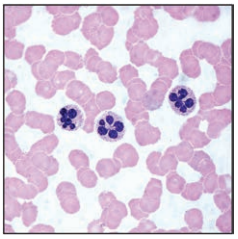
SCIENCE, MEDICINE, AND THE ANESTHESIOLOGIST

ANESTHESIOLOGY

Martin J. London, M.D., Editor

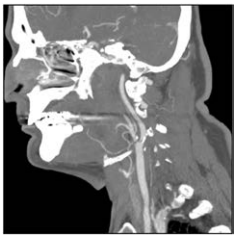
Key Papers from the Most Recent Literature Relevant to Anesthesiologists



An ACE inhibitor reduces bactericidal activity of human neutrophils in vitro and impairs mouse neutrophil activity in vivo. Sci Transl Med 2021; 13:eabj2138. PMID: 34321319.

Angiotensin-converting enzyme (ACE) inhibitors represent a valuable class of drugs used to treat hypertension, diabetic kidney disease, and heart failure. Recent evidence suggests that ACE inhibitors can negatively affect neutrophil function. In a translational study using *in vitro* cellular experiments and *in vivo* mouse models, loss of ACE activity either by ACE inhibition (ramipril) or gene deletion (knockout model) reduced the capacity of murine neutrophils to produce an oxidative burst and thus eliminate bacteria such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, or *Klebsiella pneumoniae*. In contrast, the angiotensin receptor blocker losartan had no adverse effect. *In vivo*, ACE inhibitor administration increased susceptibility to infection in a murine model of endocarditis in a manner similar to an ACE knockout strain alone (ACE knockout 100% infected, wild type treated with ramipril 90% infected, wild type untreated 40% infected). It also reduced the probability of survival (all ACE knockout mice dead after 3 days *vs.* only 40% of wild-type mice). In seven healthy human volunteers, neutrophils collected after short-term ramipril treatment (5 mg daily for 1 week) showed reduced antibacterial activity compared with neutrophils from volunteers without ramipril exposure or after a 7-day drug washout. *(Article Selection: Michael Zaugg, M.D., M.B.A., F.R.C.P.C. Image: Adobe Stock.)*

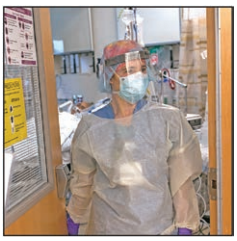
Take home message: These translational studies suggest a potentially detrimental and as yet unrecognized effect on the immune response to bacterial infections by an otherwise highly beneficial angiotensin-converting enzyme inhibitor.



Second asymptomatic carotid surgery trial (ACST-2): A randomised comparison of carotid artery stenting versus carotid endarterectomy. Lancet 2021; 398:1065–73. PMID: 34469763.

The relative clinical benefit and safety of prophylactic carotid endarterectomy *versus* carotid arterial stenting in preventing stroke in patients with asymptomatic severe (70 to 99%) carotid stenosis is unclear. Asymptomatic patients (N = 3,625) with severe unilateral or bilateral carotid stenosis recruited from 130 centers in 33 countries were randomly allocated to receive either carotid endarterectomy or stenting and followed annually for a mean of 5 yr. Overall, 1% had a disabling stroke or death and 2% a nondisabling stroke periprocedurally (30 days). There were no significant differences between the groups, except that slightly more patients having a stenting procedure had nondisabling procedural strokes (2.7% *vs.* 1.6%, $P = 0.03$). There was no difference in subsequent strokes over the 5-yr follow-up: 5.3% after stenting *versus* 4.5% after endarterectomy (rate ratio = 1.16; 95% CI, 0.86 to 1.57; $P = 0.33$). Combining rate ratios for any nonprocedural stroke in all previous published trials (this trial doubled the number of available subjects), the rate ratio between stenting and endarterectomy was similar in both symptomatic and asymptomatic patients (overall rate ratio = 1.11; 95% CI, 0.91 to 1.32; $P = 0.21$). *(Article Selection: Jamie Sleigh, Ph.D. Image: J. P. Rathmell.)*

Take home message: Carotid endarterectomy or stenting have similar periprocedural stoke risks and effect on stroke prevention at 5 yr in patients with asymptomatic severe carotid stenosis.



Therapeutic anticoagulation with heparin in critically ill patients with COVID-19. N Engl J Med 2021; 385:777–89. PMID: 34351722.

COVID-19 is known to be associated with lethal thrombotic complications. Although prophylactic and therapeutic anticoagulation have been recommended, the optimal strategy remains controversial. This pragmatic international, adaptive, multiplatform (three trials with independent data and safety monitoring boards reporting from 393 sites in 10 countries), randomized, controlled trial aimed to determine whether an initial strategy of therapeutic anticoagulation with unfractionated or low-molecular–weight heparin improved in-hospital survival and reduced the duration support in critically ill patients with COVID-19. The primary outcome was organ support–free days (cardiovascular or respiratory) up to day 21 for survivors on an ordinal scale (death in hospital by day 90 assigned –1). A total of 1,098 patients were assigned to either standard of care (n = 564) or therapeutic anticoagulation (n = 534). The percentage of patients who survived to hospital discharge was similar in the two groups (63% and 65%, respectively; adjusted odds ratio, 0.84; 95% credible interval, 0.64 to 1.11). The median value for organ support-free days was 1 (interquartile range, –1 to 16) among the patients receiving therapeutic anticoagulation and was 4 (interquartile range, –1 to 16) among the patients receiving standard of care anticoagulation (adjusted proportional odds ratio, 0.83; 95% credible interval, 0.67 to 1.03). *(Article Selection: David Faraoni, M.D., Ph.D. Image: J. P. Rathmell.)*

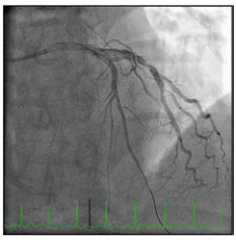
Take home message: In critically ill patients with COVID-19, therapeutic anticoagulation was not associated with better survival rates or reduced days of intensive care support when compared to standard of care thromboprophylaxis.

DOI: 10.1097/ALN.0000000000004069

Therapeutic anticoagulation with heparin in noncritically ill patients with COVID-19. N Engl J Med 2021; 385:790–802. PMID: 34351721.

The role of prophylactic anticoagulation in noncritically ill patients with COVID-19 is uncertain. This open-label, adaptive, multiplatform (three trials with independent data and safety monitoring boards reporting from 121 sites in 9 countries), controlled trial randomized noncritically ill COVID-19 patients (absence of critical care–level organ support at enrollment) to receive either therapeutic anticoagulation with heparin or usual care thromboprophylaxis. The primary outcome was organ support–free days, evaluated on an ordinal scale that combined in-hospital death (assigned a value of −1) and the number of days free of cardiovascular or respiratory organ support up to day 21. A total of 1,181 patients were enrolled in the group receiving therapeutic anticoagulation and 1,050 were enrolled in the usual care group. Prespecified criteria for superiority were set. Among 2,219 patients in the final analysis, the probability that therapeutic anticoagulation led to greater support–free days when compared to usual care was 98.6% (adjusted odds ratio, 1.27; 95% credible interval, 1.03 to 1.58). The adjusted absolute between–group difference in survival until hospital discharge without organ support favoring therapeutic anticoagulation was 4.0 percentage points (95% credible interval, 0.5 to 7.2). Major bleeding occurred more commonly in those on therapeutic anticoagulation (1.9% *vs.* 0.9%). *(Article Selection: David Faraoni, M.D., Ph.D. Image: Adobe Stock.)*

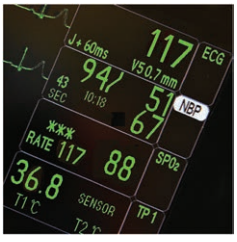
Take home message: Noncritically ill patients with COVID-19 and therapeutic anticoagulation had a greater probability of survival to hospital discharge with reduced use of cardiovascular or respiratory organ support as compared to standard of care.



Dual antiplatelet therapy after PCI in patients at high bleeding risk. N Engl J Med 2021 Aug 28 [Epub ahead of print]. PMID: 34449185.

Patients with a high risk of bleeding were randomized to discontinue dual antiplatelet therapy immediately (abbreviated therapy) or to continue for at least 2 additional months (standard therapy) 1 month after receiving a biodegradable-polymer sirolimus-eluting coronary stent. Primary outcomes assessed at 335 days were adverse clinical events (death from any cause, myocardial infarction, stroke, or major bleeding), major adverse cardiac or cerebral events (death from any cause, myocardial infarction, or stroke), and major or clinically relevant bleeding. The first two outcomes were assessed for noninferiority in the per-protocol population (4,434 patients), and the third outcome for superiority in the intention-to-treat population (4,579 patients). Adverse events occurred in 165 abbreviated therapy patients (7.5%) and in 172 standard therapy patients (7.7%; −0.23 percentage point difference; 95% CI, −1.80 to 1.33; $P < 0.001$ for noninferiority). A total of 133 abbreviated therapy patients (6.1%) and 132 standard therapy patients (5.9%) had a major adverse cardiac or cerebral event (0.11 percentage point difference; 95% CI, −1.29 to 1.51; $P = 0.001$ for non-inferiority). Major or clinically relevant nonmajor bleeding occurred in 148 abbreviated therapy patients (7%) and in 211 standard therapy patients (9%) (−2.82 percentage point difference; 95% CI, −4.40 to −1.24; $P < 0.001$ for superiority) in the intention-to-treat population. *(Article Selection: BobbieJean Sweitzer, M.D., F.A.C.P. Image: J. P. Rathmell.)*

Take home message: After the implantation of a sirolimus-eluting coronary stent, dual antiplatelet therapy for 1 month was noninferior to at least 2 additional months with regard to adverse clinical events and major adverse cardiac or cerebral events, while resulting in a lower incidence of major or clinically relevant nonmajor bleeding.



Effect of low–normal vs high–normal oxygenation targets on organ dysfunction in critically ill patients: A randomized clinical trial. JAMA 2021; 326:940–8. PMID: 34463696.

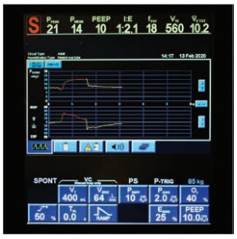
Controversy exists regarding the safety of hyperoxemia in patients with critical illness. This randomized clinical trial included 400 adult patients in The Netherlands (median age, 68 yr; 35% female; 72 to 73% intubated) admitted with two or more systemic inflammatory response criteria excluding elective surgical admissions. The low–normal oxygen target group (n = 205) had Pao_2 maintained between 8 and 12 kPa *versus* high–normal (n = 195) between 14 and 18 kPa. The primary outcome was a ranked outcome score of nonrespiratory organ failure quantified by components of the Sequential Organ Failure Assessment score (SOFARANK; lower scores indicate faster organ failure improvement) summed over the first 14 days, intensive care unit discharge or death. The median Pao_2 difference between the groups was −1.9 kPa (95% CI, −2.1 to −1.7; $P < 0.001$). The median SOFARANK score was −35 points in the low–normal Pao_2 group *versus* −40 in the high–normal Pao_2 group (median difference, 10; 95% CI, 0 to 21; $P = 0.06$). Median duration of mechanical ventilation (3.4 *vs.* 3.1 days; median difference, −0.15; 95% CI, −0.88 to 0.47; $P = 0.59$) and in-hospital mortality (32% *vs.* 31%; odds ratio, 1.04; 95% CI, 0.67 to 1.63; $P = 0.91$) were similar. *(Article Selection: Martin J. London, M.D. Image: J. P. Rathmell.)*

Take home message: Among patients admitted to the ICU with two or more systemic inflammatory response syndrome criteria, targeting a low–normal Pao_2 *versus* a high–normal Pao_2 had no significant impact on nonrespiratory organ dysfunction.

Haemodynamic-guided management of heart failure (GUIDE-HF): A randomised controlled trial. Lancet 2021; 398:991–1001. PMID: 31150790.

Hemodynamic-guided management *via* implantable pulmonary artery pressure monitors has been shown to reduce heart failure hospitalizations in patients with moderately symptomatic (New York Heart Association functional class III) heart failure irrespective of ejection fraction. Its role in patients across the spectrum of heart failure severity has not been determined. The hemodynamic-GUIDEd management of heart failure (GUIDE-HF) trial was a multicenter, single-blind study at 118 centers in the United States and Canada incorporating a randomized arm (among a larger ongoing single-arm observational study). One thousand patients of varying ejection fractions, New York Heart Association functional class II–IV chronic heart failure, and either a recent heart failure hospitalization or elevated natriuretic peptides with successful implantation of a pulmonary artery pressure monitor were randomized to either hemodynamic-guided heart failure or a usual care control group. The primary endpoint was a composite of all-cause mortality and total heart failure events (heart failure hospitalizations and urgent heart failure hospital visits) at 12 months. There were 253 primary endpoint events (0.563 per patient-year) in the hemodynamic-guided management group and 289 (0.640 per patient-year; hazard ratio, 0.88; 95% CI, 0.74 to 1.05; $P = 0.6$). A prespecified pre-COVID-19 impact analysis demonstrated a significant effect (hazard ratio, 0.81; 95% CI, 0.66 to 1.00; $P = 0.049$). *(Article Selection: Martin J. London, M.D. Image: Adobe Stock.)*

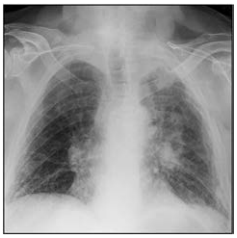
Take home message: Overall, hemodynamic-guided management of heart failure did not result in a lower composite endpoint rate of mortality and total heart failure events. However, a pre-COVID-19 impact analysis indicated a possible benefit of hemodynamic-guided management on the primary outcome in the pre-COVID-19 period, driven by a lower heart failure hospitalization rate.



Effect of lower tidal volume ventilation facilitated by extracorporeal carbon dioxide removal vs standard care ventilation on 90-day mortality in patients with acute hypoxemic respiratory failure: The REST randomized clinical trial. JAMA 2021; 326:1013–23. PMID: 34463700.

The role of extracorporeal carbon dioxide removal to facilitate further reduction in tidal volume below the current 6 ml/kg standard in patients with acute hypoxemic respiratory failure has not been tested. This multicenter, randomized, open-label, pragmatic clinical trial with a planned sample size of 1,120 from 51 intensive care units in the United Kingdom randomized patients to lower tidal volume ventilation (3 ml/kg ideal body weight) facilitated by extracorporeal carbon dioxide removal for 48 h to 7 days (n = 202) or conventional low tidal volume ventilation (6 ml/kg ideal body weight; n = 210). The primary outcome was all-cause mortality 90 days after randomization. Among 412 patients who were randomized (mean age, 59 yr; 35% female), 405 completed the trial. The trial was stopped early by the data monitoring and ethics committee for futility. There was no significant difference in the primary outcome (42% in the extracorporeal carbon dioxide removal group *vs.* 40% in the standard care group; risk ratio, 1.05; 95% CI, 0.83 to 1.33; difference, 2%; 95% CI, –7.6 to 11.5%; $P = 0.68$). Serious adverse events occurred in 31% in the extracorporeal carbon dioxide removal group *versus* 9% in the standard care group, including intracranial hemorrhage (5% *vs.* 0%). *(Article Selection: Martin J. London, M.D. Image: J. P. Rathmell.)*

Take home message: The use of extracorporeal carbon dioxide removal to facilitate lower tidal volume mechanical ventilation in patients with acute hypoxemic respiratory failure, compared to standard care, did not significantly reduce 90-day mortality and was associated with more adverse events.



Tracheal aspirate RNA sequencing identifies distinct immunological features of COVID-19 ARDS. Nat Commun 2021; 12:5152. PMID: 34446707.

Transcriptional profiling of RNA from tracheal aspirates from ventilated patients with acute respiratory distress syndrome (ARDS) revealed dysregulated host responses with reduced proinflammatory gene expression in patients with COVID-19 compared to patients with other etiologies. The findings conflict with the classical "cytokine storm" hypothesis proposed in other studies of COVID-19 ARDS. A complex picture of upregulation of genes with nontraditional roles in inflammation and granulocyte colony-stimulating factor signaling were identified and were predicted to be therapeutically decreased by dexamethasone. Increased phosphatase and tensin homolog protein, interferon-γ and ciliary neurotrophic factor gene expressions were present with decreased genes classically activated by IL-10, an anti-inflammatory cytokine. These findings demonstrate that dysregulated inflammatory activation combined with impaired attenuation of inflammation (*e.g.*, decreased IL-10) may contribute to COVID-19 ARDS. *In silico* modeling was used to predict which therapeutics would target dysregulated gene expressions using a database containing 13,000 drug treatment-induced transcriptional profiles. Dexamethasone had the highest predicted likelihood to counteract the dysregulated gene expression patterns. This matching of *in silico* predictions with clinical data for dexamethasone provides a remarkable translational correlation with the identified dysregulated gene profiles herein. *(Article Selection: Charles Emala, M.D. Image: J. P. Rathmell.)*

Take home message: RNA profiling of genes in the tracheal aspirates of ventilated patients with ARDS from COVID-19 challenges the classical description of "cytokine storm" and instead reveals a complex upregulation of genes not classically linked to inflammation and immunity and the downregulation of anti-inflammatory genes. *In silico* profiling predicted dexamethasone would have beneficial effects on these dysregulated genes.

Battery-free, wireless soft sensors for continuous multi-site measurements of pressure and temperature from patients at risk for pressure injuries. Nature Commun 2021; 12:5008. PMID: 34429436.

Continuous monitoring of pressure and temperature at critical skin locations has the potential to reduce pressure injuries in a variety of hospitalized or immobile patients, including those undergoing prolonged surgical procedures. This article introduces the development and operating characteristics of a soft, skin-mountable sensor system incorporating a pressure-responsive element using membrane deflection and battery-free, wireless operation using multisite measurements on vulnerable locations. Pressure and temperature are transmitted using a pair of antennas mounted under the bedding to a multiplexer at the bedside. The pressure sensor can measure pressures across the entire relevant range (less than 10 kPa) without hysteresis or drift, and with high degrees of linearity, verified in benchtop studies and numerical simulations. Clinical trials were conducted of two hemiplegic and a tetraplegic patient verifying the feasibility, functionality, and long-term stability of this technology in the clinical setting. *(Article Selection: Martin J. London, M.D. Image: Adobe Stock.)*

Take home message: A new class of wireless, battery-free soft skin sensors capable of reporting local pressure and temperature at multiple body sites has been developed, which ultimately may assist in reducing pressure injuries in immobilized patients.

Lactate sensing mechanisms in arterial chemoreceptor cells. Nat Commun 2021; 12:4166. PMID: 34230483.

Although previously considered only a byproduct of anaerobic metabolism, lactate is gaining relevance as a signaling molecule. Murine models were used to evaluate the role of the carotid body in lactate signaling. Using mice with deficient carotid bodies and wild-type mice, they found that hypoxia-induced lactatemia was reduced by the carotid body. Lactate stimulated the carotid body in an external calcium-dependent manner, similar to the effects of hypoxemia. They found that lactate activates the carotid body specifically by binding to an atypical olfactory receptor (Olfr78) highly expressed in the glomus cells, the main oxygen-sensing arterial chemoreceptor cells of the carotid body. As lactate is transported into the glomus cells, it causes a rapid increase in the cytosolic NADH/NAD+ ratio, leading to action potential firing and calcium influx. It also leads to decreased intracellular pH and increased mitochondrial reactive oxygen species, further activating the glomus cells. These data demonstrate the importance of the carotid body to lactate homeostasis, and that lactate and hypoxia (although sensed by different mechanisms) share the same signaling pathway to activate the carotid body glomus cells and cause compensatory cardiorespiratory reflexes. *(Article Selection: Meghan Prin, M.D., M.S. Image: Adobe Stock.)*

Take home message: The carotid body glomus cells are lactate sensors and the carotid body is essential to lactate homeostasis. Lactate and hypoxia share the same signaling pathway to elicit compensatory cardiorespiratory responses.

Trends in prevalence of diabetes and control of risk factors in diabetes among US adults, 1999–2018. JAMA 2021; 326:704–16. PMID: 34170288.

Understanding the prevalence of diabetes as well as the control of risk factors for cardiovascular disease in diabetics are critical from a public health perspective. The data was evaluated from both the self-report interview and mobile examination components of the National Health and Nutrition Examination Survey (NHANES) reports from 1999 to 2000 through 2017 to 2018 to identify trends in the prevalence of diabetes and cardiovascular risk factors. They found that the age-standardized prevalence of diabetes increased significantly from 9.8% (95% CI, 8.6 to 11.1%) in 1999 to 2000 to 14.3% (95% CI, 12.9 to 15.8%) in 2017 to 2018 ($P < 0.001$). The trends in many subgroups, including men, women, and persons of all educational levels, showed similar patterns. Of particular concern, the prevalence of diabetes rose in populations already disproportionately affected, including Mexican Americans and those with abdominal obesity. Only 21% of those with diagnosed diabetes achieved their individualized hemoglobin A1c targets, blood pressure less than 130/80 mmHg, and low-density lipoprotein cholesterol level less than 100 mg/dl: three key goals in reducing the risk of cardiovascular disease. *(Article Selection: J. David Clark, M.D., Ph.D. Image: Adobe Stock.)*

Take home message: There has been a steady rise in the prevalence of diabetes in the American population over the past two to three decades with only approximately 20% achieving adequate control of cardiovascular risk factors.