%, $P = 0.01$). However, no differences in all-cause or cardiac death, two individual components of the primary outcome, were observed. *(Article Selection: Michael Zaugg, M.D., M.B.A., F.R.C.P.C. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: In patients requiring indefinite antiplatelet monotherapy after percutaneous coronary intervention, clopidogrel outperformed aspirin in the secondary prevention of future adverse cardiovascular events.

 DOI: 10.1097/ALN.0000000000003990

Effects of intraoperative auditory stimulation on pain and agitation on awakening after pediatric adenotonsillectomy: A randomized clinical trial. JAMA Otolaryngol Head Neck Surg 2021; 147:638–45. PMID: 34014258.

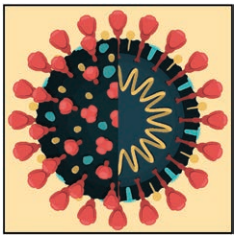
Pain and emergence delirium are common in children on emergence from adenotonsillectomy. Intraoperative auditory stimulation may reduce postoperative pain, anxiety, and analgesic requirements in adults. Its effect in pediatric populations has not been studied. In this single-center, double-blinded, four-armed, randomized clinical trial, children undergoing adenotonsillectomy were randomized to one of the following groups: (1) auditory stimulation with music (Mozart classical harmony symphonies; n = 26); (2) auditory stimulation with noise (rhythmic heartbeat; n = 25); (3) ambient noise insulation with masking earplug (n = 25); or (4) standard treatment (n = 28). The primary outcome was pain on awakening as assessed by a 10-point age-appropriate pain scale. The secondary outcome was emergence delirium as assessed by the 20-point Pediatric Anesthesia Emergence Delirium scale. Median pain on awakening was 2 (interquartile range, 0 to 5) in the music, 4 (interquartile range, 0 to 6) in the noise, 6 (interquartile range, 3 to 9) in the earplug, and 7 (interquartile range, 6 to 8) in the standard treatment group. Median emergence delirium scale was 9 (interquartile range, 0 to 13) in the music, 7 (interquartile range, 0 to 10) in the noise, 11 (interquartile range, 10 to 16) in the earplug, and 14 (interquartile range, 11 to 17) in the standard treatment group. Effect size analyses revealed significantly less pain on awakening with music or noise relative to control. *(Article Selection: Laszlo Vutskits, M.D., Ph.D. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: In children undergoing adenotonsillectomy, intraoperative auditory stimulation, either by music or rhythmic noise, resulted in lower pain scores at awakening and the extent of emergence delirium.

STS/SCA/AmSECT/SABM update to the clinical practice guidelines on patient blood management. Ann Thorac Surg 2021; 112:981–1004. PMID: 34217505.

The concept of patient blood management was developed to operationalize blood utilization and optimize patient outcomes. Such strategies are constantly evolving, forcing guidelines to be re-evaluated periodically. A multidisciplinary panel of experts was convened by the Society of Thoracic Surgeons, including members of the Society of Cardiovascular Anesthesiologists, the American Society of ExtraCorporeal Technology, and the Society for the Advancement of Blood Management, to review the latest evidence on patient blood management to update their 2011 version of the blood conservation clinical practice guidelines. The guidelines cover preoperative interventions, management of preoperative anticoagulants, use of antifibrinolytic agents, use of blood products and derivatives, perfusion interventions, blood salvage, standardized transfusion protocols, fluid management, and management of blood resources. Of note, recent data on use of preoperative IV iron regimens, large-scale randomized data on transfusion thresholds, data on safety and clinical benefit of tranexamic acid, use of nonvitamin K oral anticoagulants, emphasis on algorithmic approaches guided by point-of-care testing, and avoidance of prophylactic blood component transfusion are highlighted. *(Article Selection: David Faraoni, M.D., Ph.D. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: A multisociety collaboration of cardiac surgical, anesthesia, and perfusion stakeholders has updated their 2011 guidelines for patient blood management in cardiac surgery.



Structural basis for SARS-CoV-2 envelope protein recognition of human cell junction protein PALS1. Nat Commun 2021; 12:3433. PMID: 34103506.

The authors utilized cryoelectron microscopy to resolve the binding of the SARS-CoV-2 envelope protein to the human cell junction protein PALS1, a protein present at many cell junctions, including those on airway epithelial and vascular endothelial cells. Four amino acids (DLLV) on the C-terminal portion of the envelope protein are responsible for the binding of the envelope protein to a pocket formed between the PDZ and SH3 domains of PALS1. PDZ and SH3 domains are common motifs on more than 100 unique human proteins. The virus has evolved a region of one of its surface proteins to exploit this common mammalian protein motif as a binding site. Subsequently, the envelope protein-PALS1 complex translocates from the cell surface to the endoplasmic-reticulum–Golgi intermediate compartment, an organelle responsible for intracellular protein trafficking, a process thought to account for leakage between epithelial and vascular cells, diffuse alveolar damage, initiation of cytokine cascades, and acute respiratory distress syndrome. The most virulent members of this coronavirus family, SARS-CoV-1 and SARS-CoV-2, contain the DLLV amino acid sequence, while the less virulent MERS-CoV virus conserves two of the four amino acids (DEWV) in their C-terminal portions of the E protein. *(Article Selection: Charles Emala, M.D. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: The protein binding site of SARS-CoV-2 has been identified at a high resolution using cryoelectron microscopy within a protein pocket formed by PDZ and SH3 domains on the human cell junction protein PALS1. This finding holds promise for the development of pharmacologic inhibitors of the binding of SARS-CoV-2 to human cells.