

## Perioperative Organ Injury

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### 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.

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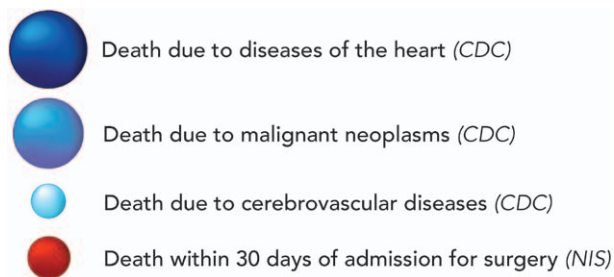
Address correspondence to Dr. Eltzschig: Organ Protection Program, Department of Anesthesiology, University of Colorado School of Medicine, 12700 E 19th Avenue, Mailstop B112, Research Complex 2, Room 7124, Aurora, Colorado 80045. holger.eltzschig@ucdenver.edu. This article may be accessed for personal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

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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.<sup>1</sup> 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.<sup>2</sup> 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.<sup>2,3</sup> Although severe sepsis is the typical precursor to multiple-organ dysfunction, systemic inflammatory response syndrome is a common trigger in surgical patients.<sup>4</sup> 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 Beecher<sup>5</sup> 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,<sup>6</sup> in Japan, 21 deaths per million surgeries,<sup>7</sup> and in a global meta-analysis, 34 deaths per million surgeries were attributed to the anesthetic.<sup>8</sup> 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%.<sup>9</sup> Semel *et al.*<sup>10</sup> 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](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.*<sup>10</sup> 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.<sup>#</sup> 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 Miller<sup>1</sup> 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.<sup>11</sup> 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.”<sup>12</sup> 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%.<sup>13–15</sup> Higher-risk procedures, such as coronary artery bypass surgery and cardiac valve surgery, are complicated by stroke in 1.6<sup>16</sup> and 2.2%<sup>17</sup> of cases, respectively. Mortality levels in patients who suffer from perioperative stroke are significantly increased and range from 12–32.6%.<sup>13,14,18</sup>

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.<sup>19</sup> 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.<sup>20</sup> Watershed infarcts occur in the distal perfusion territories of cerebral arteries and can be due to hypoperfusion and concurrent microembolization.<sup>21</sup> Most strokes occur after an uneventful emergence from anesthesia, and do not present until postoperative day 2.<sup>16,19</sup> 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.<sup>22</sup> Major surgery induces a patient-specific inflammatory profile.<sup>23</sup> 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.<sup>20</sup>

Risk factor modification to prevent stroke hinges on lifestyle changes and medical therapy for hyperlipidemia, diabetes, and hypertension.<sup>24</sup> Patients with a history of cerebral ischemia are at higher risk for stroke, and are commonly maintained on lifelong lipid-lowering<sup>25</sup> and antiplatelet

<sup>#</sup> Available at: [http://www.cdc.gov/nchs/data/dvs/LCWK9\\_2006.pdf](http://www.cdc.gov/nchs/data/dvs/LCWK9_2006.pdf). Accessed July 16, 2013.

therapy.<sup>26</sup> 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.<sup>27</sup> Although intraoperative hypotension is associated with stroke,<sup>18</sup> 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.<sup>28</sup> 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.<sup>29</sup>

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.<sup>30</sup> 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.<sup>31,32</sup> 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.<sup>33,34</sup>

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.<sup>35,36</sup> 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.<sup>37</sup> Immuno-adaptive host responses by lymphocytes have both detrimental<sup>38</sup> and protective<sup>39</sup> 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.

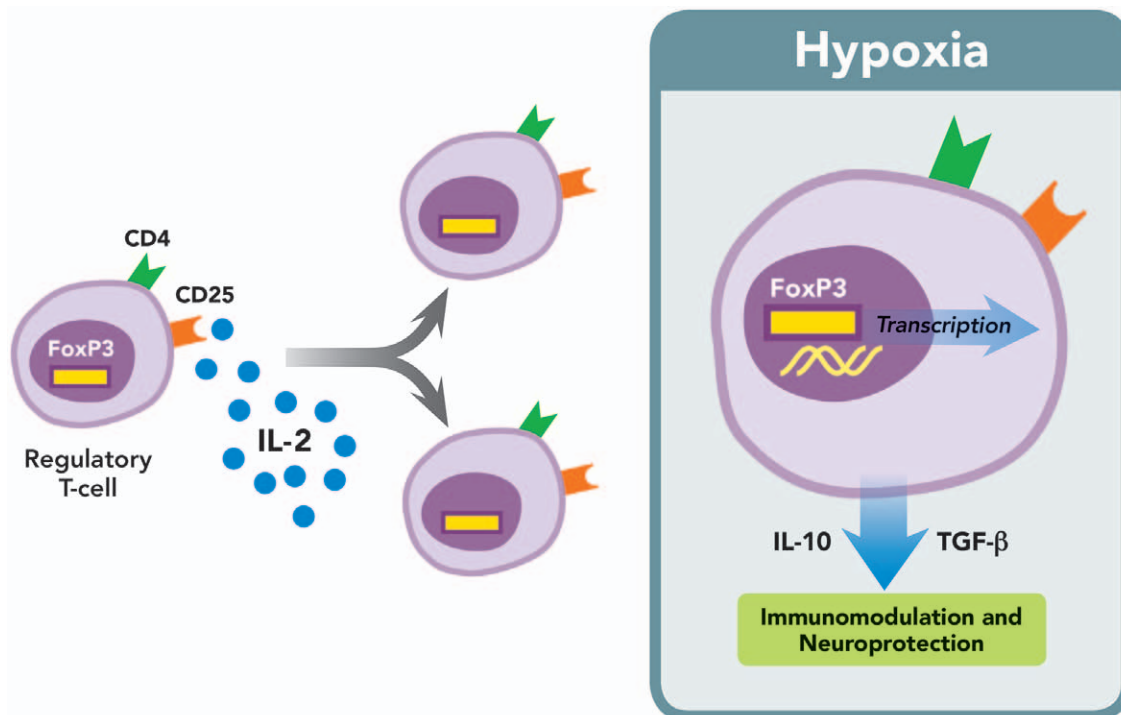
The brain mounts a profound inflammatory response to postischemic reperfusion. The innate immune response includes polynuclear cells, macrophages, and other resident cells that are activated through damage-associated molecular patterns released from damaged host cells.<sup>40</sup> Innate immunity is 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.<sup>36</sup> To better understand the role of lymphocytes in stroke, Hurn *et al.*<sup>38</sup> 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.*<sup>41</sup> 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,<sup>42</sup> a key mediator of oxidative stress leading to exaggerated brain damage after I/R.<sup>43</sup> 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.<sup>44,45</sup> 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-cells<sup>46</sup> and regulatory T-cells<sup>39,47</sup> 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).<sup>48</sup> Hypoxia leads to induction of FoxP3 and thereby solicits antiinflammatory mechanisms conferred by regulatory T-cells.<sup>49</sup> 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.<sup>39</sup> 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.<sup>50</sup> 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 disease<sup>51</sup> and hepatitis C-induced vasculitis.<sup>52</sup> 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.<sup>48</sup> FoxP3 expression is induced under hypoxic conditions and regulates target genes that govern immuno-modulatory functions.<sup>49</sup> Neuroprotective effects are mediated by regulatory augmentation of T-cell proliferation and activity as well as by synthesis of antiinflammatory cytokines such as IL-10<sup>39</sup> and transforming growth factor (TGF)- $\beta$ .<sup>37</sup> Therapeutic activation of regulatory T-cells has been successfully achieved through exogenous administration of IL-2 in clinical trials of primarily nonneurologic diseases.<sup>51,52</sup> 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.<sup>53</sup> During the perioperative period of major noncardiac surgery, the incidence of MI is 1–3%,<sup>54,55</sup> 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.<sup>56</sup>

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.<sup>57,58</sup> 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).<sup>53</sup> 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.<sup>59,60</sup> Because histopathologic examination of the coronaries is only possible after death, plaque disruption found on autopsy in 46–55% of cases<sup>61,62</sup> 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.<sup>63</sup>

Standard pharmacologic approaches for the treatment of coronary artery disease and prevention of myocardial ischemia include  $\beta$ -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  $\beta$ -blockade, have not succeeded in decreasing postoperative mortality.<sup>64</sup> 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,<sup>65</sup> but also an independent predictor of mortality after surgery.<sup>66</sup> 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).<sup>67</sup>

Although restoration of flow through acutely obstructed coronaries is the goal of interventional treatment for MI, reperfusion itself can exacerbate tissue injury,<sup>68</sup> for example, *via* leukocyte transmigration leading to exacerbation of local inflammation.<sup>69</sup> Extracellular adenosine triphosphate is the precursor to adenosine and its release is modulated in the setting of hypoxia and inflammation.<sup>70–72</sup> Adenosine signaling has been strongly implicated in the attenuation of I/R injury in multiple organs, including the heart.<sup>73–79</sup> In 2005 Ross *et al.*<sup>80</sup> 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* analysis<sup>81</sup> 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,<sup>82–87</sup> or use of direct pharmacological adenosine receptor agonists<sup>88</sup> may yield even better therapeutic effects for the treatment of ischemic disease states.<sup>89,90</sup>

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,<sup>91,92</sup> whereas a specific

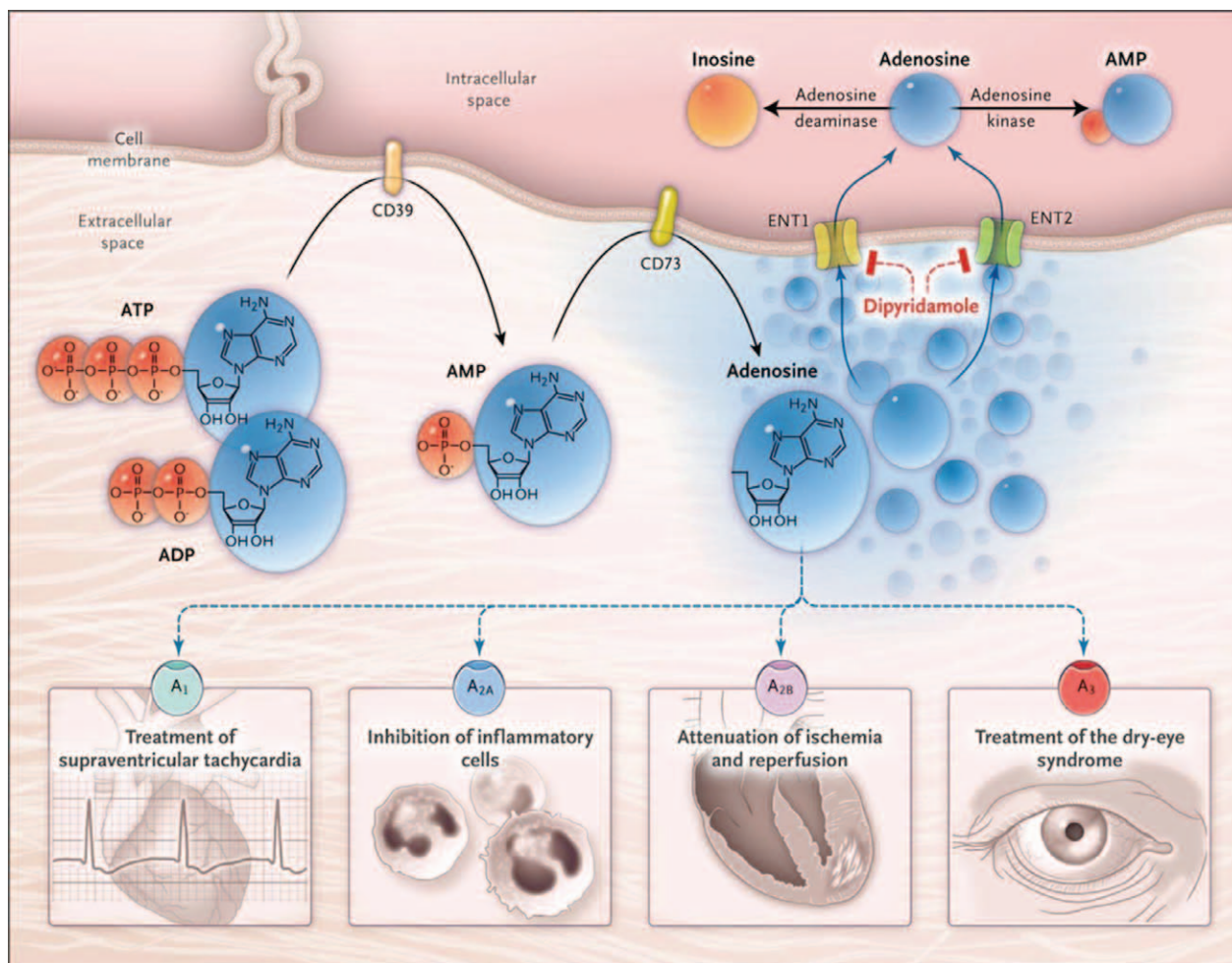
agonist of the ADORA2B (BAY 60–6583)<sup>93–95</sup> attenuates myocardial I/R injury.<sup>91,92,96</sup> Mechanistic studies link ADORA2B-dependent cardio-protection to the circadian rhythm protein Period 2 (Per2). Per2 stabilization by adenosine receptor activation or by light therapy emulates adenosine-mediated cardio-protection.<sup>96</sup> These findings are consistent with studies that show increased susceptibility to the detrimental effects of myocardial ischemia in the early morning hours.<sup>89</sup> 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.<sup>97</sup> 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  $\leq 300$ ,  $\leq 200$ , and  $\leq 100$  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 H<sub>2</sub>O 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%.<sup>98</sup> In higher-risk surgeries, ARDS occurs in 2–15% of patients.<sup>99</sup> Mortality in affected surgical patients is high and ranges from 27 to 40%.<sup>98,100</sup> Surprisingly, Phua *et al.*<sup>101</sup> 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.<sup>102</sup> 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.<sup>103</sup> Influx of neutrophils and activation of alveolar macrophages constitute the basis for the innate immune response. Maintaining a balance between activation of pro- and antiinflammatory 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.<sup>104</sup> 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 neutrophils<sup>180</sup> or lymphocytes in the attenuation of inflammation.<sup>181,182</sup> Other experimental studies provide evidence of signaling events through A2B in tissue adaptation to hypoxia and attenuation of ischemia and reperfusion.<sup>93,94,96</sup> 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.<sup>183</sup> Adenosine signaling is terminated by adenosine 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: Eltzhig HK, Sitkovsky MV, Robson SC: Purinergic signaling during inflammation. *N Engl J Med* 2012; 367:2322–33. © (2012) Massachusetts Medical Society.<sup>67</sup> Reprinted with permission.

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

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).<sup>107</sup> Ongoing biophysical injury by repeated opening and closing of alveoli (atelectrauma), overdistention (volutrauma), and high transpulmonary pressures (barotrauma) exacerbates the initial lung injury.<sup>105</sup>

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 H<sub>2</sub>O or less, and appropriate positive end-expiratory pressure based on the required minimal F<sub>IO<sub>2</sub></sub>.<sup>108</sup> Prone positioning promotes ventilation of dependent parts of the lung. In a multicenter, prospective, randomized, controlled trial, Guerin *et al.*<sup>109</sup> 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.<sup>110,111</sup> Other therapeutic strategies used to limit harmful effects of VILI include limiting the volume of administered intravenous fluids<sup>112</sup> and considering early administration of neuromuscular blocking agents.<sup>113</sup> Multiple attempts have been made to pharmacologically attenuate the proinflammatory cascade encountered in ARDS. Unfortunately, randomized clinical trials using methylprednisolone<sup>114</sup> or omega-3 fatty acids<sup>115</sup> 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,<sup>116</sup> 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,<sup>117</sup> the reports of its successful use during the H1N1 influenza outbreak,<sup>118</sup> and the encouraging results of a randomized clinical trial by Peek *et al.*<sup>119</sup> 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.<sup>120</sup> 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.<sup>121</sup> 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

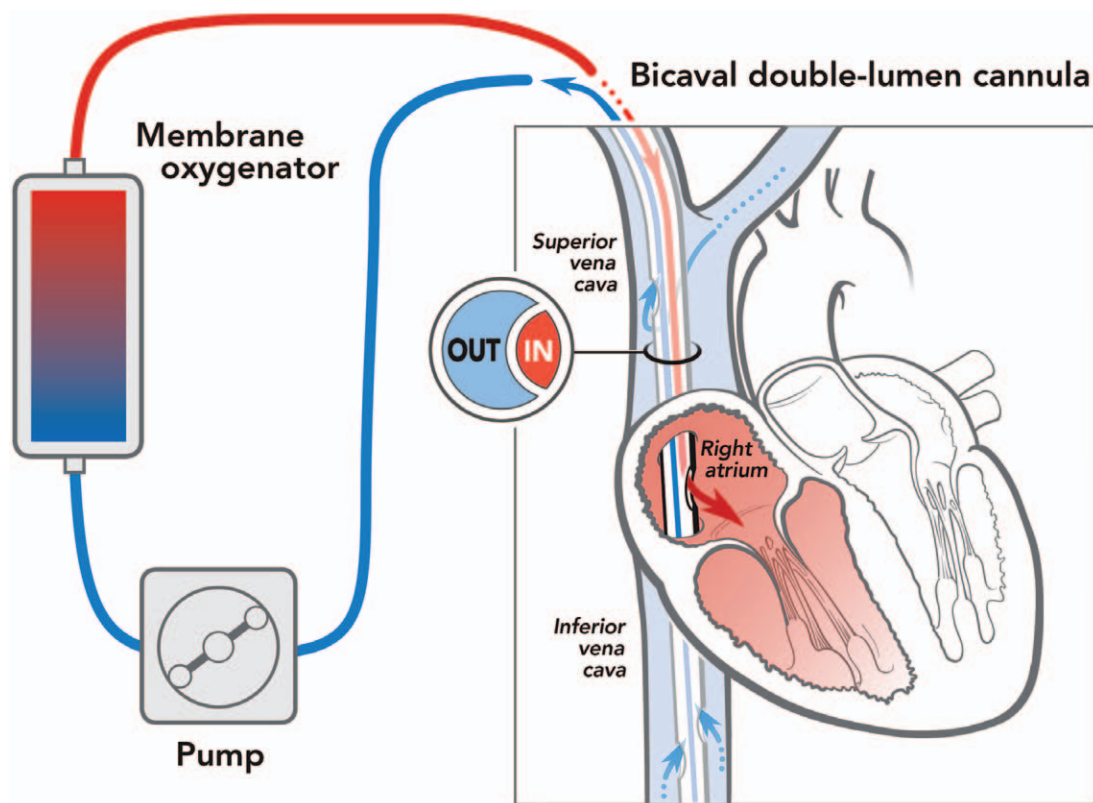
Two sets of criteria that define AKI have gained widespread acceptance and form the basis for the current *Kidney Disease Improving Global Outcomes* guidelines; these are:<sup>122</sup> First, the classification into Risk, Injury, Failure, Loss or End Stage Kidney Disease by the *Acute Dialysis Quality Initiative*.<sup>123</sup> 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*.<sup>124</sup> 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.<sup>125</sup> 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.*<sup>126</sup> 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.<sup>127</sup> AKI represents a continuum of injury, and the distinction between prerenal azotemia and acute tubular necrosis is likely not reflective of tubular biology.<sup>123</sup> 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.<sup>128</sup>

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.<sup>129</sup> Recent clinical trials identified low-molecular-weight hydroxyethylstarches as potent nephrotoxins in a diverse cohort of intensive care unit patients<sup>130</sup> and as a cause of an increased death rate in septic patients.<sup>131</sup>

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.<sup>132</sup> It was, however, associated with higher rates of atrial fibrillation after cardiac surgery.<sup>133</sup> 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.

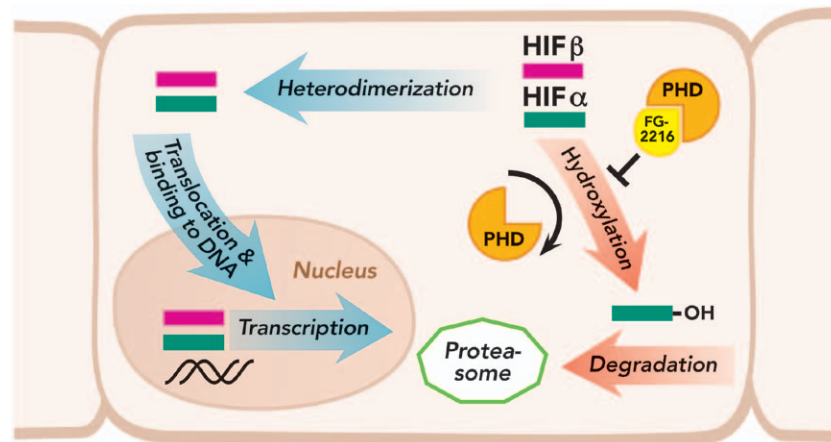
of patients after cardiac surgery.<sup>134</sup> Glomerular filtration rate can decrease after furosemide administration,<sup>135</sup> potentially raising plasma creatinine concentrations. However, forced diuresis can also lead to hypovolemia, secondary renal hypoperfusion, and subsequent AKI. Renal 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.<sup>136</sup>

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).<sup>87</sup> 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.<sup>137,138</sup> HIF is a heterodimer that consists of two subunits—the oxygen-sensitive HIF- $\alpha$  and the constitutively expressed HIF- $\beta$ .<sup>139</sup> 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- $\alpha$  via oxygen-dependent prolyl hydroxylases, which tag HIF- $\alpha$  for degradation in the cell proteasome (fig. 5).<sup>140</sup>

Hypoxia-sensitive signaling mechanisms may inform the development of novel perioperative organ protective strategies.<sup>87,94</sup> Conde *et al.*<sup>141</sup> reported HIF-1 $\alpha$  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/R<sup>142</sup> and in a model of gentamicin-induced AKI.<sup>143</sup> 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.<sup>144</sup> 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- $\alpha$  and the constitutively expressed HIF- $\beta$  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- $\alpha$  and thereby mark it for proteasomal degradation, effectively inhibiting HIF-dependent gene expression. Prevention of proteasomal HIF- $\alpha$  degradation using prolyl hydroxylase inhibitors, for example, FG-2216,<sup>144</sup> 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%).<sup>145,146</sup>

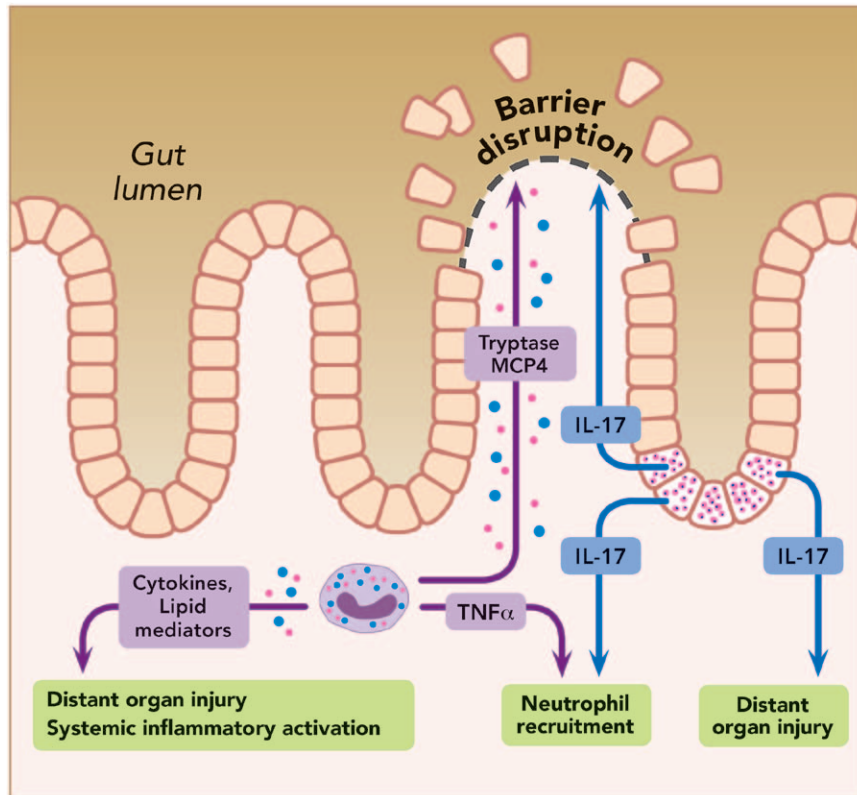
Different specific factors influence particular AGI manifestations, for example, the altered coagulation state after cardiopulmonary bypass in the context of gastrointestinal bleeding. Beyond this, splanchnic perfusion abnormalities and associated mucosal I/R injury form a central common pathophysiologic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

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.<sup>154–156</sup> 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.<sup>157</sup> 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.<sup>158</sup> Until recently, Paneth cell function has been regarded as host-protective, particularly in the sense of antimicrobial control.<sup>159</sup> 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,<sup>160</sup> but also plays a critical role in multiorgan dysfunction after hepatic I/R injury,<sup>161</sup> and after tumor necrosis factor- $\alpha$ -induced shock.<sup>162</sup> 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.<sup>163</sup> As such, shock-induced AGI is toll-like receptor 4 dependent.<sup>164</sup> New data suggest that IL-17 constitutes an important activator of this pathway,<sup>165</sup> 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.<sup>164</sup>

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]- $\alpha$ , IL-6).

surveillance cells strategically positioned within the gut wall, their physiologic role is slowly evolving beyond the traditional focus on allergy.<sup>166–168</sup> MCs exert local and systemic effects *via* rapid release of preformed proteases, mediators, and cytokines. For example, MC-tryptase,<sup>169,170</sup> as well as MC-protease 4<sup>171</sup> have been implicated in the breakdown of tight junctions in various mucosal epithelia, including the gut. Release of preformed tumor necrosis factor- $\alpha$  from MCs is a powerful inflammatory stimulus that not only promotes local pathogen clearance,<sup>172</sup> but also drives detrimental systemic inflammatory deregulation in critical illness.<sup>173,174</sup> The role of MCs in intestinal I/R injury has been studied extensively,<sup>175–177</sup> 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.<sup>178</sup> Similarly, in a piglet model of ECMO, systemic inflammatory responses appeared to stem from mediators released by splanchnic MCs.<sup>179</sup>

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.

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