

Perioperative Organ Injury

Karsten Bartels, M.D.,* Jörn Karhausen, M.D.,† Eric T. Clambey, Ph.D.,‡ Almut Grenz, M.D., Ph.D.,§ Holger K. Eltzschig, M.D., Ph.D.||

ABSTRACT

Despite the fact that a surgical procedure may have been performed for the appropriate indication and in a technically perfect manner, patients are threatened by perioperative organ injury. For example, stroke, myocardial infarction, acute respiratory distress syndrome, acute kidney injury, or acute gut injury are among the most common causes for morbidity and mortality in surgical patients. In the current review, the authors discuss the pathogenesis of perioperative organ injury, and provide select examples for novel treatment concepts that have emerged over the past decade. Indeed, the authors are of the opinion that research to provide mechanistic insight into acute organ injury and identification of novel therapeutic approaches for the prevention or treatment of perioperative organ injury represent the most important opportunity to improve outcomes of anesthesia and surgery.

* Fellow in Critical Care Medicine and Cardiothoracic Anesthesiology, † Assistant Professor of Anesthesiology, Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina. ‡ Assistant Professor of Anesthesiology, § Associate Professor of Anesthesiology, || Professor of Anesthesiology, Department of Anesthesiology, University of Colorado Denver, Aurora, Colorado.

Received from the Organ Protection Program, Department of Anesthesiology, University of Colorado School of Medicine, Aurora, Colorado. Submitted for publication June 26, 2013. Accepted for publication July 22, 2013. This work was supported by a Society of Cardiovascular Anesthesiologists, Roizen Anesthesia Research Foundation, Richmond, Virginia, grant (to Dr. Karhausen); by American Heart Association, Dallas, Texas, grant (to Drs. Clambey and Grenz); by National Institutes of Health, Bethesda, Maryland, grant Nos. R01-DK097075, R01-HL0921, R01-DK083385, R01-HL098294, and POIHL114457-01; and a grant by the Crohn's and Colitis Foundation of America, New York, New York (to Dr. Eltzschig). The authors declare no competing interests. James C. Eisenach, M.D., served as Handling Editor for this article. Figures 1, 2, 4, 5, and 6 were prepared by Annemarie B. Johnson, C.M.I., Medical Illustrator, Vivo Visuals, Winston-Salem, North Carolina.

Address correspondence to Dr. Eltzschig: Organ Protection Program, Department of Anesthesiology, University of Colorado School of Medicine, 12700 E 19th Avenue, Mailstop B112, Research Complex 2, Room 7124, Aurora, Colorado 80045. holger.eltzschig@ucdenver.edu. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

Copyright © 2013, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins. Anesthesiology 2013; 119:1474–89

IF perioperative death constituted its own category in the annual mortality tables from the Center for Disease Control and Prevention, it would represent a leading cause of death in the United States. Although substantial advancements in anesthesia safety have been made over the past 50 yr, similarly improved outcomes throughout the perioperative period have not been achieved.¹ Regardless of many advances in the care we provide, acute organ injury leading to single- or multiple-organ failure remains the leading precursor to death after surgery.² Inpatient mortality in the setting of postoperative critical illness is as high as 20.6% and occurs secondary to multiple-organ dysfunction in 47–53% of cases.^{2,3} Although severe sepsis is the typical precursor to multiple-organ dysfunction, systemic inflammatory response syndrome is a common trigger in surgical patients.⁴ The purpose of this review is to discuss some of the more frequent causes of acute organ injury in context with their clinical relevance and pathophysiologic mechanisms. To highlight the enormous potential for anesthesiologists to impact outcomes of surgical patients, we present recent, exemplary findings that have improved our understanding of acute organ injury and could lead to successful therapeutic strategies.

Patient risk for adverse events in the context of anesthesia has steadily decreased over the last 60 yr. In a study of 599,548 patients from 1948 to 1952, Henry Beecher⁵ reported that the anesthesia-related death rate was 1 in 1560 anesthetics. Recent studies report much lower incidences of death thought to be related to anesthesia: in the United States, 8.2 deaths per million surgical hospital discharges,⁶ in Japan, 21 deaths per million surgeries,⁷ and in a global meta-analysis, 34 deaths per million surgeries were attributed to the anesthetic.⁸ These data may lead some to conclude that the technological and pharmacological advances in the delivery of anesthesia care have made surgery relatively safe.

When all-cause perioperative mortality is assessed, current studies in fact report much poorer outcomes. And, the perceived improvements in surgical care appear to be modest at best. In a Dutch study of 3.7 million patients who underwent surgical procedures between 1991 and 2005, perioperative death before discharge or within 30 days after elective open surgery occurred at a rate of 1.85%.⁹ Semel *et al.*¹⁰ reported a 30-day death rate of 1.32% in a U.S.-based

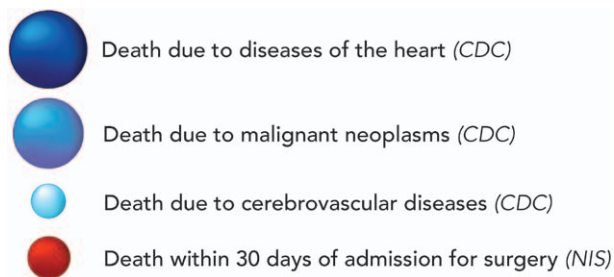


Fig. 1. Magnitude of perioperative mortality. The three leading causes of death in the Center for Disease Control's (CDC) annual death table for the United States in 2006 were: (1) Diseases of heart ($n = 631,636$); (2) Malignant neoplasms ($n = 559,888$); and (3) Cerebrovascular diseases ($n = 137,119$) (Available at: http://www.cdc.gov/nchs/data/dvs/LCWK9_2006.pdf. Accessed July 16, 2013.). Using the Nationwide Inpatient Sample (NIS) for the same year, Semel *et al.*¹⁰ reported 189,690 deaths within 30 days of admission for inpatients having a surgical procedure. In magnitude, all-cause 30-day inpatient mortality after surgery approximated the third leading cause of death in the United States.

inpatient surgical population for the year 2006. This translates to 189,690 deaths in 14.3 million admitted surgical patients in 1 yr in the United States alone. For the same year, only two categories reported by the Center for Disease Control—heart disease and cancer—caused more deaths in the general population (fig. 1). Cerebrovascular disease, the third most common cause of death, was responsible for 137,119 deaths.[#] Thus, all-cause perioperative death occurs more frequently than stroke in the general population, further emphasizing the potential impact of improved perioperative organ protection.

Even though the rate of anesthesia-related deaths has dramatically declined over the past 60 yr, perioperative mortality has not. In a 2007 editorial, Evers and Miller¹ challenged us to take on the charge of “dramatically improving perioperative outcomes.” Although a Herculean task, we have immense opportunities for advancing patient care through improved pre-, intra-, and postoperative medicine. Anesthesiologists have a unique chance to preempt insults through pharmacological and interventional therapy. Prevention of organ injury has the potential to avoid the need for postoperative escalation of care, which is not only costly, but also associated with decreased health-related quality of life up to 6 yr after admission to a surgical intensive care unit.¹¹ To exemplify promising areas of ongoing and future research in acute organ injury, we have summarized new findings for five select pathologies—stroke, myocardial infarction (MI), acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), and acute gut injury (AGI). We present newly identified mechanisms of injury in the context of past, current, and emerging therapeutic strategies. Although our selection of findings is not intended to be complete or

exclusive, we chose to present innovative approaches that can serve as examples of how research that is aimed at impacting common hypoxic and inflammatory pathways has the potential to advance perioperative medicine. Improved understanding of the pathophysiology of acute organ injury and multiple-organ failure is imperative or *conditio sine qua non* for the design of innovative and successful interventions that will help us reach our ultimate goal: improving outcomes for surgical patients.

Stroke

The World Health Organization has defined stroke as “rapidly developed clinical signs of focal or global disturbance of cerebral function, lasting more than 24 h or until death, with no apparent non-vascular cause.”¹² The clinical diagnosis of perioperative stroke is often delayed, because the mental status of patients can be impaired by sedative or analgesic drugs, and motor or sensory function can be limited by the nature of an operation. In recent studies, the incidence of stroke in noncardiac and nonneurologic surgery is 0.1–0.7%.^{13–15} Higher-risk procedures, such as coronary artery bypass surgery and cardiac valve surgery, are complicated by stroke in 1.6¹⁶ and 2.2%¹⁷ of cases, respectively. Mortality levels in patients who suffer from perioperative stroke are significantly increased and range from 12–32.6%.^{13,14,18}

Rupture of a blood vessel leading to hemorrhagic stroke is rare after surgery. Most strokes are due to acute occlusion of a blood vessel, and thus are ischemic in nature.¹⁹ Blockage can develop from local arterial thrombosis or from embolization of material originating in the heart or the vasculature. Vascular sources commonly include proximal large arteries, such as the internal carotid or the aorta. Paradoxical embolization from a venous source can cause stroke, if a right-to-left cardiac shunt permits direct passage from the venous circulation to the brain.²⁰ Watershed infarcts occur in the distal perfusion territories of cerebral arteries and can be due to hypoperfusion and concurrent microembolization.²¹ Most strokes occur after an uneventful emergence from anesthesia, and do not present until postoperative day 2.^{16,19} Although intraoperative events, such as hypotension or thromboembolism from aortic manipulation in cardiac surgery, can cause intraoperative strokes that manifest immediately after anesthesia, the more commonly encountered delayed form of stroke after surgery likely has a different pathophysiology.²² Major surgery induces a patient-specific inflammatory profile.²³ The acute stress response to surgery likely contributes to the creation of a hypercoagulable and neuro-inflammatory milieu that impairs neuroprotective mechanisms and can lead to stroke.²⁰

Risk factor modification to prevent stroke hinges on lifestyle changes and medical therapy for hyperlipidemia, diabetes, and hypertension.²⁴ Patients with a history of cerebral ischemia are at higher risk for stroke, and are commonly maintained on lifelong lipid-lowering²⁵ and antiplatelet

[#] Available at: http://www.cdc.gov/nchs/data/dvs/LCWK9_2006.pdf. Accessed July 16, 2013.

therapy.²⁶ Pharmacologic anticoagulation for patients with atrial fibrillation or a mechanical heart valve is managed by using different perioperative bridging strategies, after weighing the risk for stroke against the risk for procedural bleeding.²⁷ Although intraoperative hypotension is associated with stroke,¹⁸ defining optimal blood pressure targets for an individual patient remains challenging. New approaches use near-infrared spectroscopy to delineate patient-specific limits of cerebral blood flow autoregulation.²⁸ The gaining of more insight into intraoperative cerebral perfusion is an intriguing concept to better tailor hemodynamic management, even though available studies do not yet link monitoring of cerebral oxygenation to reliable prevention of neurologic injury.²⁹

For the treatment of stroke, current guidelines emphasize early diagnosis and transfer to a stroke unit, general supportive therapy, including airway management and mechanical ventilation, and avoidance of further cerebral insults, for example, through prevention of hyperthermia.³⁰ The enthusiasm for endovascular therapy to treat acute ischemic stroke using intra-arterial thrombolysis or clot disruption has recently been dampened by two trials that showed no benefit when compared with systemic thrombolysis.^{31,32} However, given that systemic tissue plasminogen activator administration is contraindicated after surgery, endovascular stroke therapy may still hold promise for select cases of perioperative stroke. Concepts for stroke therapy remain in flux, and many previously pursued strategies, such as intensive insulin treatment, are now obsolete.^{33,34}

Although at least 1,000 substances have been experimentally proven to exert neuroprotective properties, more than 280 clinical studies have not identified a drug that approaches the (low) efficacy of tissue plasminogen activator.^{35,36} Emerging knowledge has led to a new appreciation for the role of the immune system in the pathophysiology of stroke. It is no longer considered a mere bystander, but an active mediator of processes linked to brain damage and reconstruction.³⁷ Immuno-adaptive host responses by lymphocytes have both detrimental³⁸ and protective³⁹ effects after ischemia reperfusion (I/R) injury to the brain. Recent advances in the understanding of their key differential role for immune-mediated cerebro-protection have the potential to inform the development of novel approaches for the treatment of stroke.

The brain mounts a profound inflammatory response to postischemic reperfusion. The innate immune response includes polynuclear cells, macrophages, and other resident cells that are activated through damage-associated molecular patterns released from damaged host cells.⁴⁰ Innate immunity is nonspecific and dominates the early phase of the body's defense. Adaptive immune responses refer to antigen-specific actions by lymphocytes that require more time to develop and also induce memory.³⁶ To better understand the role of lymphocytes in stroke, Hurn *et al.*³⁸ examined the effects of temporary occlusion of the middle cerebral

artery in severe combined immuno-deficient mice that lack B-cells and T-cells. The observation that the severe combined immuno-deficient mice showed a less pronounced inflammatory response might seem intuitive; however, they also displayed a decrease in brain infarct volume compared with that of the wild-type mice. Kleinschnitz *et al.*⁴¹ showed that when B-cells are reconstituted in mice lacking T- and B-cells, infarct volumes are not affected, thereby indicating that T-cells are likely responsible for the observed greater degree of brain damage in wild-type animals. The detrimental effects of T-lymphocytes in the postischemic brain are thought to be in part due to superoxide production,⁴² a key mediator of oxidative stress leading to exaggerated brain damage after I/R.⁴³ Translation of these findings into clinical therapies is not straightforward. Infectious complications are a primary cause of death after stroke, and previous clinical trials that tested immunosuppressive strategies have failed.^{44,45} An appealing alternative approach to general immunosuppression could be the targeted augmentation of protective and restorative components of the adaptive immune response.

Specific subpopulations of T-lymphocytes including natural killer T-cells⁴⁶ and regulatory T-cells^{39,47} have beneficial effects in models of cerebral ischemia. Regulatory T-cells are characterized by their expression of the surface molecules cluster of differentiation (CD)4 and CD25 in conjunction with the transcription factor forkhead box P3 (FoxP3). Interleukin-2 (IL-2) binds to CD25 and induces proliferation of regulatory T-cells to ensure their physiologic maintenance (fig. 2).⁴⁸ Hypoxia leads to induction of FoxP3 and thereby solicits antiinflammatory mechanisms conferred by regulatory T-cells.⁴⁹ Depletion of regulatory T-cells using a CD25-specific antibody leads to increased brain damage and worse functional outcomes in a mouse model of middle cerebral artery occlusion, thereby suggesting a protective role for these cells mediated by the antiinflammatory cytokine IL-10.³⁹ In a genetic association study of participants in the PROspective Study of Pravastatin in the Elderly at Risk trial, the clinical relevance of decreased IL-10 production was highlighted by the association of cerebrovascular events and the single-nucleotide polymorphism 2849AA in the promoter region of IL-10.⁵⁰ Successful therapeutic activation of regulatory T-cells using low doses of IL-2 has been reported in clinical trials with patients suffering from graft-versus-host disease⁵¹ and hepatitis C-induced vasculitis.⁵² Targeting the immunologic response to cerebral I/R, for example, by administering cytokine therapy to foster neuroprotective effects mediated by regulatory T-cells, might prove to be a valuable approach to perioperative organ protection in the future (fig. 2).

MI

MI is defined as an increased plasma cardiac troponin concentration that exceeds the 99th percentile of a normal reference population in conjunction with one of the following: (1) symptoms of ischemia; (2) ST-segment-T wave changes, new left

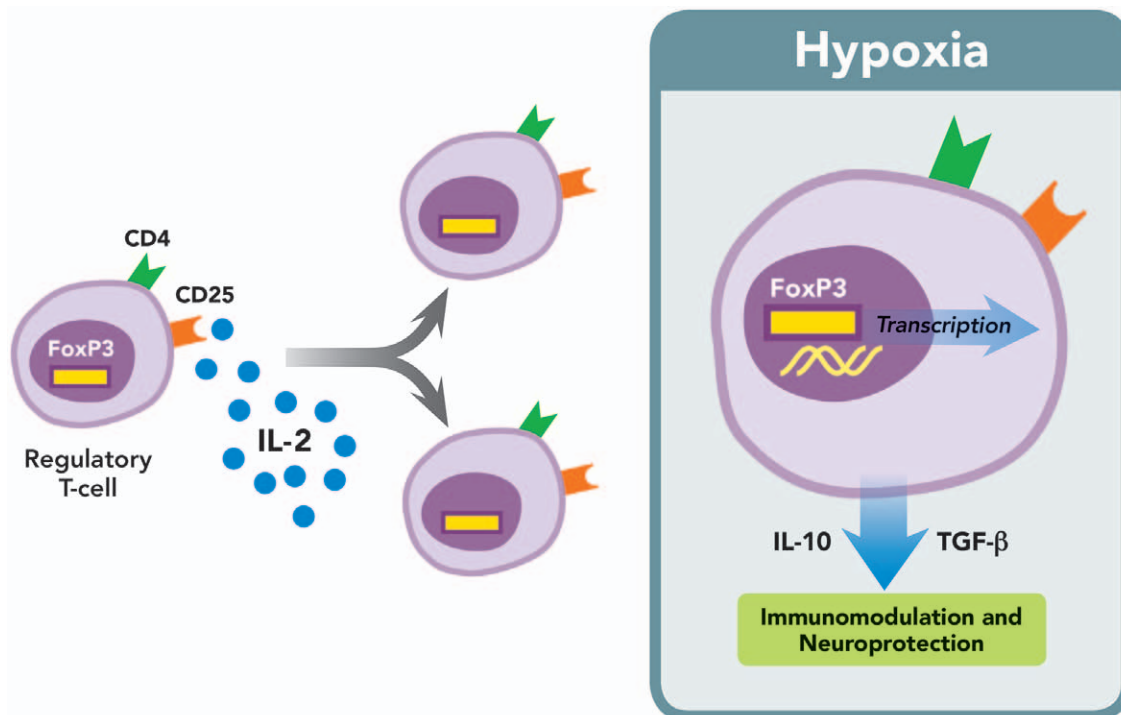


Fig. 2. Activation of regulatory T-cells. Regulatory T-cells are a subpopulation of immuno-modulatory T-cells characterized by expression of the cell surface molecules cluster of differentiation (CD)4 and CD25, and by the presence of the transcription factor forkhead box P3 (FoxP3). Binding of interleukin (IL)-2 to CD25 induces proliferation of regulatory T-cells and is required to ensure their physiologic maintenance.⁴⁸ FoxP3 expression is induced under hypoxic conditions and regulates target genes that govern immuno-modulatory functions.⁴⁹ Neuroprotective effects are mediated by regulatory augmentation of T-cell proliferation and activity as well as by synthesis of antiinflammatory cytokines such as IL-10³⁹ and transforming growth factor (TGF)- β .³⁷ Therapeutic activation of regulatory T-cells has been successfully achieved through exogenous administration of IL-2 in clinical trials of primarily nonneurologic diseases.^{51,52} This approach may serve as a model for studying neuroprotective effects of regulatory T-cells in perioperative stroke.

bundle branch block, or development of pathological Q-waves on electrocardiogram; (3) evidence of new wall motion abnormalities or loss of viable myocardium on imaging; or (4) detection of an intracoronary thrombus.⁵³ During the perioperative period of major noncardiac surgery, the incidence of MI is 1–3%,^{54,55} and is associated with an increased risk for death. In a recent multicenter international cohort study of 8,351 surgical patients at risk for atherosclerotic disease, 30-day mortality was 11.6% in patients who suffered perioperative MI, compared with 2.2% in those who did not.⁵⁶

Myocardial infarction occurs when cardiomyocytes die, which is a consequence of prolonged ischemia. Ischemia can result from acute intracoronary flow occlusion, usually secondary to the rupture of a fissured atherosclerotic plaque (type 1 MI). Nonsurgical MI is more often associated with intracoronary thrombus formation.^{57,58} Alternatively, an ischemic imbalance is caused by a supply/demand mismatch brought on by conditions other than coronary artery disease alone, for example, anemia, arrhythmia, hypotension, or hypertension (type 2 MI).⁵³ Because such conditions are frequently encountered in the operating room and intensive care unit, one might suspect that demand ischemia is responsible for most perioperative MIs. Angiographic

studies of patients treated for postoperative MI have shown conflicting data regarding classification into type-1 *versus* type-2 MI.^{59,60} Because histopathologic examination of the coronaries is only possible after death, plaque disruption found on autopsy in 46–55% of cases^{61,62} is not likely representative of the MI mechanism in the surviving majority of surgical patients. The pathophysiologic mechanisms probably vary, but a common pathway for MI in the perioperative environment is a supply/demand mismatch in which hemodynamic instability and a hypercoagulable state lead to cardiac ischemia and ST depression with eventual cell death and troponin increase.⁶³

Standard pharmacologic approaches for the treatment of coronary artery disease and prevention of myocardial ischemia include β -blockers, antiplatelet agents, statins, angiotensin-converting enzyme inhibitors, and nitrates. Unfortunately, effective preemptive medical therapy for high-risk surgery patients has not yet been developed. Even promising strategies, such as perioperative β -blockade, have not succeeded in decreasing postoperative mortality.⁶⁴ Invasive therapeutic options for coronary artery disease and MI include catheter-based, as well as operative revascularization techniques. When myocardial ischemia progresses to heart

failure, temporary and permanent tools, designed to support or assume the pump function of the heart include intra-aortic balloon pumps and an ever-growing armamentarium of ventricular assist and extracorporeal membrane oxygenation (ECMO) devices. Although the progression of MI to severe heart failure within the immediate perioperative period is uncommon, myocardial injury leading to troponin increases remains not only a frequent occurrence,⁶⁵ but also an independent predictor of mortality after surgery.⁶⁶ This has reinforced efforts to develop more effective cardio-protective strategies.

Many novel approaches to prevent and treat MI are currently under investigation. Here we discuss new and emerging concepts developed from an improved understanding of the function and metabolism of an old drug—adenosine. Adenosine is well known to clinicians for its ability to arrest conduction of the atrioventricular node, thereby permitting diagnosis and treatment of supraventricular tachyarrhythmias. Although this mechanism of action is based on activation of the A1 adenosine receptor (ADORA1), a total of four adenosine receptors mediate distinctly different biologic effects *via* separate signaling pathways (fig. 3).⁶⁷

Although restoration of flow through acutely obstructed coronaries is the goal of interventional treatment for MI, reperfusion itself can exacerbate tissue injury,⁶⁸ for example, *via* leukocyte transmigration leading to exacerbation of local inflammation.⁶⁹ Extracellular adenosine triphosphate is the precursor to adenosine and its release is modulated in the setting of hypoxia and inflammation.^{70–72} Adenosine signaling has been strongly implicated in the attenuation of I/R injury in multiple organs, including the heart.^{73–79} In 2005 Ross *et al.*⁸⁰ studied the effect of intravenous adenosine infusion on clinical outcomes and infarct size in ST-segment increase in MI patients undergoing reperfusion therapy (AMISTAD-2 trial). This study and a *post hoc* analysis⁸¹ showed that patients who received higher concentrations of adenosine infusion ($70 \mu\text{g kg}^{-1} \text{min}^{-1}$) had smaller myocardial infarct sizes, a finding that correlated with fewer adverse clinical events. In a subset of patients who received adenosine within 3.17 h of onset of evolving MI, early and late survival was enhanced and the composite clinical endpoint of death at 6 months was reduced. The fact that this study did not show even more dramatic therapeutic effects of adenosine infusions could be related to the extremely short extracellular half-life of adenosine. Alternatively, combining adenosine infusions with an adenosine uptake inhibitor, such as dipyridamole,^{82–87} or use of direct pharmacological adenosine receptor agonists⁸⁸ may yield even better therapeutic effects for the treatment of ischemic disease states.^{89,90}

Basic research studies provide compelling evidence that the A2B adenosine receptor (ADORA2B) in particular can provide potent cardioprotection against I/R injury. Mice with genetic deletion of the *Adora2b* gene have shown increased myocardial infarct sizes,^{91,92} whereas a specific

agonist of the ADORA2B (BAY 60–6583)^{93–95} attenuates myocardial I/R injury.^{91,92,96} Mechanistic studies link ADORA2B-dependent cardio-protection to the circadian rhythm protein Period 2 (Per2). Per2 stabilization by adenosine receptor activation or by light therapy emulates adenosine-mediated cardio-protection.⁹⁶ These findings are consistent with studies that show increased susceptibility to the detrimental effects of myocardial ischemia in the early morning hours.⁸⁹ Taken together, these data provide strong evidence that adenosine signaling could become a novel therapeutic approach to prevent or treat ischemic myocardial tissue injury in surgical patients. In future studies, the effectiveness of specific adenosine receptor agonists (*e.g.*, for ADORA2B) must be tested in a clinical setting.

ARDS

A 2011 consensus conference held in Berlin redefined the diagnostic criteria of ARDS.⁹⁷ These now include: (1) acute onset within 1 week of a pulmonary insult or manifestation of symptoms, (2) bilateral opacities not fully explained by another cause, (3) exclusion of heart failure or fluid overload as causative for respiratory failure, and (4) differentiation into mild, moderate, and severe ARDS based on a value of ≤ 300 , ≤ 200 , and ≤ 100 mmHg, respectively, for the ratio of partial pressure of arterial oxygen to fraction of inspiratory oxygen ($\text{PaO}_2/\text{FiO}_2$) at a minimum of 5 cm H₂O positive end-expiratory pressure. The previously used definition of acute lung injury is now referred to as mild ARDS. In a single-institution cohort study of 50,367 general surgery patients the reported incidence of ARDS was only 0.2%.⁹⁸ In higher-risk surgeries, ARDS occurs in 2–15% of patients.⁹⁹ Mortality in affected surgical patients is high and ranges from 27 to 40%.^{98,100} Surprisingly, Phua *et al.*¹⁰¹ found that the mortality rate secondary to ARDS has not changed since the introduction of the first standard definition of the syndrome in 1993.

Acute respiratory distress syndrome can occur as a result of direct injury, such as pneumonia, aspiration, or pulmonary contusion. Indirect insults causing ARDS include sepsis, transfusion of blood products, shock, or pancreatitis.¹⁰² Breakdown of the alveolar-capillary membrane causes accumulation of proteinaceous intraalveolar fluid that is accompanied by formation of hyaline membranes on the denuded epithelial basement membrane of the alveolus. Washout of alveolar surfactant predisposes the lungs to atelectasis and decreased compliance.¹⁰³ Influx of neutrophils and activation of alveolar macrophages constitute the basis for the innate immune response. Maintaining a balance between activation of pro- and anti-inflammatory signaling pathways might determine whether the initial pulmonary insult is resolved or progresses to ARDS.

Triggers that exacerbate lung inflammation include microbial products and damage-associated molecular patterns, which are recognized by Toll-like receptors.¹⁰⁴ A complex interplay of inflammasomes, cytokines, complement, prostaglandins, leukotrienes, and mediators

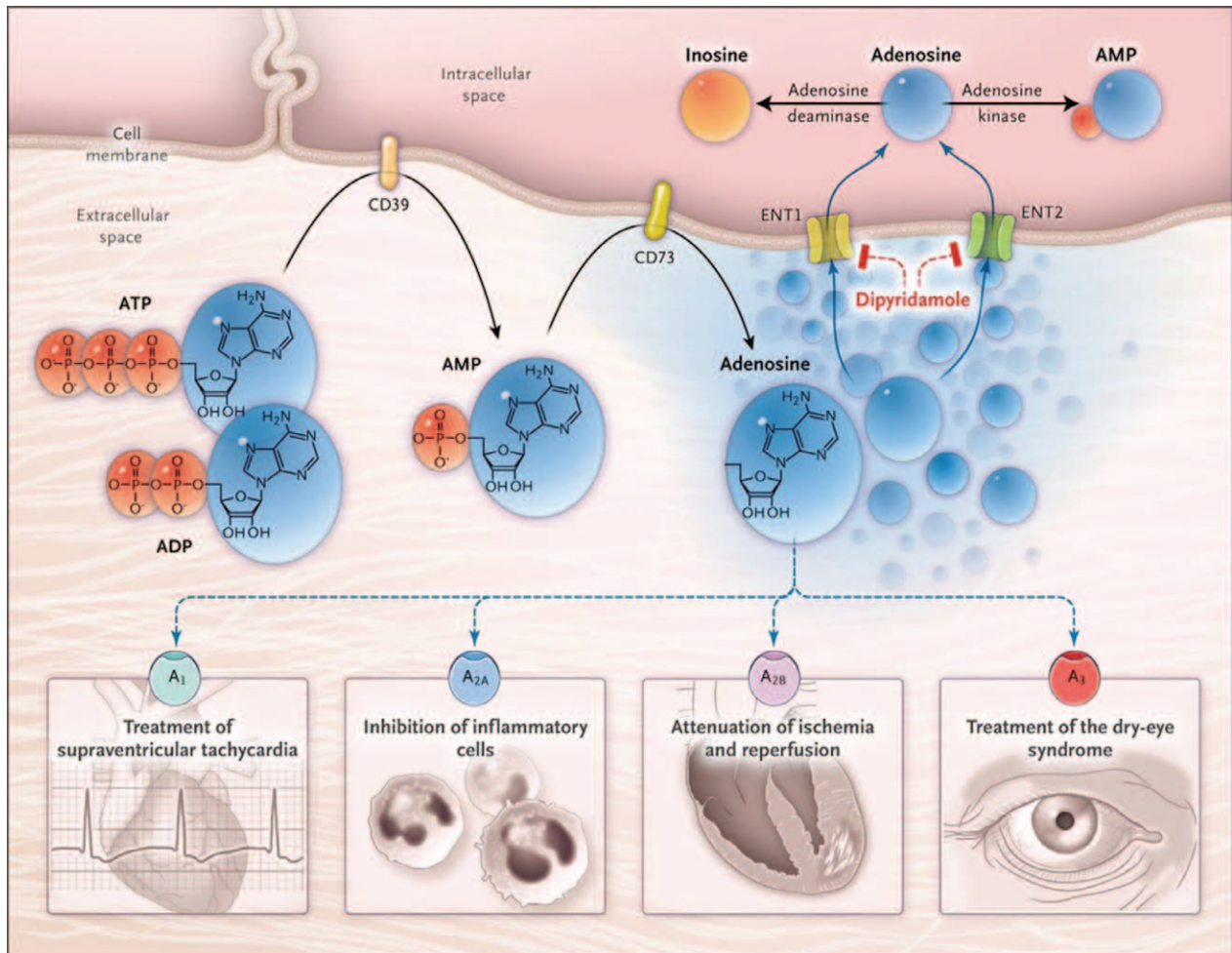


Fig. 3. Extracellular adenosine signaling and its termination: In inflammatory conditions, extracellular adenosine is derived predominantly from the enzymatic conversion of the precursor nucleotides adenosine triphosphate (ATP) and adenosine diphosphate (ADP) to adenosine monophosphate (AMP) through the enzymatic activity of the ectonucleoside triphosphate diphosphohydrolase 1 (CD39) and the subsequent conversion of AMP to adenosine through ecto-5'-nucleotidase (CD73). Extracellular adenosine can signal through four distinct adenosine receptors: ADORA1 (A1), ADORA2A (A2A), ADORA2B (A2B), and ADORA3 (A3). An example of the functional role of extracellular adenosine signaling is A1-receptor activation during intravenous administration of adenosine for the treatment of supraventricular tachycardia. In addition, experimental studies implicate activation of A2A that is expressed on inflammatory cells such as neutrophils¹⁸⁰ or lymphocytes in the attenuation of inflammation.^{181,182} Other experimental studies provide evidence of signaling events through A2B in tissue adaptation to hypoxia and attenuation of ischemia and reperfusion.^{93,94,96} A clinical trial has shown that an oral agonist of the A3 adenosine receptor may be useful in the treatment of the dry-eye syndrome.¹⁸³ Adenosine signaling is terminated by uptake from the extracellular space toward the intracellular space, predominantly through equilibrative nucleoside transporter 1 (ENT1) and equilibrative nucleoside transporter 2 (ENT2), followed by metabolism of adenosine to AMP through the adenosine kinase or to inosine through the adenosine deaminase. Blockade of equilibrative nucleoside transporters by dipyridamole is associated with increased extracellular adenosine concentrations and signaling (e.g., during pharmacologic stress echocardiography or in protection of tissue from ischemia). From: Eltzschig HK, Sitkovsky MV, Robson SC: Purinergic signaling during inflammation. *N Engl J Med* 2012; 367:2322–33. © (2012) Massachusetts Medical Society.⁶⁷ Reprinted with permission.

of oxidative stress sustains the biochemical injury.^{105,106} Fibrosing alveolitis, characterized by neovascularization and infiltration of the alveolar space with mesenchymal cells, develops in some patients and is associated with poorer outcomes.¹⁰³

A key dilemma in the therapeutic approach to ARDS is the double-edged nature of the most commonly applied treatment—mechanical ventilation. Mechanical ventilation

per se induces lung injury *via* a complex combination of mechanisms referred to as ventilator-induced lung injury (VILI).¹⁰⁷ Ongoing biophysical injury by repeated opening and closing of alveoli (atelectrauma), overdistention (volutrauma), and high transpulmonary pressures (barotrauma) exacerbates the initial lung injury.¹⁰⁵

Current therapy for ARDS consists of limiting further iatrogenic damage to the injured lungs by applying a

lung-protective ventilation strategy with tidal volumes of 6 ml/kg or less, plateau pressures of 30 cm H₂O or less, and appropriate positive end-expiratory pressure based on the required minimal F_{IO₂}.¹⁰⁸ Prone positioning promotes ventilation of dependent parts of the lung. In a multicenter, prospective, randomized, controlled trial, Guerin *et al.*¹⁰⁹ recently demonstrated a survival benefit when proning is initiated early in severe ARDS. High-frequency oscillation ventilation constitutes yet another alternative to conventional mechanical ventilation; however, it does not seem to confer a mortality benefit.^{110,111} Other therapeutic strategies used to limit harmful effects of VILI include limiting the volume of administered intravenous fluids¹¹² and considering early administration of neuromuscular blocking agents.¹¹³ Multiple attempts have been made to pharmacologically attenuate the proinflammatory cascade encountered in ARDS. Unfortunately, randomized clinical trials using methylprednisolone¹¹⁴ or omega-3 fatty acids¹¹⁵ have failed to prove any benefit, and have actually suggested harmful effects from these drugs.

Extracorporeal membrane oxygenation has been used to treat respiratory failure for more than 40 yr,¹¹⁶ but it has recently experienced a *renaissance*. The concept of attenuating the effects of ongoing VILI in patients suffering from ARDS (fig. 4) has received new interest with the advent of modern veno-venous ECMO technology,¹¹⁷ the reports of its successful use during the H1N1 influenza outbreak,¹¹⁸ and the encouraging results of a randomized clinical trial by Peek *et al.*¹¹⁹ using ECMO in adult patients with severe respiratory failure. In this study, 180 patients were randomized to continue conventional management or be referred for transport to a specialized center for consideration of ECMO therapy. Sixty-three percent of patients in the group that was transferred for ECMO consideration survived 6 months without disability compared with 47% in the conventional group. An obvious source of bias for the interpretation of these results is that ECMO initiation did not occur at the site of randomization, but rather was preceded by evaluation and treatment after transport to the ECMO center. Ultralow tidal volume mechanical ventilation has also been used in combination with veno-venous ECMO in an attempt to limit VILI by reducing plateau pressures in conjunction with extracorporeal carbon dioxide removal in ARDS patients.¹²⁰ In a recent prospective randomized trial, ECMO combined with ultralow tidal volume mechanical ventilation (3 ml/kg) was compared with conventional protective mechanical ventilation (6 ml/kg) and confirmed feasibility of this approach.¹²¹ Although the primary outcomes (ventilator-free days in a 28- and 60-day period) were not statistically different, a *post hoc* analysis of patients with severe ARDS showed a shorter mechanical ventilation time within a 60-day period.

Although it is too early to endorse ECMO as a routine therapy for patients with severe ARDS, the concept of attenuating ongoing VILI by enabling ultraprotective mechanical ventilation *via* extracorporeal carbon dioxide removal deserves further study.

AKI

Two sets of criteria that define AKI have gained widespread acceptance and form the basis for the current *Kidney Disease Improving Global Outcomes* guidelines; these are:¹²² First, the classification into Risk, Injury, Failure, Loss or End Stage Kidney Disease by the *Acute Dialysis Quality Initiative*.¹²³ Second, the three stages of the modified version of the Risk, Injury, Failure, Loss or End Stage Kidney Disease criteria created by the *AKI Network*.¹²⁴ Both systems use serum creatinine or urine output in addition to glomerular filtration rate (Risk, Injury, Failure, Loss or End Stage Kidney Disease) or need for renal replacement therapy (*AKI Network*) as the basis for classification, and both have high sensitivity and specificity to detect AKI. However, decreased urine output and increased serum creatinine occur relatively late after the initial insult, and newer biomarkers permit earlier detection of injury. These include neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, and more recently insulin-like growth factor-binding protein 7 and tissue inhibitor of metalloproteinases-2.¹²⁵ Whether improved biomarkers will affect clinical outcomes still needs to be determined. The incidence of AKI remains high. In a cohort of 75,952 general surgical procedures, Kheterpal *et al.*¹²⁶ reported a rate of 1%. In this study, mortality of patients with perioperative AKI was increased eight-fold to 42%.

Historically, the origins of AKI have been classified as prerenal, intrinsic, and postrenal. The ischemic forms, prerenal azotemia and acute tubular necrosis, are the most common causes of AKI in hospitalized patients.¹²⁷ AKI represents a continuum of injury, and the distinction between prerenal azotemia and acute tubular necrosis is likely not reflective of tubular biology.¹²³ Focus has shifted to the importance of early detection and intervention to prevent worsening of AKI, as even modest decreases in glomerular filtration rate have profound effects on mortality of hospitalized patients.¹²⁸

Therapy of AKI rests on treating the underlying cause, such as infection, anemia, low cardiac output, or postrenal obstruction. Protecting the kidney from additional insults includes avoiding nephrotoxic drugs such as nonsteroidal antiinflammatory drugs, aminoglycosides, and intravenous contrast agents whenever possible.¹²⁹ Recent clinical trials identified low-molecular-weight hydroxyethylstarches as potent nephrotoxins in a diverse cohort of intensive care unit patients¹³⁰ and as a cause of an increased death rate in septic patients.¹³¹

Pharmacologic therapy for AKI is still attempted, although clinical trials have shown that most drugs are ineffective or even harmful. In a randomized, placebo-controlled, double-blind trial in 328 critically ill patients, low-dose dopamine had no impact on mortality or indices of renal function.¹³² It was, however, associated with higher rates of atrial fibrillation after cardiac surgery.¹³³ Although furosemide can be used to treat hypervolemia, it actually increased serum creatinine values in a double-blind, randomized, controlled trial

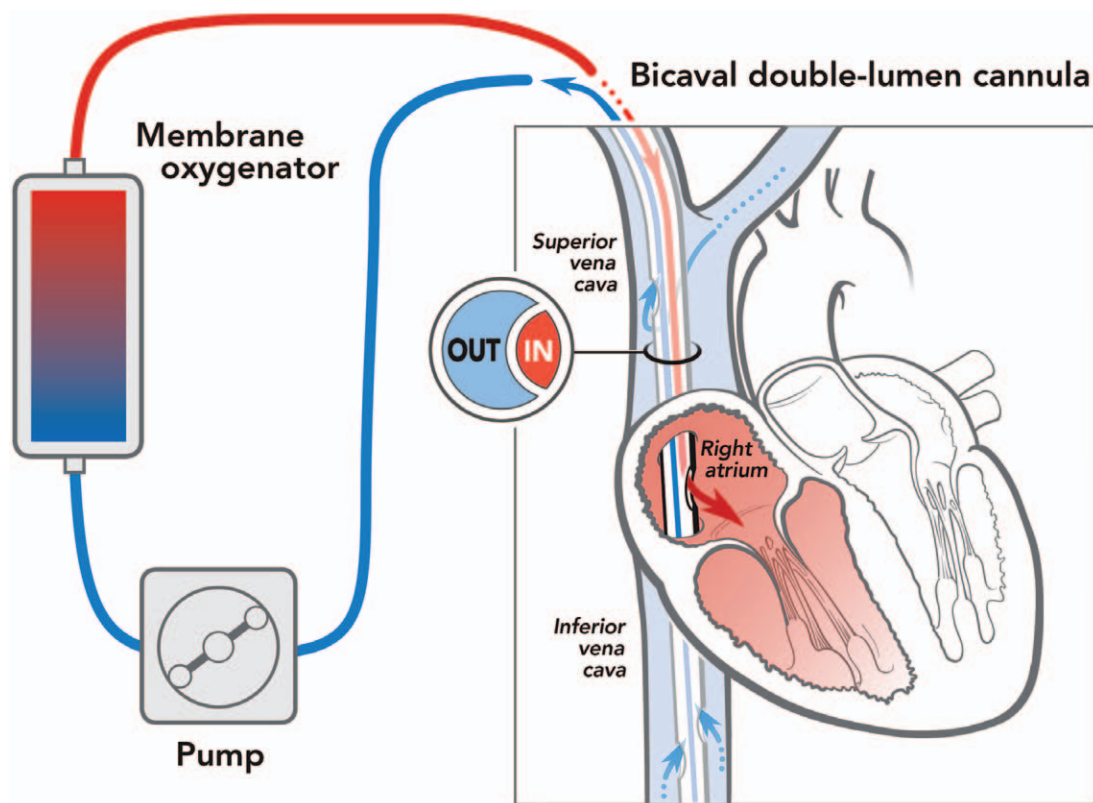


Fig. 4. Veno-venous extracorporeal membrane oxygenation (VV-ECMO). A bicaval, double-lumen central venous cannula is placed in the right internal jugular vein. Deoxygenated blood is collected from both the inferior and the superior vena cava. After passing through a centrifugal pump and a membrane oxygenator, the oxygenated blood is then returned to the right atrium through the cannula's second lumen's orifice. Various configurations are currently in use, including pumpless systems and alternative cannulation techniques.

of patients after cardiac surgery.¹³⁴ Glomerular filtration rate can decrease after furosemide administration,¹³⁵ potentially raising plasma creatinine concentrations. However, forced diuresis can also lead to hypovolemia, secondary renal hypoperfusion, and subsequent AKI. Renal replacement therapy is initiated if the decreased clearance function leads to severe metabolic sequelae such as acidemia, hyperkalemia, volume overload, or uremia. In a clinical trial that evaluated different strategies for renal replacement therapy for AKI in critically ill patients, only 5.6% of the patients needed to continue replacement therapy at 90 days postinitiation; however, 44.7% had died.¹³⁶

Several recent studies have increased our understanding of the kidney's response to ischemia. Renal ischemia drives persistent renal hypoxia, which leads to concomitant stabilization of hypoxia-inducible factor (HIF).⁸⁷ In a hypoxic environment, HIF controls the expression of more than 100 genes that are involved with vital cell functions, such as glucose metabolism, pH-control, angiogenesis, and erythropoiesis.^{137,138} HIF is a heterodimer that consists of two subunits—the oxygen-sensitive HIF- α and the constitutively expressed HIF- β .¹³⁹ These subunits translocate to the cell nucleus, where they become highly effective regulators of

gene expression by binding to the hypoxia response promoter element. HIF-activated gene expression is repressed under normoxic conditions. One control mechanism that inhibits HIF-dependent gene transcription involves hydroxylation of HIF- α via oxygen-dependent prolyl hydroxylases, which tag HIF- α for degradation in the cell proteasome (fig. 5).¹⁴⁰

Hypoxia-sensitive signaling mechanisms may inform the development of novel perioperative organ protective strategies.^{87,94} Conde *et al.*¹⁴¹ reported HIF-1 α to be expressed in human renal tubular cells obtained from kidney biopsies after renal transplantation, and its presence was negatively correlated with the degree of acute tubular necrosis. Prevention of proteasomal degradation of HIF by inhibiting prolyl hydroxylases confers renal protection in animal models of I/R¹⁴² and in a model of gentamicin-induced AKI.¹⁴³ The oral drug FG-2216 inhibits prolyl hydroxylases, and it has already been successfully used in a clinical phase-1 study to increase endogenous erythropoietin synthesis in patients with end-stage renal disease.¹⁴⁴ Thus, clinically tested prolyl hydroxylase inhibitors in conjunction with emerging evidence from animal studies suggest that hypoxia-activated signaling pathways are promising targets for prevention of perioperative AKI.

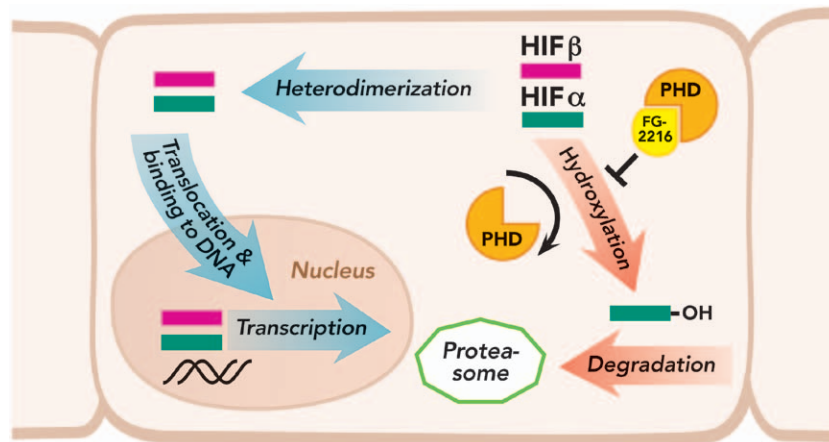


Fig. 5. Activation of hypoxia-inducible factor (HIF)-dependent gene expression *via* prolyl hydroxylase inhibition. Under hypoxic conditions (blue arrows), HIF- α and the constitutively expressed HIF- β bind and translocate into the cell nucleus. After binding to the DNA hypoxia response promoter element, the HIF heterodimer induces expression of hypoxia-sensitive genes. Under normoxic conditions (red arrows), prolyl hydroxylases (PHDs) hydroxylate HIF- α and thereby mark it for proteasomal degradation, effectively inhibiting HIF-dependent gene expression. Prevention of proteasomal HIF- α degradation using prolyl hydroxylase inhibitors, for example, FG-2216,¹⁴⁴ activates hypoxia-activated signaling pathways even under normoxic conditions.

Acute Gut Injury

The true medical impact of perioperative AGI remains the target of intense clinical and experimental investigation. The incidence of clinically overt AGI after major nonabdominal surgery, such as cardiopulmonary bypass or lung transplantation surgery, is relatively low (0.3–6.1%), but is associated with significant morbidity and a high mortality risk (18–58%).^{145,146}

Different specific factors influence particular AGI manifestations, for example, the altered coagulation state after cardiopulmonary bypass in the context of gastrointestinal bleeding. Beyond this, splanchnic perfusion abnormalities and associated mucosal I/R injury form a central common pathophysiologic insult. The intestinal mucosa is supported by a complex underlying vasculature.¹⁴⁷ Especially in low-flow states (shock, cardiopulmonary bypass perfusion), oxygen is shunted away from the villus tip *via* a countercurrent mechanism, therefore exposing the epithelium to significant hypoxia.^{148–150} In its most extensive form, such intestinal hypoperfusion presents as mesenteric ischemia, which occurs in approximately 0.15%¹⁴⁵ of cardiopulmonary bypass patients compared with 0.00012% of the general medical population.¹⁵¹ Although hard evidence is limited, ischemia in low-flow states appears to be largely nonocclusive.^{152,153} However, in the general medical population, about 84% of mesenteric ischemia is caused by embolism, arterial, or venous thrombosis.¹⁵¹

Major mesenteric ischemia is a clinical emergency because of the rapid development of a systemic inflammatory response syndrome, which is associated with distant organ injury and ultimately, multiple-organ failure. Consequently, the question has been raised of whether mesenteric ischemia represents only the “tip-of-the-iceberg,” and whether beyond this, subclinical AGI secondary to episodes of low blood flow

is the insidious source of perioperative inflammatory activation. Indeed, in critical illness or after cardiopulmonary bypass, signs of intestinal injury and parallel loss of intestinal barrier function are regularly observed.^{154–156} However, lack of clear evidence that directly links bacterial translocation to outcome has triggered a reevaluation of the concept of gut-origin sepsis, and has led to an increased focus on the concomitant release of nonbacterial gut-derived inflammatory and tissue injurious factors.¹⁵⁷ The rapid release of preformed effectors from cellular sources such as mucosal mast cells (MCs) or Paneth cells at the base of the epithelial crypt may explain both the promptness and the potency of intestinal responses to I/R (fig. 6).

Paneth cells are highly secretory cells of the intestine that release various antimicrobial peptides and important inflammatory mediators.¹⁵⁸ Until recently, Paneth cell function has been regarded as host-protective, particularly in the sense of antimicrobial control.¹⁵⁹ More recently, it was revealed that Paneth cell-derived IL-17 not only mediates local damage and distant organ injury in murine intestinal I/R,¹⁶⁰ but also plays a critical role in multiorgan dysfunction after hepatic I/R injury,¹⁶¹ and after tumor necrosis factor- α -induced shock.¹⁶² Much attention has focused on inflammatory activation by nonmicrobial damage-associated molecular patterns and the role of the toll-like receptors in I/R injury.¹⁶³ As such, shock-induced AGI is toll-like receptor 4 dependent.¹⁶⁴ New data suggest that IL-17 constitutes an important activator of this pathway,¹⁶⁵ which is noteworthy, as the established endogenous toll-like receptor 4 ligands high-mobility group box 1 protein (HMGB1), heat shock protein-70 or -27, or hyaluronic acid do not seem to be involved.¹⁶⁴

Another source of potent effectors of tissue injury and inflammation are mucosal MCs. As important immune

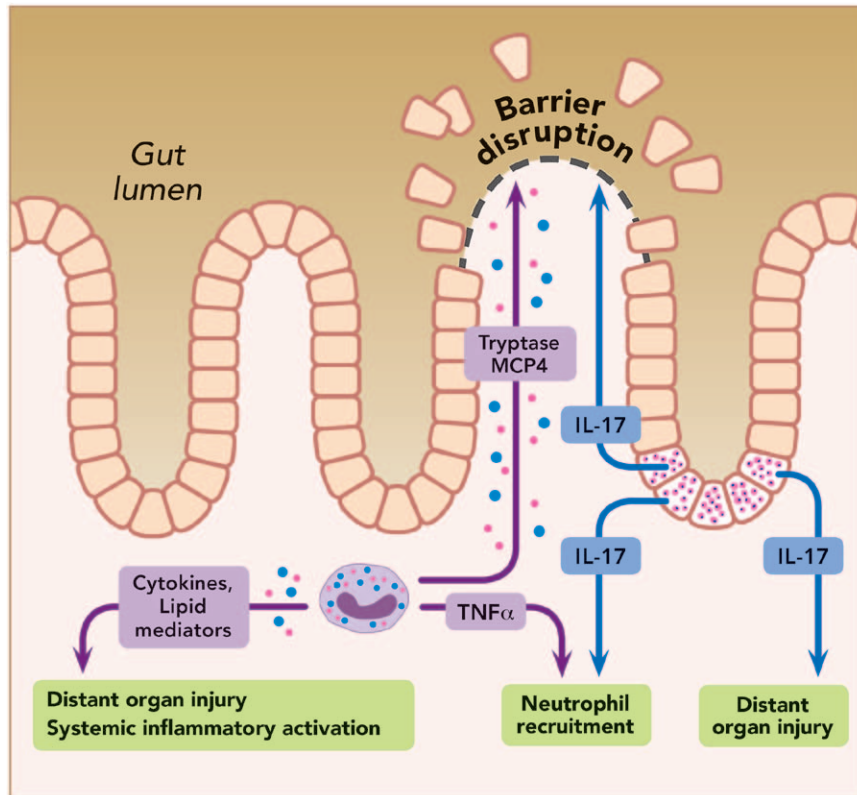


Fig. 6. Paneth cells and intestinal mast cells release potent effectors to regulate local injury and systemic inflammation after intestinal ischemia/reperfusion. Most prominently, the Paneth cell-dependent pathway (blue) depends on release of interleukin (IL)-17 from Paneth cells localized at the base of small intestinal crypts. Mast cell responses (purple) use a number of preformed and *de novo* synthesized products such as proteases (tryptase, mast cell protease [MCP]-4), lipid mediators (leukotriens, prostaglandins), and cytokines (tumor necrosis factor [TNF]- α , IL-6).

surveillance cells strategically positioned within the gut wall, their physiologic role is slowly evolving beyond the traditional focus on allergy.^{166–168} MCs exert local and systemic effects *via* rapid release of preformed proteases, mediators, and cytokines. For example, MC-tryptase,^{169,170} as well as MC-protease 4¹⁷¹ have been implicated in the breakdown of tight junctions in various mucosal epithelia, including the gut. Release of preformed tumor necrosis factor- α from MCs is a powerful inflammatory stimulus that not only promotes local pathogen clearance,¹⁷² but also drives detrimental systemic inflammatory deregulation in critical illness.^{173,174} The role of MCs in intestinal I/R injury has been studied extensively,^{175–177} with recent reports suggesting that MCs may influence perioperative outcomes: In a rat model of deep hypothermic circulatory arrest, intestinal MC activation contributed to intestinal injury and intestinal barrier disruption, as well as to the release of systemic cytokines.¹⁷⁸ Similarly, in a piglet model of ECMO, systemic inflammatory responses appeared to stem from mediators released by splanchnic MCs.¹⁷⁹

Although this overview is incomplete, the highlighted mechanisms exemplify an increased appreciation for non-classical pathways in the control of tissue injury and inflammatory activation. Because they constitute very early events

in intestinal I/R, such mechanisms show great promise for the development of novel therapeutic approaches to reduce the local and systemic consequences of intestinal hypoperfusion.

Conclusions

Despite significant advances in the delivery of anesthesia, perioperative morbidity and mortality remain a major public health problem. The magnitude of all-cause mortality after surgery approximates the third leading cause of death in the United States, after heart disease and cancer. Although this serves as a sobering recognition of the *status quo*, it also points to tremendous opportunities in anesthesiology to drive medical progress and fundamentally improve patient outcomes.

This review did not attempt to encompass the abundance of worthy approaches that are currently underway to improve survival from acute organ injury. Its purpose was instead to summarize current strategies and to present an exemplary outlook of promising ideas for prevention and treatment of commonly encountered perioperative pathologies—stroke, MI, ARDS, AKI, and AGI. A key conclusion is that the discussed cellular and molecular responses to injury are active,

interrelated components. They play key roles in the development of the disease process and are not merely bystander reactions. The injury-induced adaptations are complex and convey both protective and injurious effects on the tissues. Future approaches to reduce perioperative morbidity and mortality will require ongoing efforts to better understand mechanisms of acute organ injury. Nevertheless, we believe that this area of research represents the most important opportunity to improve outcomes of surgery and anesthesia.

The authors thank Kathy Gage, B.S., Research Development Associate, Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina, for her editorial contributions to this article.

References

- Evers AS, Miller RD: Can we get there if we don't know where we're going? *ANESTHESIOLOGY* 2007; 106:651–2
- Lobo SM, Rezende E, Knibel MF, Silva NB, Páramo JA, Nácúl FE, Mendes CL, Assunção M, Costa RC, Grion CC, Pinto SF, Mello PM, Maia MO, Duarte PA, Gutierrez F, Silva JM Jr, Lopes MR, Cordeiro JA, Mellot C: Early determinants of death due to multiple organ failure after noncardiac surgery in high-risk patients. *Anesth Analg* 2011; 112:877–83
- Mayr VD, Dünser MW, Greil V, Jochberger S, Luckner G, Ulmer H, Friesenecker BE, Takala J, Hasibeder WR: Causes of death and determinants of outcome in critically ill patients. *Crit Care* 2006; 10:R154
- Dulhunty JM, Lipman J, Finfer S; Sepsis Study Investigators for the ANZICS Clinical Trials Group: Does severe non-infectious SIRS differ from severe sepsis? Results from a multi-centre Australian and New Zealand intensive care unit study. *Intensive Care Med* 2008; 34:1654–61
- Beecher HK, Todd DP: A study of the deaths associated with anesthesia and surgery: Based on a study of 599, 548 anesthetics in ten institutions 1948–1952, inclusive. *Ann Surg* 1954; 140:2–35
- Li G, Warner M, Lang BH, Huang L, Sun LS: Epidemiology of anesthesia-related mortality in the United States, 1999–2005. *ANESTHESIOLOGY* 2009; 110:759–65
- Kawashima Y, Takahashi S, Suzuki M, Morita K, Irita K, Iwao Y, Seo N, Tsuzaki K, Dohi S, Kobayashi T, Goto Y, Suzuki G, Fujii A, Suzuki H, Yokoyama K, Kugimiya T: Anesthesia-related mortality and morbidity over a 5-year period in 2,363,038 patients in Japan. *Acta Anaesthesiol Scand* 2003; 47:809–17
- Bainbridge D, Martin J, Arango M, Cheng D; Evidence-based Peri-operative Clinical Outcomes Research (EPiCOR) Group: Perioperative and anaesthetic-related mortality in developed and developing countries: A systematic review and meta-analysis. *Lancet* 2012; 380:1075–81
- Noordzij PG, Poldermans D, Schouten O, Bax JJ, Schreiner FA, Boersma E: Postoperative mortality in The Netherlands: A population-based analysis of surgery-specific risk in adults. *ANESTHESIOLOGY* 2010; 112:1105–15
- Semel ME, Lipsitz SR, Funk LM, Bader AM, Weiser TG, Gawande AA: Rates and patterns of death after surgery in the United States, 1996 and 2006. *Surgery* 2012; 151:171–82
- Timmers TK, Verhofstad MH, Moons KG, van Beeck EF, Leenen LP: Long-term quality of life after surgical intensive care admission. *Arch Surg* 2011; 146:412–8
- The World Health Organization MONICA Project (monitoring trends and determinants in cardiovascular disease): A major international collaboration. WHO MONICA Project Principal Investigators. *J Clin Epidemiol* 1988; 41:105–14
- Bateman BT, Schumacher HC, Wang S, Shaefi S, Berman MF: Perioperative acute ischemic stroke in noncardiac and nonvascular surgery: Incidence, risk factors, and outcomes. *ANESTHESIOLOGY* 2009; 110:231–8
- Mashour GA, Shanks AM, Kheterpal S: Perioperative stroke and associated mortality after noncardiac, nonneurologic surgery. *ANESTHESIOLOGY* 2011; 114:1289–96
- Sharifpour M, Moore LE, Shanks AM, Didier TJ, Kheterpal S, Mashour GA: Incidence, predictors, and outcomes of perioperative stroke in noncarotid major vascular surgery. *Anesth Analg* 2013; 116:424–34
- Tarakji KG, Sabik JF III, Bhudia SK, Batizy LH, Blackstone EH: Temporal onset, risk factors, and outcomes associated with stroke after coronary artery bypass grafting. *JAMA* 2011; 305:381–90
- Filsoufi F, Rahmanian PB, Castillo JG, Bronster D, Adams DH: Incidence, imaging analysis, and early and late outcomes of stroke after cardiac valve operation. *Am J Cardiol* 2008; 101:1472–8
- Bijker JB, Persoon S, Peelen LM, Moons KG, Kalkman CJ, Kappelle LJ, van Klei WA: Intraoperative hypotension and perioperative ischemic stroke after general surgery: A nested case-control study. *ANESTHESIOLOGY* 2012; 116:658–64
- Selim M: Perioperative stroke. *N Engl J Med* 2007; 356:706–13
- Ng JL, Chan MT, Gelb AW: Perioperative stroke in noncardiac, nonneurosurgical surgery. *ANESTHESIOLOGY* 2011; 115:879–90
- Momjian-Mayor I, Baron JC: The pathophysiology of watershed infarction in internal carotid artery disease: Review of cerebral perfusion studies. *Stroke* 2005; 36:567–77
- Hogue CW Jr, Murphy SF, Schechtman KB, Dávila-Román VG: Risk factors for early or delayed stroke after cardiac surgery. *Circulation* 1999; 100:642–7
- Pillai PS, Leeson S, Porter TF, Owens CD, Kim JM, Conte MS, Serhan CN, Gelman S: Chemical mediators of inflammation and resolution in post-operative abdominal aortic aneurysm patients. *Inflammation* 2012; 35:98–113
- Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, Cates CU, Creager MA, Fowler SB, Friday G, Hertzberg VS, McCliff EB, Moore WS, Panagos PD, Riles TS, Rosenwasser RH, Taylor AJ; American College of Cardiology Foundation; American Stroke Association; American Association of Neurological Surgeons; American College of Radiology; American Society of Neuroradiology; Congress of Neurological Surgeons; Society of Atherosclerosis Imaging and Prevention; Society for Cardiovascular Angiography and Interventions; Society of Interventional Radiology; Society of NeuroInterventional Surgery; Society for Vascular Medicine; Society for Vascular Surgery: 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: Executive summary. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. *Circulation* 2011; 124:489–532
- Amarenco P, Bogousslavsky J, Callahan A III, Goldstein LB, Hennerici M, Rudolph AE, Silleisen H, Simunovic L, Szarek M, Welch KM, Zivin JA: Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators: High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med* 2006; 355:549–59
- Antithrombotic Trialists' Collaboration: Collaborative meta-analysis of randomised trials of antiplatelet therapy for

- prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002; 324:71–86
27. Wysokinski WE, McBane RD II: Periprocedural bridging management of anticoagulation. *Circulation* 2012; 126:486–90
 28. Ono M, Zheng Y, Joshi B, Sigl JC, Hogue CW: Validation of a stand-alone near-infrared spectroscopy system for monitoring cerebral autoregulation during cardiac surgery. *Anesth Analg* 2013; 116:198–204
 29. Zheng F, Sheinberg R, Yee MS, Ono M, Zheng Y, Hogue CW: Cerebral near-infrared spectroscopy monitoring and neurologic outcomes in adult cardiac surgery patients: A systematic review. *Anesth Analg* 2013; 116:663–76
 30. Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM, Khatri P, McMullan PW Jr, Qureshi AI, Rosenfield K, Scott PA, Summers DR, Wang DZ, Wintermark M, Yonas H; American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Peripheral Vascular Disease; Council on Clinical Cardiology: Guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013; 44:870–947
 31. Ciccone A, Valvassori L, Nichelatti M, Sgòifo A, Ponzio M, Sterzi R, Boccardi E; SYNTHESIS Expansion Investigators: Endovascular treatment for acute ischemic stroke. *N Engl J Med* 2013; 368:904–13
 32. Broderick JP, Palesch YY, Demchuk AM, Yeatts SD, Khatri P, Hill MD, Jauch EC, Jovin TG, Yan B, Silver FL, von Kummer R, Molina CA, Demaerschalk BM, Budzik R, Clark WM, Zaidat OO, Malisch TW, Goyal M, Schonewille WJ, Mazighi M, Engelter ST, Anderson C, Spilker J, Carrozzella J, Ryckborst KJ, Janis LS, Martin RH, Foster LD, Tomsick TA; Interventional Management of Stroke (IMS) III Investigators: Endovascular therapy after intravenous t-PA *versus* t-PA alone for stroke. *N Engl J Med* 2013; 368:893–903
 33. Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR, Hebert PC, Heritier S, Heyland DK, McArthur C, McDonald E, Mitchell I, Myburgh JA, Norton R, Potter J, Robinson BG, Ronco JJ: Intensive *versus* conventional glucose control in critically ill patients. *N Engl J Med* 2009; 360:1283–97
 34. Gandhi GY, Nuttall GA, Abel MD, Mullany CJ, Schaff HV, O'Brien PC, Johnson MG, Williams AR, Cutshall SM, Mundy LM, Rizza RA, McMahon MM: Intensive intraoperative insulin therapy *versus* conventional glucose management during cardiac surgery: A randomized trial. *Ann Intern Med* 2007; 146:233–43
 35. Young AR, Ali C, Duretête A, Vivien D: Neuroprotection and stroke: Time for a compromise. *J Neurochem* 2007; 103:1302–9
 36. Macrez R, Ali C, Toutirais O, Le Mauff B, Defer G, Dirnagl U, Vivien D: Stroke and the immune system: From pathophysiology to new therapeutic strategies. *Lancet Neurol* 2011; 10:471–80
 37. Iadecola C, Anrather J: The immunology of stroke: From mechanisms to translation. *Nat Med* 2011; 17:796–808
 38. Hurn PD, Subramanian S, Parker SM, Afentoulis ME, Kaler LJ, Vandenbark AA, Offner H: T- and B-cell-deficient mice with experimental stroke have reduced lesion size and inflammation. *J Cereb Blood Flow Metab* 2007; 27:1798–805
 39. Liesz A, Suri-Payer E, Veltkamp C, Doerr H, Sommer C, Rivest S, Giese T, Veltkamp R: Regulatory T cells are key cerebroprotective immunomodulators in acute experimental stroke. *Nat Med* 2009; 15:192–9
 40. Chen GY, Nuñez G: Sterile inflammation: Sensing and reacting to damage. *Nat Rev Immunol* 2010; 10:826–37
 41. Kleinschnitz C, Schwab N, Kraft P, Hagedorn I, Dreykluft A, Schwarz T, Austinat M, Nieswandt B, Wiendl H, Stoll G: Early detrimental T-cell effects in experimental cerebral ischemia are neither related to adaptive immunity nor thrombus formation. *Blood* 2010; 115:3835–42
 42. Brait VH, Jackman KA, Walduck AK, Selemidis S, Diep H, Mast AE, Guida E, Broughton BR, Drummond GR, Sobey CG: Mechanisms contributing to cerebral infarct size after stroke: Gender, reperfusion, T lymphocytes, and Nox2-derived superoxide. *J Cereb Blood Flow Metab* 2010; 30:1306–17
 43. Warner DS, Sheng H, Batinić-Haberle I: Oxidants, antioxidants and the ischemic brain. *J Exp Biol* 2004; 207(Pt 18):3221–31
 44. The Enlimomab Acute Stroke Trial Investigators: Use of anti-ICAM-1 therapy in ischemic stroke: Results of the Enlimomab Acute Stroke Trial. *Neurology* 2001; 57:1428–34
 45. Krams M, Lees KR, Hacke W, Grieve AP, Orgogozo JM, Ford GA; ASTIN Study Investigators: Acute Stroke Therapy by Inhibition of Neutrophils (ASTIN): An adaptive dose-response study of UK-279,276 in acute ischemic stroke. *Stroke* 2003; 34:2543–8
 46. Wong CH, Jenne CN, Lee WY, Léger C, Kuberski P: Functional innervation of hepatic iNKT cells is immunosuppressive following stroke. *Science* 2011; 334:101–5
 47. Zhu P, Hata R, Ogasawara M, Cao F, Kameda K, Yamauchi K, Schinkel AH, Maeyama K, Sakanaka M: Targeted disruption of organic cation transporter 3 (Oct3) ameliorates ischemic brain damage through modulating histamine and regulatory T cells. *J Cereb Blood Flow Metab* 2012; 32:1897–908
 48. Setoguchi R, Hori S, Takahashi T, Sakaguchi S: Homeostatic maintenance of natural Foxp3(+) CD25(+) CD4(+) regulatory T cells by interleukin (IL)-2 and induction of autoimmune disease by IL-2 neutralization. *J Exp Med* 2005; 201:723–35
 49. Clambey ET, McNamee EN, Westrich JA, Glover LE, Campbell EL, Jedlicka P, de Zoeten EF, Cambier JC, Stenmark KR, Colgan SP, Eltzschig HK: Hypoxia-inducible factor-1 alpha-dependent induction of FoxP3 drives regulatory T-cell abundance and function during inflammatory hypoxia of the mucosa. *Proc Natl Acad Sci U S A* 2012; 109: E2784–93
 50. Trompet S, Pons D, DE Craen AJ, Slagboom P, Shepherd J, Blauw GJ, Murphy MB, Cobbe SM, Bollen EL, Buckley BM, Ford I, Hyland M, Gaw A, Macfarlane PW, Packard CJ, Norrie J, Perry IJ, Stott DJ, Sweeney BJ, Twomey C, Westendorp RG, Jukema JW: Genetic variation in the interleukin-10 gene promoter and risk of coronary and cerebrovascular events: The PROSPER study. *Ann N Y Acad Sci* 2007; 1100:189–98
 51. Koreth J, Matsuoka K, Kim HT, McDonough SM, Bindra B, Alyea EP III, Armand P, Cutler C, Ho VT, Treister NS, Bienfang DC, Prasad S, Tzachanis D, Joyce RM, Avigan DE, Antin JH, Ritz J, Soiffer RJ: Interleukin-2 and regulatory T cells in graft-*versus*-host disease. *N Engl J Med* 2011; 365:2055–66
 52. Saadoun D, Rosenzweig M, Joly F, Six A, Carrat F, Thibault V, Sene D, Cacoub P, Klatzmann D: Regulatory T-cell responses to low-dose interleukin-2 in HCV-induced vasculitis. *N Engl J Med* 2011; 365:2067–77
 53. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Katus HA, Lindahl B, Morrow DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasché P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S; Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction: Third universal definition of myocardial infarction. *Circulation* 2012; 126:2020–35
 54. Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, Sugarbaker DJ, Donaldson MC, Poss R, Ho KK, Ludwig LE, Pedan A, Goldman L: Derivation and prospective validation of a simple index for prediction of

- cardiac risk of major noncardiac surgery. *Circulation* 1999; 100:1043–9
55. Devereaux PJ, Goldman L, Yusuf S, Gilbert K, Leslie K, Guyatt GH: Surveillance and prevention of major perioperative ischemic cardiac events in patients undergoing noncardiac surgery: A review. *CMAJ* 2005; 173:779–88
 56. Devereaux PJ, Xavier D, Pogue J, Guyatt G, Sigamani A, Garutti I, Leslie K, Rao-Melacini P, Chrolavicius S, Yang H, Macdonald C, Avezum A, Lanthier L, Hu W, Yusuf S; POISE (PeriOperative ISchemic Evaluation) Investigators: Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery: A cohort study. *Ann Intern Med* 2011; 154:523–8
 57. Davies MJ, Thomas AC: Plaque fissuring—The cause of acute myocardial infarction, sudden ischaemic death, and crescendo angina. *Br Heart J* 1985; 53:363–73
 58. DeWood MA, Spores J, Notske R, Mouser LT, Burroughs R, Golden MS, Lang HT: Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. *N Engl J Med* 1980; 303:897–902
 59. Duvall WL, Sealove B, Pungoti C, Katz D, Moreno P, Kim M: Angiographic investigation of the pathophysiology of perioperative myocardial infarction. *Catheter Cardiovasc Interv* 2012; 80:768–76
 60. Gualandro DM, Campos CA, Calderaro D, Yu PC, Marques AC, Pastana AF, Lemos PA, Caramelli B: Coronary plaque rupture in patients with myocardial infarction after noncardiac surgery: Frequent and dangerous. *Atherosclerosis* 2012; 222:191–5
 61. Cohen MC, Aretz TH: Histological analysis of coronary artery lesions in fatal postoperative myocardial infarction. *Cardiovasc Pathol* 1999; 8:133–9
 62. Dawood MM, Gutpa DK, Southern J, Walia A, Atkinson JB, Eagle KA: Pathology of fatal perioperative myocardial infarction: Implications regarding pathophysiology and prevention. *Int J Cardiol* 1996; 57:37–44
 63. Landesberg G: The pathophysiology of perioperative myocardial infarction: Facts and perspectives. *J Cardiothorac Vasc Anesth* 2003; 17:90–100
 64. Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, Xavier D, Chrolavicius S, Greenspan L, Pogue J, Pais P, Liu L, Xu S, Malaga G, Avezum A, Chan M, Montori VM, Jacka M, Choi P: Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): A randomised controlled trial. *Lancet* 2008; 371:1839–47
 65. Landesberg G, Mosseri M, Shatz V, Akopnik I, Bocher M, Mayer M, Anner H, Berlatzky Y, Weissman C: Cardiac troponin after major vascular surgery: The role of perioperative ischemia, preoperative thallium scanning, and coronary revascularization. *J Am Coll Cardiol* 2004; 44:569–75
 66. Levy M, Heels-Ansdell D, Hiralal R, Bhandari M, Guyatt G, Yusuf S, Cook D, Villar JC, McQueen M, McFalls E, Filipovic M, Schünemann H, Sear J, Foex P, Lim W, Landesberg G, Godet G, Poldermans D, Bursi F, Kertai MD, Bhatnagar N, Devereaux PJ: Prognostic value of troponin and creatine kinase muscle and brain isoenzyme measurement after noncardiac surgery: A systematic review and meta-analysis. *ANESTHESIOLOGY* 2011; 114:796–806
 67. Eltzschig HK, Sitkovsky MV, Robson SC: Purinergic signaling during inflammation. *N Engl J Med* 2012; 367:2322–33
 68. Eltzschig HK, Collard CD: Vascular ischaemia and reperfusion injury. *Br Med Bull* 2004; 70:71–86
 69. Petzelbauer P, Zacharowski PA, Miyazaki Y, Friedl P, Wickenhauser G, Castellino FJ, Gröger M, Wolff K, Zacharowski K: The fibrin-derived peptide Bbeta15–42 protects the myocardium against ischemia-reperfusion injury. *Nat Med* 2005; 11:298–304
 70. Faigle M, Seessle J, Zug S, El Kasmi KC, Eltzschig HK: ATP release from vascular endothelia occurs across Cx43 hemichannels and is attenuated during hypoxia. *PLoS One* 2008; 3:e2801
 71. Hart ML, Gorzolla IC, Schittenhelm J, Robson SC, Eltzschig HK: SP1-dependent induction of CD39 facilitates hepatic ischemic preconditioning. *J Immunol* 2010; 184:4017–24
 72. Riegel AK, Faigle M, Zug S, Rosenberger P, Robaye B, Boeynaems JM, Idzko M, Eltzschig HK: Selective induction of endothelial P2Y6 nucleotide receptor promotes vascular inflammation. *Blood* 2011; 117:2548–55
 73. Bauerle JD, Grenz A, Kim JH, Lee HT, Eltzschig HK: Adenosine generation and signaling during acute kidney injury. *J Am Soc Nephrol* 2011; 22:14–20
 74. Eltzschig HK, Macmanus CF, Colgan SP: Neutrophils as sources of extracellular nucleotides: Functional consequences at the vascular interface. *Trends Cardiovasc Med* 2008; 18:103–7
 75. Eltzschig HK: Adenosine: An old drug newly discovered. *ANESTHESIOLOGY* 2009; 111:904–15
 76. Hart ML, Henn M, Köhler D, Kloor D, Mittelbronn M, Gorzolla IC, Stahl GL, Eltzschig HK: Role of extracellular nucleotide phosphohydrolysis in intestinal ischemia-reperfusion injury. *FASEB J* 2008; 22:2784–97
 77. Hart ML, Much C, Gorzolla IC, Schittenhelm J, Kloor D, Stahl GL, Eltzschig HK: Extracellular adenosine production by ecto-5'-nucleotidase protects during murine hepatic ischemic preconditioning. *Gastroenterology* 2008; 135:1739–1750.e3
 78. Eckle T, Koeppen M, Eltzschig HK: Role of extracellular adenosine in acute lung injury. *Physiology (Bethesda)* 2009; 24:298–306
 79. Hart ML, Grenz A, Gorzolla IC, Schittenhelm J, Dalton JH, Eltzschig HK: Hypoxia-inducible factor-1 α -dependent protection from intestinal ischemia/reperfusion injury involves ecto-5'-nucleotidase (CD73) and the A2B adenosine receptor. *J Immunol* 2011; 186:4367–74
 80. Ross AM, Gibbons RJ, Stone GW, Kloner RA, Alexander RW; AMISTAD-II Investigators: A randomized, double-blinded, placebo-controlled multicenter trial of adenosine as an adjunct to reperfusion in the treatment of acute myocardial infarction (AMISTAD-II). *J Am Coll Cardiol* 2005; 45:1775–80
 81. Kloner RA, Forman MB, Gibbons RJ, Ross AM, Alexander RW, Stone GW: Impact of time to therapy and reperfusion modality on the efficacy of adenosine in acute myocardial infarction: The AMISTAD-2 trial. *Eur Heart J* 2006; 27:2400–5
 82. Eckle T, Hughes K, Ehrentraut H, Brodsky KS, Rosenberger P, Choi DS, Ravid K, Weng T, Xia Y, Blackburn MR, Eltzschig HK: Crosstalk between the equilibrative nucleoside transporter ENT2 and alveolar Adora2b adenosine receptors dampens acute lung injury. *FASEB J* 2013; 27:3078–89
 83. Morote-Garcia JC, Rosenberger P, Nivillac NM, Coe IR, Eltzschig HK: Hypoxia-inducible factor-dependent repression of equilibrative nucleoside transporter 2 attenuates mucosal inflammation during intestinal hypoxia. *Gastroenterology* 2009; 136:607–18
 84. Löffler M, Morote-Garcia JC, Eltzschig SA, Coe IR, Eltzschig HK: Physiological roles of vascular nucleoside transporters. *Arterioscler Thromb Vasc Biol* 2007; 27:1004–13
 85. Eckle T, Grenz A, Köhler D, Redel A, Falk M, Rolauffs B, Osswald H, Kehl F, Eltzschig HK: Systematic evaluation of a novel model for cardiac ischemic preconditioning in mice. *Am J Physiol Heart Circ Physiol* 2006; 291:H2533–40
 86. Eltzschig HK, Abdulla P, Hoffman E, Hamilton KE, Daniels D, Schönfeld C, Löffler M, Reyes G, Duszenko M, Karhausen J, Robinson A, Westerman KA, Coe IR, Colgan SP: HIF-1-dependent repression of equilibrative nucleoside transporter (ENT) in hypoxia. *J Exp Med* 2005; 202:1493–505
 87. Grenz A, Bauerle JD, Dalton JH, Ridyard D, Badulak A, Tak E, McNamee EN, Clambey E, Moldovan R, Reyes G, Klawitter J, Ambler K, Magee K, Christians U, Brodsky KS, Ravid K, Choi DS, Wen J, Lukashov D, Blackburn MR, Osswald H, Coe IR, Nürnberg B, Haase VH, Xia Y, Sitkovsky M, Eltzschig HK: Equilibrative nucleoside transporter 1 (ENT1) regulates post-ischemic blood flow during acute kidney injury in mice. *J Clin Invest* 2012; 122:693–10

88. Thiel M, Chouker A, Ohta A, Jackson E, Caldwell C, Smith P, Lukashev D, Bittmann I, Sitkovsky MV: Oxygenation inhibits the physiological tissue-protecting mechanism and thereby exacerbates acute inflammatory lung injury. *PLoS Biol* 2005; 3:e174
89. Eltzschig HK, Bonney SK, Eckle T: Attenuating myocardial ischemia by targeting A2B adenosine receptors. *Trends Mol Med* 2013; 19:345–54
90. Eltzschig HK, Eckle T: Ischemia and reperfusion—From mechanism to translation. *Nat Med* 2011; 17:1391–401
91. Eckle T, Köhler D, Lehmann R, El Kasmi K, Eltzschig HK: Hypoxia-inducible factor-1 is central to cardioprotection: A new paradigm for ischemic preconditioning. *Circulation* 2008; 118:166–75
92. Eckle T, Krahn T, Grenz A, Köhler D, Mittelbronn M, Ledent C, Jacobson MA, Osswald H, Thompson LF, Unertl K, Eltzschig HK: Cardioprotection by ecto-5'-nucleotidase (CD73) and A2B adenosine receptors. *Circulation* 2007; 115:1581–90
93. Eckle T, Faigle M, Grenz A, Laucher S, Thompson LF, Eltzschig HK: A2B adenosine receptor dampens hypoxia-induced vascular leak. *Blood* 2008; 111:2024–35
94. Grenz A, Osswald H, Eckle T, Yang D, Zhang H, Tran ZV, Klingel K, Ravid K, Eltzschig HK: The reno-vascular A2B adenosine receptor protects the kidney from ischemia. *PLoS Med* 2008; 5:e137
95. Hart ML, Jacobi B, Schittenhelm J, Henn M, Eltzschig HK: Cutting Edge: A2B Adenosine receptor signaling provides potent protection during intestinal ischemia/reperfusion injury. *J Immunol* 2009; 182:3965–8
96. Eckle T, Hartmann K, Bonney S, Reithel S, Mittelbronn M, Walker LA, Lowes BD, Han J, Borchers CH, Buttrick PM, Kominsky DJ, Colgan SP, Eltzschig HK: Adora2b-elicited Per2 stabilization promotes a HIF-dependent metabolic switch crucial for myocardial adaptation to ischemia. *Nat Med* 2012; 18:774–82
97. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS: Acute respiratory distress syndrome: The Berlin Definition. *JAMA* 2012; 307:2526–33
98. Blum JM, Stentz MJ, Dechert R, Jewell E, Engoren M, Rosenberg AL, Park PK: Preoperative and intraoperative predictors of postoperative acute respiratory distress syndrome in a general surgical population. *ANESTHESIOLOGY* 2013; 118:19–29
99. Gajic O, Dabbagh O, Park PK, Adesanya A, Chang SY, Hou P, Anderson H III, Hoth JJ, Mikkelsen ME, Gentile NT, Gong MN, Talmor D, Bajwa E, Watkins TR, Festic E, Yilmaz M, Iscimen R, Kaufman DA, Esper AM, Sadikot R, Douglas I, Sevransky J, Malinchoc M: Early identification of patients at risk of acute lung injury: Evaluation of lung injury prediction score in a multicenter cohort study. *Am J Respir Crit Care Med* 2011; 183:462–70
100. Dulu A, Pastores SM, Park B, Riedel E, Rusch V, Halpern NA: Prevalence and mortality of acute lung injury and ARDS after lung resection. *Chest* 2006; 130:73–8
101. Phua J, Badia JR, Adhikari NK, Friedrich JO, Fowler RA, Singh JM, Scales DC, Stather DR, Li A, Jones A, Gattas DJ, Hallett D, Tomlinson G, Stewart TE, Ferguson ND: Has mortality from acute respiratory distress syndrome decreased over time? A systematic review. *Am J Respir Crit Care Med* 2009; 179:220–7
102. Wheeler AP, Bernard GR: Acute lung injury and the acute respiratory distress syndrome: A clinical review. *Lancet* 2007; 369:1553–64
103. Ware LB, Matthay MA: The acute respiratory distress syndrome. *N Engl J Med* 2000; 342:1334–49
104. Matthay MA, Ware LB, Zimmerman GA: The acute respiratory distress syndrome. *J Clin Invest* 2012; 122:2731–40
105. Fan E, Villar J, Slutsky AS: Novel approaches to minimize ventilator-induced lung injury. *BMC Med* 2013; 11:85
106. Dolinay T, Kim YS, Howrylak J, Hunninghake GM, An CH, Fredenburgh L, Massaro AF, Rogers A, Gazourian L, Nakahira K, Haspel JA, Landazury R, Eppanapally S, Christie JD, Meyer NJ, Ware LB, Christiani DC, Ryter SW, Baron RM, Choi AM: Inflammasome-regulated cytokines are critical mediators of acute lung injury. *Am J Respir Crit Care Med* 2012; 185:1225–34
107. Tremblay LN, Slutsky AS: Ventilator-induced lung injury: From the bench to the bedside. *Intensive Care Med* 2006; 32:24–33
108. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000; 342:1301–8
109. Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, Mercier E, Badet M, Mercat A, Baudin O, Clavel M, Chatellier D, Jaber S, Rosselli S, Mancebo J, Sirodot M, Hilbert G, Bengler C, Richecoeur J, Gannier M, Bayle F, Bourdin G, Leray V, Girard R, Baboi L, Ayzac L; PROSEVA Study Group: Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013; 368:2159–68
110. Ferguson ND, Cook DJ, Guyatt GH, Mehta S, Hand L, Austin P, Zhou Q, Matte A, Walter SD, Lamontagne F, Granton JT, Arabi YM, Arroliga AC, Stewart TE, Slutsky AS, Meade MO; OSCILLATE Trial Investigators; Canadian Critical Care Trials Group: High-frequency oscillation in early acute respiratory distress syndrome. *N Engl J Med* 2013; 368:795–805
111. Young D, Lamb SE, Shah S, MacKenzie I, Tunnicliffe W, Lall R, Rowan K, Cuthbertson BH; OSCAR Study Group: High-frequency oscillation for acute respiratory distress syndrome. *N Engl J Med* 2013; 368:806–13
112. Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, Connors AF Jr, Hite RD, Harabin AL: Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006; 354:2564–75
113. Papazian L, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, Jaber S, Arnal JM, Perez D, Seghboyan JM, Constantin JM, Courant P, Lefrant JY, Guérin C, Prat G, Morange S, Roch A; ACURASYS Study Investigators: Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med* 2010; 363:1107–16
114. Steinberg KP, Hudson LD, Goodman RB, Hough CL, Lanken PN, Hyzy R, Thompson BT, Ancukiewicz M; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network: Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med* 2006; 354:1671–84
115. Rice TW, Wheeler AP, Thompson BT, deBoisblanc BP, Steingrub J, Rock P; NIH NHLBI Acute Respiratory Distress Syndrome Network of Investigators; NHLBI ARDS Clinical Trials Network: Enteral omega-3 fatty acid, gamma-linolenic acid, and antioxidant supplementation in acute lung injury. *JAMA* 2011; 306:1574–81
116. Zapol WM, Snider MT, Schneider RC: Extracorporeal membrane oxygenation for acute respiratory failure. *ANESTHESIOLOGY* 1977; 46:272–85
117. Combes A, Bréchet N, Luyt CE, Schmidt M: What is the niche for extracorporeal membrane oxygenation in severe acute respiratory distress syndrome? *Curr Opin Crit Care* 2012; 18:527–32
118. Noah MA, Peek GJ, Finney SJ, Griffiths MJ, Harrison DA, Grieve R, Sadique MZ, Sekhon JS, McAuley DF, Firmin RK, Harvey C, Cordingley JJ, Price S, Vuylsteke A, Jenkins DP, Noble DW, Bloomfield R, Walsh TS, Perkins GD, Menon D, Taylor BL, Rowan KM: Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). *JAMA* 2011; 306:1659–68

119. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, Hibbert CL, Truesdale A, Clemens F, Cooper N, Firmin RK, Elbourne D; CESAR Trial Collaboration: Efficacy and economic assessment of conventional ventilatory support *versus* extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): A multicentre randomised controlled trial. *Lancet* 2009; 374:1351–63
120. Terragni PP, Del Sorbo L, Mascia L, Urbino R, Martin EL, Birocco A, Faggiano C, Quintel M, Gattinoni L, Ranieri VM: Tidal volume lower than 6ml/kg enhances lung protection: Role of extracorporeal carbon dioxide removal. *ANESTHESIOLOGY* 2009; 111:826–35
121. Bein T, Weber-Carstens S, Goldmann A, Müller T, Staudinger T, Brederlau J, Muellenbach R, Dembinski R, Graf BM, Wewalka M, Philipp A, Wernecke KD, Lubnow M, Slutsky AS: Lower tidal volume strategy (≈ 3 ml/kg) combined with extracorporeal CO₂ removal *versus* 'conventional' protective ventilation (6 ml/kg) in severe ARDS: The prospective randomized Xtravent-study. *Intensive Care Med* 2013; 39:847–56
122. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group: KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl* 2012; 2:1–138
123. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P; Acute Dialysis Quality Initiative Workgroup: Acute renal failure—Definition, outcome measures, animal models, fluid therapy and information technology needs: The Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 2004; 8:R204–12
124. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A; Acute Kidney Injury Network: Acute Kidney Injury Network: Report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007; 11:R31
125. Kashani K, Al-Khafaji A, Ardiles T, Artigas A, Bagshaw SM, Bell M, Bihorac A, Birkhahn R, Cely CM, Chawla LS, Davison DL, Feldkamp T, Forni LG, Gong MN, Gunnerson KJ, Haase M, Hackett J, Honore PM, Hoste EA, Joannes-Boyau O, Joannidis M, Kim P, Koyner JL, Laskowitz DT, Lissauer ME, Marx G, McCullough PA, Mullaney S, Ostermann M, Rimmelé T, Shapiro NI, Shaw AD, Shi J, Sprague AM, Vincent JL, Vinsonneau C, Wagner L, Walker MG, Wilkerson RG, Zacharowski K, Kellum JA: Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. *Crit Care* 2013; 17:R25
126. Kheterpal S, Tremper KK, Heung M, Rosenberg AL, Englesbe M, Shanks AM, Campbell DA Jr: Development and validation of an acute kidney injury risk index for patients undergoing general surgery: Results from a national data set. *ANESTHESIOLOGY* 2009; 110:505–15
127. Abuelo JG: Normotensive ischemic acute renal failure. *N Engl J Med* 2007; 357:797–805
128. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW: Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol* 2005; 16:3365–70
129. Kellum JA, Lameire N; For the KDIGO AKI Guideline Work Group: Diagnosis, evaluation, and management of acute kidney injury: A KDIGO summary (Part 1). *Crit Care* 2013; 17:204
130. Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, Glass P, Lipman J, Liu B, McArthur C, McGuinness S, Rajbhandari D, Taylor CB, Webb SA; CHEST Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group: Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med* 2012; 367:1901–11
131. Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzon G, Åneman A, Madsen KR, Møller MH, Elkjær JM, Poulsen LM, Bendtsen A, Winding R, Steensen M, Berezowicz P, Søb-Jensen P, Bestle M, Strand K, Wiis J, White JO, Thornberg KJ, Quist L, Nielsen J, Andersen LH, Holst LB, Thormar K, Kjældgaard AL, Fabritius ML, Mondrup F, Pott FC, Møller TP, Winkel P, Wetterslev J; 6S Trial Group; Scandinavian Critical Care Trials Group: Hydroxyethyl starch 130/0.42 *versus* Ringer's acetate in severe sepsis. *N Engl J Med* 2012; 367:124–34
132. Bellomo R, Chapman M, Finfer S, Hickling K, Myburgh J: Low-dose dopamine in patients with early renal dysfunction: A placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. *Lancet* 2000; 356:2139–43
133. Argalious M, Motta P, Khandwala F, Samuel S, Koch CG, Gillinov AM, Yared JP, Starr NJ, Bashour CA: "Renal dose" dopamine is associated with the risk of new-onset atrial fibrillation after cardiac surgery. *Crit Care Med* 2005; 33:1327–32
134. Lassnigg A, Donner E, Grubhofer G, Prestler E, Druml W, Hiesmayr M: Lack of renoprotective effects of dopamine and furosemide during cardiac surgery. *J Am Soc Nephrol* 2000; 11:97–104
135. Swärd K, Valsson F, Sellgren J, Ricksten SE: Differential effects of human atrial natriuretic peptide and furosemide on glomerular filtration rate and renal oxygen consumption in humans. *Intensive Care Med* 2005; 31:79–85
136. Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lo S, McArthur C, McGuinness S, Myburgh J, Norton R, Scheinkestel C, Su S: Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med* 2009; 361:1627–38
137. Kaelin WG Jr, Ratcliffe PJ: Oxygen sensing by metazoans: The central role of the HIF hydroxylase pathway. *Mol Cell* 2008; 30:393–402
138. Kaelin WG: Von Hippel-Lindau disease. *Annu Rev Pathol* 2007; 2:145–73
139. Semenza GL: Hypoxia-inducible factors in physiology and medicine. *Cell* 2012; 148:399–408
140. Eltzschig HK, Carmeliet P: Hypoxia and inflammation. *N Engl J Med* 2011; 364:656–65
141. Conde E, Alegre L, Blanco-Sánchez I, Sáenz-Morales D, Aguado-Fraile E, Ponte B, Ramos E, Sáiz A, Jiménez C, Ordoñez A, López-Cabrera M, del Peso L, de Landázuri MO, Liaño F, Selgas R, Sanchez-Tomero JA, García-Bermejo ML: Hypoxia inducible factor 1-alpha (HIF-1 alpha) is induced during reperfusion after renal ischemia and is critical for proximal tubule cell survival. *PLoS One* 2012; 7:e33258
142. Hill P, Shukla D, Tran MG, Aragones J, Cook HT, Carmeliet P, Maxwell PH: Inhibition of hypoxia inducible factor hydroxylases protects against renal ischemia-reperfusion injury. *J Am Soc Nephrol* 2008; 19:39–46
143. Ahn JM, You SJ, Lee YM, Oh SW, Ahn SY, Kim S, Chin HJ, Chae DW, Na KY: Hypoxia-inducible factor activation protects the kidney from gentamicin-induced acute injury. *PLoS One* 2012; 7:e48952
144. Bernhardt WM, Wiesener MS, Scigalla P, Chou J, Schmieder RE, Günzler V, Eckardt KU: Inhibition of prolyl hydroxylases increases erythropoietin production in ESRD. *J Am Soc Nephrol* 2010; 21:2151–6
145. Rodriguez R, Robich MP, Plate JF, Trooskin SZ, Sellke FW: Gastrointestinal complications following cardiac surgery: A comprehensive review. *J Card Surg* 2010; 25:188–97
146. Lahon B, Mordant P, Thabut G, Georger JF, Dauriat G, Mal H, Lesèche G, Castier Y: Early severe digestive complications after lung transplantation. *Eur J Cardiothorac Surg* 2011; 40:1419–24
147. Karhausen J, Stafford-Smith M: The role of non-occlusive sources of acute gut injury ("AGI") in cardiac surgery: A review. *J Cardiothorac Vasc Anesth* 2013; (in press)
148. Vollmar B, Menger MD: Intestinal ischemia/reperfusion: Microcirculatory pathology and functional consequences. *Langenbecks Arch Surg* 2011; 396:13–29
149. Reilly PM, Wilkins KB, Fuh KC, Haglund U, Bulkley GB: The mesenteric hemodynamic response to circulatory shock: An overview. *Shock* 2001; 15:329–43

150. Jakob SM: Splanchnic blood flow in low-flow states. *Anesth Analg* 2003; 96:1129–38
151. Acosta S: Epidemiology of mesenteric vascular disease: Clinical implications. *Semin Vasc Surg* 2010; 23:4–8
152. Groesdonk HV, Klingele M, Schlempp S, Bomberg H, Schmied W, Minko P, Schäfers HJ: Risk factors for nonocclusive mesenteric ischemia after elective cardiac surgery. *J Thorac Cardiovasc Surg* 2013; 145:1603–10
153. Kolkman JJ, Mensink PB: Non-occlusive mesenteric ischaemia: A common disorder in gastroenterology and intensive care. *Best Pract Res Clin Gastroenterol* 2003; 17:457–73
154. Kats S, Schönberger JP, Brands R, Seinen W, van Oeveren W: Endotoxin release in cardiac surgery with cardiopulmonary bypass: Pathophysiology and possible therapeutic strategies. An update. *Eur J Cardiothorac Surg* 2011; 39:451–8
155. Gatt M, Reddy BS, MacFie J: Review article: Bacterial translocation in the critically ill—Evidence and methods of prevention. *Aliment Pharmacol Ther* 2007; 25:741–57
156. Ohri SK, Velissaris T: Gastrointestinal dysfunction following cardiac surgery. *Perfusion* 2006; 21:215–23
157. Deitch EA: Gut lymph and lymphatics: A source of factors leading to organ injury and dysfunction. *Ann N Y Acad Sci* 2010; 1207(suppl 1):E103–11
158. Ouellette AJ: Paneth cell α -defensins in enteric innate immunity. *Cell Mol Life Sci* 2011; 68:2215–29
159. Salzman NH: Paneth cell defensins and the regulation of the microbiome: Détente at mucosal surfaces. *Gut Microbes* 2010; 1:401–6
160. Lee HT, Kim M, Kim JY, Brown KM, Ham A, D'Agati VD, Mori-Akiyama Y: Critical role of interleukin-17A in murine intestinal ischemia-reperfusion injury. *Am J Physiol Gastrointest Liver Physiol* 2013; 304:G12–25
161. Park SW, Kim M, Brown KM, D'Agati VD, Lee HT: Paneth cell-derived interleukin-17A causes multiorgan dysfunction after hepatic ischemia and reperfusion injury. *Hepatology* 2011; 53:1662–75
162. Takahashi N, Vanlaere I, de Rycke R, Cauwels A, Joosten LA, Lubberts E, van den Berg WB, Libert C: IL-17 produced by Paneth cells drives TNF-induced shock. *J Exp Med* 2008; 205:1755–61
163. Gill R, Tsung A, Billiar T: Linking oxidative stress to inflammation: Toll-like receptors. *Free Radic Biol Med* 2010; 48:1121–32
164. Reino DC, Palange D, Feketeova E, Bonitz RP, Xu da Z, Lu Q, Sheth SU, Peña G, Ulloa L, De Maio A, Feinman R, Deitch EA: Activation of toll-like receptor 4 is necessary for trauma hemorrhagic shock-induced gut injury and polymorphonuclear neutrophil priming. *Shock* 2012; 38:107–14
165. Tang H, Pang S, Wang M, Xiao X, Rong Y, Wang H, Zang YQ: TLR4 activation is required for IL-17-induced multiple tissue inflammation and wasting in mice. *J Immunol* 2010; 185:2563–9
166. Kunder CA, St John AL, Abraham SN: Mast cell modulation of the vascular and lymphatic endothelium. *Blood* 2011; 118:5383–93
167. Abraham SN, St John AL: Mast cell-orchestrated immunity to pathogens. *Nat Rev Immunol* 2010; 10:440–52
168. Bischoff SC: Physiological and pathophysiological functions of intestinal mast cells. *Semin Immunopathol* 2009; 31:185–205
169. Jacob C, Yang PC, Darmoul D, Amadesi S, Saito T, Cottrell GS, Coelho AM, Singh P, Grady EF, Perdue M, Bunnett NW: Mast cell tryptase controls paracellular permeability of the intestine. Role of protease-activated receptor 2 and beta-arrestins. *J Biol Chem* 2005; 280:31936–48
170. Wilcz-Villega EM, McClean S, O'Sullivan MA: Mast cell tryptase reduces junctional adhesion molecule-A (JAM-A) expression in intestinal epithelial cells: Implications for the mechanisms of barrier dysfunction in irritable bowel syndrome. *Am J Gastroenterol* 2013; 108:1140–51
171. Lin L, Bankaitis E, Heimbach L, Li N, Abrink M, Pejler G, An L, Diaz LA, Werb Z, Liu Z: Dual targets for mouse mast cell protease-4 in mediating tissue damage in experimental bullous pemphigoid. *J Biol Chem* 2011; 286:37358–67
172. Malaviya R, Ikeda T, Ross E, Abraham SN: Mast cell modulation of neutrophil influx and bacterial clearance at sites of infection through TNF- α . *Nature* 1996; 381:77–80
173. Seeley EJ, Sutherland RE, Kim SS, Wolters PJ: Systemic mast cell degranulation increases mortality during polymicrobial septic peritonitis in mice. *J Leukoc Biol* 2011; 90:591–7
174. Cai C, Cao Z, Loughran PA, Kim S, Darwiche S, Korff S, Billiar TR: Mast cells play a critical role in the systemic inflammatory response and end-organ injury resulting from trauma. *J Am Coll Surg* 2011; 213:604–15
175. Kanwar S, Hickey MJ, Kubes P: Postischemic inflammation: A role for mast cells in intestine but not in skeletal muscle. *Am J Physiol* 1998; 275(2 Pt 1):G212–8
176. Huang P, Liu D, Gan X, Zhang R, Gao W, Xia Z, Hei Z: Mast cells activation contribute to small intestinal ischemia reperfusion induced acute lung injury in rats. *Injury* 2012; 43:1250–6
177. Andoh A, Kimura T, Fukuda M, Araki Y, Fujiyama Y, Bamba T: Rapid intestinal ischaemia-reperfusion injury is suppressed in genetically mast cell-deficient Ws/Ws rats. *Clin Exp Immunol* 1999; 116:90–3
178. Karhausen J, Qing M, Gibson A, Moeser AJ, Griefingholt H, Hale LP, Abraham A, Mackensen GB: Intestinal mast cells mediate gut injury and systemic inflammation in a rat model of deep hypothermic circulatory arrest. *Crit Care Med* 2013; 41:e200–10
179. McIlwain RB, Timpa JG, Kurundkar AR, Holt DW, Kelly DR, Hartman YE, Neel ML, Karnatak RK, Schelonka RL, Anantharamaiah GM, Killingsworth CR, Maheshwari A: Plasma concentrations of inflammatory cytokines rise rapidly during ECMO-related SIRS due to the release of preformed stores in the intestine. *Lab Invest* 2010; 90:128–39
180. Cronstein BN, Daguma L, Nichols D, Hutchison AJ, Williams M: The adenosine/neutrophil paradox resolved: Human neutrophils possess both A1 and A2 receptors that promote chemotaxis and inhibit O₂ generation, respectively. *J Clin Invest* 1990; 85:1150–7
181. Wallace KL, Linden J: Adenosine A2A receptors induced on iNKT and NK cells reduce pulmonary inflammation and injury in mice with sickle cell disease. *Blood* 2010; 116:5010–20
182. Yang Z, Day YJ, Toufektsian MC, Ramos SI, Marshall M, Wang XQ, French BA, Linden J: Infarct-sparing effect of A2A-adenosine receptor activation is due primarily to its action on lymphocytes. *Circulation* 2005; 111:2190–7
183. Avni I, Garzozzi HJ, Barequet IS, Segev F, Varssano D, Sartani G, Chetrit N, Bakshi E, Zadok D, Tomkins O, Litvin G, Jacobson KA, Fishman S, Harpaz Z, Farbstein M, Yehuda SB, Silverman MH, Kerns WD, Bristol DR, Cohn I, Fishman P: Treatment of dry eye syndrome with orally administered CF101: Data from a phase 2 clinical trial. *Ophthalmology* 2010; 117:1287–93