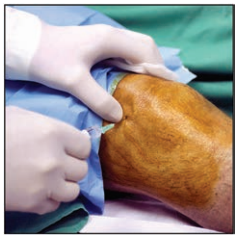
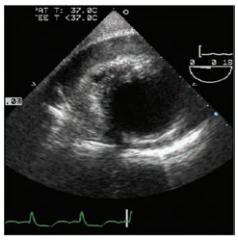
SCIENCE, MEDICINE, AND THE ANESTHESIOLOGIST
ANESTHESIOLOGY
Martin J. London, M.D., Editor
Key Papers from the Most Recent Literature Relevant to Anesthesiologists



Effect of intra-articular platelet-rich plasma vs placebo injection on pain and medial tibial cartilage volume in patients with knee osteoarthritis: The RESTORE randomized clinical trial. JAMA 2021; 326:2021–30. PMID: 34812863.

Intra-articular autologous platelet rich plasma injection for osteoarthritis has been pursued as a treatment alternative, although high-quality trials are lacking. This multicenter, randomized, triple-blinded, placebo-controlled trial injected knees with platelet rich plasma or saline weekly three times (weekly intervals) in 288 participants with mild to moderate osteoarthritis. The coprimary outcomes were 12-month change in pain on an 11-point pain scale (0 to 10) and percentage change in medial tibial cartilage volume as assessed by magnetic resonance imaging. At 12 months, those in the platelet-rich plasma group demonstrated a pain score improvement of mean ± SD, 2.1 ± 2.7 points *versus* 1.8 ± 2.5 points in the saline group, $P = 0.17$. Likewise, the reduction in medial tibial cartilage volume at 12 months was 1.4% ± 7.2 for the platelet-rich plasma group *versus* 1.2 ± 6.8 for the saline group, $P = 0.81$. Secondary pain and function-related endpoints were followed as well with the majority showing no advantage of platelet-rich plasma. *(Article Selection: J. David Clark, M.D., Ph.D. Image: Getty Images.)*

Take home message: Intra-articular platelet-rich plasma injections in subjects with symptomatic mild to moderate knee osteoarthritis did not improve symptoms or joint structure compared to saline placebo over a 12-month period.



Posterior left pericardiotomy for the prevention of atrial fibrillation after cardiac surgery: An adaptive, single-centre, single-blind, randomised, controlled trial. Lancet 2021; 398:2075–83. PMID: 34788640.

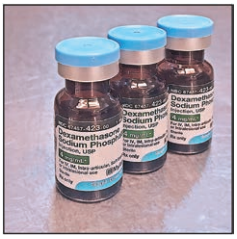
Pericardial effusion is common after cardiac surgery and may trigger atrial fibrillation. Posterior left pericardiotomy drains fluid into the left pleural cavity, potentially reducing the incidence of atrial fibrillation. This adaptive, controlled trial randomized adult patients undergoing elective cardiac surgery at a single U.S. center to posterior left pericardiotomy or no intervention with follow-up until 30 days after discharge. The primary outcome was the incidence of atrial fibrillation during the in-hospital stay using intention-to-treat analysis. Between 2017 and 2021, 420 patients (76% male; median CHA_2DS_2-VASc score of 2) were randomly assigned to the intervention (n = 212) or the no intervention group (n = 208). Three patients did not receive the planned intervention. The primary outcome was significantly lower in the intervention group (17% [37 of 212] *vs.* 32% [66 of 208]; $P = 0.0007$; odds ratio adjusted for CHA_2DS_2-VASc score 0.44 [95% CI, 0.27 to 0.70], $P = 0.0005$). The incidence of pericardial effusion was lower in the intervention group (12% [26 of 209] *vs.* 21% [45 of 211]; relative risk 0.58 [95% CI, 0.37 to 0.91]). Postoperative major adverse events occurred in six (3%) patients in the posterior left pericardiotomy group and in four (2%) in the no intervention group. *(Article Selection: Martin J. London, M.D. Image: D. Shook, Brigham and Women's Hospital.)*

Take home message: In this randomized trial, posterior left pericardiotomy significantly lowered the incidence of atrial fibrillation after elective cardiac surgery without greater postoperative complications.

Selective targeting of NaV1.7 via inhibition of the CRMP2-Ubc9 interaction reduces pain in rodents. Sci Transl Med 2021; 13:eabh1314. PMID: 34757807.

The importance of the NaV1.7 voltage-gated sodium channel in nociception (including acute and chronic pain) is well established. NaV1.7 channel reduces the threshold of pain-related action potentials by amplifying depolarizing signals. However, direct blockade of NaV1.7 in clinical studies has been disappointing. This study employed a novel approach to target the cell surface expression of NaV1.7. Using *in silico* computational docking studies and a library of 50,000 small molecules, a compound (a benzoylated 2-[4-piperidinyl]-1,3-benzimidazole analog named 194) was identified, which could directly regulate the cell surface expression of the NaV1.7 channel by blocking Ubc9 (E2 small ubiquitin-like modifier [SUMO] conjugated enzyme) from interacting (*via* SUMOylation, a post-translational modification) with CRMP2, a protein that binds to NaV1.7 and transports it to the cell membrane. Blocking the Ubc9-CRMP2 protein-protein interaction led to increased endocytosis and internalization of the NaV1.7 channel. Compound 194 demonstrated dose-dependent reversal of pain in six different models including postsurgical pain and paclitaxel-induced neuropathy in two species, mice and rats of both sexes, *via* four routes of administration (intrathecal, intraperitoneal, subcutaneous, and oral). Compound 194 also elicited synergistic effects with gabapentin and morphine and had no motor, depressive, or addictive side effects. *(Article Selection: Michael Zaugg, M.D., M.B.A. Image: Adobe Stock.)*

Take home message: Preventing SUMOylation of CRMP2 using a small molecule reduces cell surface expression of NaV1.7 channel and nociceptive signal propagation, allowing delivery of safe analgesia in small animal models.



Effect of 12 mg vs 6 mg of dexamethasone on the number of days alive without life support in adults with COVID-19 and severe hypoxemia: The COVID STEROID 2 randomized trial. JAMA 2021; 326:1807–17. PMID: 34673895.

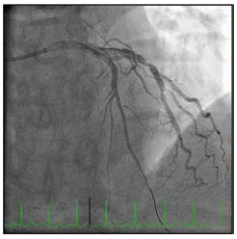
Based on previous studies, inpatients with severe COVID-19 are treated with 6 mg/d dexamethasone for 10 days. The effects of a higher dose are unknown. This blinded, randomized trial (including 26 international centers) compared treatment with 12 mg/d *versus* 6 mg/d of intravenous dexamethasone in adults requiring mechanical ventilation or substantial oxygen therapy. The primary outcome was the number of days alive without life support (invasive mechanical ventilation, circulatory support, or kidney replacement therapy) at 28 days. The secondary outcomes were number of days alive without life support at 90 days, mortality at 28 and 90 days, and serious adverse reactions. A total of 982 patients (41% female) were analyzed: 12 mg group, n = 491; 6 mg, n = 480. No significant difference was noted in the primary outcome between groups: median number of days alive without life support in the 12 mg group: 22 days (interquartile range, 6 to 28 days) *versus* 20 days (interquartile range, 4 to 28 days) in the 6 mg group (adjusted mean difference 1.3 days [95% CI, 0 to 2.6 days], $P = 0.07$). There were no significant differences in mortality at 28 or 90 days or in the incidence of serious adverse treatment reactions. *(Article Selection: Beatrice Beck-Schimmer, M.D. Image: J. P. Rathmell.)*

Take home message: In a randomized trial of inpatients with severe COVID-19, the use of a higher dose of the current recommendation of 6 mg of dexamethasone did not improve outcome.

Epinephrine before defibrillation in patients with shockable in-hospital cardiac arrest: Propensity matched analysis. BMJ 2021; 375:e066534. PMID: 34759038.

Current guidelines (U.S. and European) recommend prompt defibrillation for patients sustaining in-hospital shockable rhythms (ventricular fibrillation or pulseless ventricular tachycardia) with subsequent administration of epinephrine in whom defibrillation is unsuccessful after the second attempt. Given previous data documenting a high rate of earlier epinephrine administration in the Get With The Guidelines-Resuscitation registry, a time-dependent propensity-matched analysis of timing of epinephrine administration was performed utilizing 2000 to 2018 data from 497 hospitals participating in the Get With The Guidelines-Resuscitation registry. Among 34,820 patients with an initial shockable rhythm, 28% were treated with epinephrine before defibrillation. Such patients were more likely to have renal failure, sepsis, pneumonia, and receive mechanical ventilation before in-hospital cardiac arrest ($P < 0.0001$ for all). Treatment with epinephrine before defibrillation was strongly associated with delayed defibrillation (median 3 min *vs.* 0 min). In propensity-matched analysis (9,011 matched pairs), epinephrine before defibrillation was associated with lower odds of survival to discharge (25% *vs.* 30%; adjusted odds ratio 0.81; 95% CI, 0.74 to 0.88; $P < 0.001$), favorable neurological survival (19% *vs.* 21%; adjusted odds ratio 0.85; 95% CI, 0.76 to 0.92; $P < 0.001$), and survival after acute resuscitation (64% *vs.* 69%; adjusted odds ratio 0.76; 95% CI, 0.70 to 0.83; $P < 0.001$). *(Article Selection: Martin J. London, M.D. Image: J. P. Rathmell.)*

Take home message: Despite guidelines that prioritize immediate defibrillation for in-hospital cardiac arrest due to a shockable rhythm, more than 25% of patients were treated with epinephrine before defibrillation, which in propensity-matched analyses is associated with worse survival.



Fractional flow reserve–guided PCI as compared with coronary bypass surgery. NEJM 2022; 386:128–37. PMID: 34735046.

Current evidence suggests that coronary artery bypass grafting (CABG) offers better outcome in patients with three-vessel coronary artery disease when compared to multivessel percutaneous coronary intervention (PCI). This noninferiority randomized controlled study compared the incidence of major cardiac and cerebrovascular events (death from any cause, myocardial infarction, stroke, or repeat revascularization: primary composite outcome; death, myocardial infarction, or stroke: secondary composite outcome) within a year after treatment in patients with three-vessel coronary artery disease undergoing either CABG or PCI using current generation drug-eluting stents and fractional flow reserve guidance. Noninferiority was prespecified as an upper boundary of less than 1.65 for the 95% CI of the hazard ratio. A total of 1,500 patients were randomized across 48 international centers. The primary outcome occurred in 11% of patients assigned to undergo fractional flow reserve–guided PCI *versus* 7% of those assigned to undergo CABG (hazard ratio 1.5; 95% CI, 1.1 to 2.2; $P = 0.35$ for noninferiority). The secondary composite outcome occurred in 7.3% in the fractional flow reserve–guided PCI group *versus* 5.2% in the CABG group (hazard ratio, 1.4; 95% CI, 0.9 to 2.1). *(Article Selection: David Faraoni, M.D., Ph.D. Image: J. P. Rathmell.)*

Take home message: In this noninferiority trial comparing multivessel fractional flow reserve–guided PCI to CABG, patient outcomes were not statistically significantly different between treatment groups with respect to the primary composite outcome.

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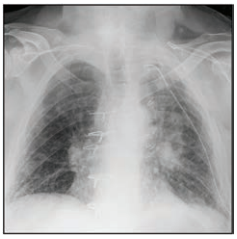

Inhaled pulmonary vasodilator therapy in adult lung transplant: A randomized clinical trial. JAMA Surg 2022; 157:e215856. PMID: 34787647.

Inhaled nitric oxide is routinely administered after lung transplantation to decrease pulmonary vascular resistance and help mitigate the risk of severe primary graft dysfunction. Inhaled epoprostenol is increasingly considered as a less expensive alternative, but studies comparing the therapeutic effect of the two drugs are sparse. In this prospective randomized controlled trial, 201 adult patients who underwent single or bilateral lung transplant were randomized to receive either inhaled nitric oxide (n = 98) or inhaled epoprostenol (n = 103) in the operating room before lung allograft reperfusion. The primary outcome was the incidence of severe (grade 3) primary graft dysfunction at 24, 48, or 72 h after transplant. The primary outcome occurred in 44.7% of the epoprostenol group and 39.8% of the nitric oxide group (risk difference of 4.9%; two one-sided test 90% CI, –6.4 to 16.2%; $P = 0.02$ for equivalence). There were no significant between-group differences for secondary outcomes, such as duration of mechanical ventilation, acute kidney injury, ICU length of stay, and mortality. *(Article Selection: David Faraoni, M.D., Ph.D. Image: J. P. Rathmell.)*

Take home message: The incidence of severe (grade 3) primary graft dysfunction after single or bilateral lung transplant were comparable between patients who received the less expensive inhaled epoprostenol *versus* inhaled nitric oxide.

Post-discharge after surgery Virtual Care with Remote Automated Monitoring-1 (PVC-RAM-1) technology versus standard care: Randomised controlled trial. BMJ 2021; 374:n2209. PMID: 34593374.

Interest in the of use of virtual care with remote automated monitoring to reduce readmissions of patients discharged after semi-urgent, urgent, and emergent surgery, potentially easing pressure on overburdened hospitals, is growing. This randomized trial at eight Canadian hospitals compared a virtual care program utilizing remote vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation, temperature, and body weight *via* the Cloud DX system) and transmitting daily wound photographs interfaced with a tablet computer with the patient interacting with a trained nurse to track their progress (n = 451) *versus* standard care (n = 454). The primary outcome was survival at home at 31 days. There were12 secondary outcomes. Days alive at home were similar for both groups (30 d *vs.* 30 d, relative risk 1.01 [95% CI, 0.99 to 1.02]; $P = 0.53$). The number of patients in the virtual group requiring readmission was 99 *versus* 124 in the usual care group (relative risk 0.80 [95% CI, –0.64 to 1.01]; $P = 0.06$). Virtual patients had more drug errors detected (134 *vs.* 25, $P < 0.001$) and corrected (128 *vs.* 18, $P < 0.001$). *(Article Selection: Jamie Sleigh, M.D. Image: Adobe Stock.)*

Take home message: The use of virtual care with remote automated monitoring after hospital discharge after nonelective surgery is feasible with potential patient benefits, but did not significantly affect readmission rates.

Evaluation of the Merit-Based Incentive Payment System and surgeons caring for patients at high social risk. JAMA Surg 2021; 156:1018–24. PMID: 34379100.

The Medicare Merit-Based Incentive Payment System (MIPS) is the latest attempt by the Centers for Medicaid and Medicare to implement pay-for-value reimbursement. However, this may not adequately account for social determinants of health in patients at high social risk. The study investigated whether MIPS implementation in practices caring for patients at high social risk threatens such patients' access to surgical care. Using a retrospective cohort design, U.S. general surgeons participating in MIPS (9,867 surgeons with complete patient data; 48% of all general surgeons) during its first year in outpatient surgical practices across the United States were analyzed, considering characteristics of surgeons participating in MIPS, overall MIPS score (from 0 to 100) assigned to a clinician, and practice-level disadvantage measures. A wide range of dual-eligible patient caseloads from 0 to 96% (mean ± SD, 27.1 ± 14.5%) was identified. Surgeons in the highest quintile of dual eligibility cared for a Medicare patient caseload ranging from 37 to 96% dual eligible for Medicare and Medicaid. Surgeons caring for the patients at highest social risk had the lowest final mean MIPS score compared with the surgeons caring for the patients at least social risk (67 ± 37 *vs.* 71 ± 36; $P < .001$). *(Article Selection: Martin J. London, M.D. Image: J. P. Rathmell.)*

Take home message: Implementation of MIPS value-based care reimbursement without adjustment for caseload of patients at high social risk appears to penalize surgeons caring for patients at highest social risk.

Effect of high-flow oxygen therapy vs conventional oxygen therapy on invasive mechanical ventilation and clinical recovery in patients with severe COVID-19: A randomized clinical trial. JAMA 2021; 326:2161–71. PMID: 34874419.

Whether or not high-flow nasal oxygen therapy reduces the need for endotracheal intubation in patients with severe COVID-19 has not been well established in randomized trials. This randomized open-label trial of adults with COVID-19, respiratory distress, and a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen of less than 200 (three hospitals in Colombia) compared high-flow to conventional nasal oxygen. The coprimary outcomes were need for intubation and time to clinical recovery until day 28 (7-category ordinal scale with higher scores indicating worse outcome). Treatment effects were adjusted for hypoxemia severity, age, and comorbidities. A total of 199 subjects were included in the analysis (median age, 60 yr; 33% female). The incidence of intubation was significantly lower in the high-flow group: 34% *versus* 51%; hazard ratio, 0.62; 95% CI, 0.39 to 0.96; $P = 0.03$. Median time to clinical recovery within 28 days was also reduced: 11 days (interquartile range, 9 to 14) *versus* 14 days (interquartile range, 11 to 19; hazard ratio, 1.39; 95% CI, 1.00 to 1.92; $P = 0.047$). The incidence of serious adverse events was similar between groups. *(Article Selection: Martin J. London, M.D. Image: J. P. Rathmell.)*

Take home message: In a randomized trial of patients with severe COVID-19, high-flow nasal oxygen therapy had significantly less risk of intubation and shorter time to clinical recovery relative to conventional low-flow oxygen therapy.

Exercise versus usual care after non-reconstructive breast cancer surgery (UK PROSPER): Multicentre randomised controlled trial and economic evaluation. BMJ 2021; 375:e066542. PMID: 34759002.

Approximately one third of women undergoing breast cancer resection surgery develop ipsilateral arm complications. The role of early prophylactic physical therapy is uncertain. This trial of women at 17 United Kingdom National Health Service cancer centers randomized patients to a physical therapy–led exercise program (n = 196) or usual care only (n = 196). At 7 to 10 postoperative days, the intervention group started stretching, strengthening, physical activity, and behavioral techniques to support exercise adherence. The primary outcome was the difference in the Disability of Arm, Hand and Shoulder (DASH) questionnaire administered at 12 months. Upper limb function was greater with exercise (mean DASH ± SD, 16 ± 18 [n = 132] compared with usual care 24 ± 23 [n = 138]; adjusted mean difference 7.8 [95% CI, 3.2 to 12.4], $P = 0.001$). Secondary outcomes at 12 months favored exercise, with lower pain intensity (adjusted mean difference on numerical rating scale –0.7, –1.2 to –0.1; $P = 0.02$). Complications, lymphedema, or adverse events were not greater in exercise participants. Exercise accrued lower costs per patient (average –£387 [€457; $533], 95% CI, –£2491 to £1718). *(Article Selection: BobbieJean Sweitzer, M.D. Image: Adobe Stock.)*

Take home message: The PROSPER exercise program had less upper limb disability 12 months after breast cancer surgery in women at risk of treatment-related postoperative complications and was cost-effective.

Patient-centered decision-making for postoperative narcotic-free endocrine surgery: A randomized clinical trial. JAMA Surg 2021; 156:e214287. PMID: 34495283.

Opioids are often overprescribed after thyroid and parathyroid surgery, potentially leading to abuse. Limiting prescriptions on an opt-in basis is a potential strategy to reduce use. A total of 102 currently opioid naïve patients (78% female, median age 52 yr) undergoing ambulatory surgery were randomized to either opt-in (n = 48; opioids only on patient request) or control (n = 50; routine prescription). The routine prescription was for 50 oral morphine equivalents based on doses received perioperatively. Pain scores (0 to 10) and medication use through day 7 were evaluated, along with factors associated with opioid consumption. The primary outcome was the daily peak pain score. Noninferiority was defined as a difference less than 2 on an 11-point numeric rating scale (0 to 10). Of the opt-in group, 48% received an opioid prescription. None of the remainder required rescue opioids. Median peak outpatient pain scores were not different between groups (6 [interquartile range, 4 to 8] control group *vs.* 6 [interquartile range, 5 to 7] in opt-in group, $P = 0.71$). Patients with a history of previous opioid exposure were 7.5 times more likely to opt in (95% CI, 1.6 to 50.1; $P = 0.02$) and 4.8 times more likely to consume opioids (95% CI, 1.04 to 1.52; $P = 0.01$). *(Article Selection: Martin J. London, M.D. Image: Adobe Stock.)*

Take home message: An opt-in strategy for postoperative opioids lessened opioid prescription without more pain after ambulatory thyroid or parathyroid surgery.

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