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Disease Mechanisms of Perioperative Organ Injury

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Abstract

Despite substantial advances in anesthesia safety within the past decades, perioperative mortality remains a prevalent problem and can be considered among the top causes of death worldwide. Acute organ failure is a major risk factor of morbidity and mortality in surgical patients and develops primarily as a consequence of a dysregulated inflammatory response and insufficient tissue perfusion. Neurological dysfunction, myocardial ischemia, acute kidney injury, respiratory failure, intestinal dysfunction, and hepatic impairment are among the most serious complications impacting patient outcome and recovery. Pre-, intra-, and post-operative arrangements, such as enhanced recovery after surgery programs, can contribute to lowering the occurrence of organ dysfunction, and mortality rates have improved with the advent of specialized intensive care units and advances in procedures relating to extracorporeal organ support. However, no specific pharmacological therapies have proven effective in the prevention or reversal of perioperative organ injury. Therefore, understanding the underlying mechanisms of organ dysfunction is essential to identify novel treatment strategies to improve perioperative care and outcomes for surgical patients. This review focuses on recent knowledge of pathophysiological and molecular pathways leading to perioperative organ injury. Additionally, we highlight potential therapeutic targets relevant to the network of events that occur in clinical settings with organ failure.

Keywords

Perioperative Organ Injury; Hypoxia; Adenosine; Hypoxia-Inducible Factor; HIF; Adenosine; microRNAs; Acute Respiratory Distress Syndrome; Myocardial Ischemia; Acute Kidney Injury; Inflammation

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Introduction

Anesthesia safety has improved steadily over the last century with the implementation of clinical practice guidelines and checklists, as well as with advances in training, medication, monitoring devices and equipment [1]. The risk of death and major complications for the general surgical patient population is less than 1 % [2]. However, recent estimates in Europe and the USA reveal that overall postoperative mortality remains higher than expected and can be considered the third leading cause of death after ischemic heart disease and cancer worldwide, if given its own category [3,4]. It should be noted with this statistic that perioperative death is multifactorial and a clear discrimination between procedure-related death and mortality resulting from pre-existing disease can be difficult. More than 4.0 million patients die within 30 days of a procedure each year, accounting for 7.7% of all deaths globally [4,5].

The aging population, increasing comorbidities, and more complex surgical procedures negatively impact recovery from surgery and contribute to rising numbers of high-risk patients [6]. Individualized integration of procedure- and patient-related risk factors into the pre-, intra-, and post-operative arrangements can contribute to improving patient outcomes, e.g. enhanced recovery after surgery programs [7]. But, despite all preventive efforts, acute organ injury is a frequent complication and a major risk factor of morbidity and mortality for surgical patients [4,8]. Common manifestations of perioperative organ injury include neurological complications [9], myocardial ischemia [10], acute kidney injury [11], respiratory failure [12], intestinal dysfunction [13], and hepatic impairment [14].

Inflammation and ischemia build the pathophysiological hallmarks of organ dysfunction. During the perioperative period, either the surgical insult or insufficient organ perfusion, initially induces a local inflammatory reaction resulting in a coordinated cytokine cascade to maintain substrate supply for essential organs and wound healing. However, dysregulated, excessive mediator release and oxidative stress can culminate in a prolonged systemic inflammatory reaction that can lead to considerable collateral damage of the host tissues [15]. Increased oxidative metabolism and immunological activity of recruited leukocytes require high levels of oxygen, causing hypoxia in the inflamed lesion [16]. Hypoxia and inflammation can exacerbate one another by bidirectional pathways, at the same time various key mediators in these signaling networks have the potential to break this loop and drive resolution and tissue repair [17]. Despite promising results from preclinical studies, no biological response modifier has been conclusively confirmed as a pharmacological treatment for the prevention or reversal of organ failure in clinical trials, and current therapeutic approaches remain limited to organ supportive strategies. Further understanding of the underlying mechanisms of organ dysfunction is essential to improve perioperative care and to identify novel targets for therapeutic intervention.

Clinical presentation and interventions targeting acute organ dysfunction

Acute organ injury is characterized by the rapid functional decline of an organ system and subsequent failure to maintain physiologic homeostasis. The impact of injury on each organ can range from mild dysfunction to complete failure and is potentially reversible. Organ

dysfunction after surgery primarily develops on the pathophysiological basis of an exacerbated inflammatory response towards local tissue injury, perioperative hemodynamic changes, sudden occlusive events, pre-existing organ susceptibility, predisposing comorbid conditions and/or procedure-related characteristics (Figure 1, Table 1). During and after the operation, cellular damage and immunological activity lead to the release of various molecules in a timely coordinated manner, which can be considered as diagnostic or predictive biomarkers for the development of organ dysfunction (Figure 2, Table 1). Initial impairment of one organ function is often followed by injury of other organs. The sequence of organ failure influences patient outcome, and mortality rates increase with the number of dysfunctional organs [18]. In the following paragraphs we will present frequent manifestations of organ injury, discuss their impact on perioperative outcomes, and highlight some of the clinical practice approaches to prevent or improve individual organ dysfunctions.

a) Cardiovascular dysfunction

Perioperative myocardial ischemia (PMI) and infarction continue to be major causes of morbidity and mortality in noncardiac surgical patients [10]. Cardiac injury is defined as myocardial cell death, reflected by elevated serum cardiac troponin levels within 30 days of non-cardiac surgery. The peak post-operative troponin (≥ 0.3 ng/ml) during the first three days after surgery has prognostic value and an absolute change of 5 ng/ml predicts 30-day mortality [38]. High-sensitivity troponin assays could increase the detection of myocardial injury [39], while post-operative troponin kinetics were not useful for further mortality risk assessment [40]. PMI peaks during the early post-operative period (24-48 hours) and is significantly associated with myocardial infarction (MI) and cardiac complications [10]. In more than half of the cases, myocardial infarction is silent and is preceded by ST-depression type ischemia rather than ST elevations [41]. Despite improved pre-operative risk stratification and advances in intra-operative care fluid resuscitation, PMI occurs in up to 6.2% of the surgeries with fatal outcomes in 2-25% of the cases [27,42].

PMI is primarily considered the result of imbalances in myocardial oxygen supply and demand (oxygen supply-demand mismatch) from tachycardia, hypotension, hypoxia, or anemia [43]. Thus, abrupt changes in heart rate, blood pressure, and intravascular volume during surgery can culminate in cardio-myocyte necrosis and subsequent infarction in susceptible patients. A strong correlation of hypotension and myocardial injury is widely accepted. However, the vulnerable threshold and critical duration of intraoperative hypotension is not consistently defined [44,45]. Prolonged exposure to either an absolute mean arterial pressure (MAP) below 65 mmHg or relative thresholds of 20% from the pre-induction MAP [45], and even short periods of an intraoperative MAP less than 55 mmHg could relate to the occurrence of myocardial injury [44].

Besides demand-supply mismatch associated cardiac ischemia, patients with preexisting coronary artery disease are at a high risk of suffering from occlusive events during surgery. Increased coronary artery sheer stress can precipitate destabilization and rupture of vulnerable plaques, low coronary flow and blood hypercoagulability, combined with stress-induced vasoconstriction, can favor thrombotic occlusion of the coronaries [43]. To protect the heart from sustained ischemia, myocardial preconditioning using volatile anesthetics has

been suggested based on the observations in animal studies [46]. However, cardio-protective effects of volatile over intravenous anesthetics have not been convincingly demonstrated in several clinical trials and meta-analyses [47,48], suggesting that myocardial ischemia cannot be prevented by anesthetic agents 'preconditioning' the heart, but depends on the anesthesiologist's skills to use the available tools to control the hemodynamic homeostasis of the patient [49].

b) Neurological complication

Cerebral dysfunction occurs frequently after surgery and can manifest as stroke or confusional states, such as delirium. Perioperative stroke, defined as either hemorrhagic or ischemic brain infarction within 30 days of the procedure, is one of the most devastating complications with significant impact on patient outcome and recovery [50]. Mortality rates are as high as 24% and a large proportion of survivors face the challenges of long-term neurological disability [9]. In particular, patients undergoing cardiovascular and carotid artery surgery (1.9 - 9.7 %) are affected [19,21]. In the general surgical patient population cerebrovascular insult is considered rare (0.1 - 1.9%) [9,51], but due to increasing patient age and comorbidities, a larger population at risk of perioperative stroke is expected in the future [51]. Diagnosis is often delayed because neurological symptoms may present mild and be incorrectly mistaken as post-operative confusional states [52]. Embolic events are considered the major etiology of strokes after surgery. Early strokes are commonly associated to direct manipulation of the heart, the aorta, or the carotid artery [19,21]. Delayed cerebrovascular accidents from the second post-operative day onward are frequently attributable to cardiogenic embolism on the basis of post-operative atrial fibrillation, myocardial infarction, or a hypercoagulable state [19,51,53]. Hypoperfusion as a cause of stroke is considered rare [54]. However, recent studies identify beta-blockade as a risk factor for perioperative stroke in the general surgical population and there is rejuvenated interest in linking intraoperative hypotension to strokes [55,56]. The cerebral perfusion is critically dependent on the mean arterial pressure, and a non-selective beta-blockade may cause malperfusion by impairing cerebral vasodilation and reducing cardiac output. Consistently, Bijker and colleagues observed an association of post-operative ischemic strokes and a MAP reduction by more than 30% from baseline blood pressure in general surgical patients [57].

Post-operative delirium, characterized by acute fluctuations in awareness, cognition and consciousness, is a more frequent neurological complication with high incidence rates reported from 5-50% and seems to affect elderly patients in particular [58]. Among those admitted to critical care units, the occurrence of delirious patients is even higher, with 60–80% of mechanically ventilated patients and 20–50% of non-mechanically ventilated patients [59]. The wide variation of reported incidence rates may reflect the fact that delirium is not a clinical diagnosis but rather a variably operationalized concept defined by decline in postoperative cognitive performance assessed by a mental testing algorithms [60]. Although often considered less serious than other types of organ injury after surgery, there is increasing evidence that delirium significantly predicts and relates to adverse surgical outcomes [58,61]. Recent studies demonstrated an association of delirium with patients' functional decline, longer duration of mechanical ventilation and intensive care unit (ICU) stay, increased length of overall hospital stay, and post-discharge mortality [62,63]. Notably,

post-operative delirium negatively impacts patient outcome and recovery independent of other risk factors such as comorbidities and illness severity [61,64]. Given the significant impact on patient outcome and the lack of evidence for efficient pharmacological treatments, early recognition and prevention of delirium is of high importance. Opioid-based analgesic regimens on the one hand, and untreated pain on the other hand, are both potential risk factors of delirium [65]. Thus, effective and opioid-sparing pain treatment is considered by many experts as an important goal to prevent acute confusional states after surgery. Until then, reducing opioids by appropriately-timed administration of dexmedetomidine can be considered a promising approach to lower the occurrence of cognitive dysfunction [66,67], whereas adjunctive treatment with Gabapentin [68] or a single subanesthetic dose of ketamine [69] did not indicate beneficial effects, but has been associated with an increased incidence of confusion and nightmares in elderly patients. For mechanically ventilated ICU patients, dexmedetomidine compared to standard sedatives was shown to increase delirium-free and coma-free days [70,71], but did not affect 90-day mortality and was more frequently associated with bradycardia and hypotension [72].

The underlying pathophysiology of delirium is considered to be multifactorial and involves acute central cholinergic deficiency, decreased GABAergic activity and abnormalities in serotonergic and dopaminergic pathways combined with cerebral inflammation [65]. Anesthetic agents were hypothesized to differentially have brain protective effects by modifying these pathways, but recent clinical trials and retrospective analysis for Xenon, Sevofluran, or Propofol-based anesthetics failed to demonstrate evidence [48,73,74]. Thus, it is more likely that the overall perioperative management, not just the anesthetic agent per se, impacts delirium risk.

c) Respiratory dysfunction

Patients are at risk for several types of respiratory dysfunctions in the perioperative period, including pneumonia, atelectasis, pneumothorax, and acute respiratory distress syndrome (ARDS) [12]. Nowadays, mechanical ventilation is an indispensable tool in general anesthesia and intensive care medicine to provide sufficient oxygenation. Though being necessary to preserve life, invasive ventilation can cause injurious forces that can precipitate or exacerbate most of the above lung damage, referred to as ventilator-induced lung injury (VILI) [75]. These mechanisms include exposure to high inflation transpulmonary pressures (barotrauma), alveolar overdistention (volutrauma), and/or high shear forces from repetitive opening and closing of atelectatic alveoli (atelectrauma), collectively leading to structural damage of the alveolar epithelial-endothelial unit and subsequent inflammation (biotrauma) [75,76]. In 2000, a landmark trial by the ARDSnet translated the advances in understanding VILI into clinical success. The implementation of lung-protective ventilation strategies (≤6 vs. 12 ml/kg predicted body weight ventilation, optimal FiO_2/PEEP titration, limited plateau pressure to ≤30 vs 50 cm H_2O) has proven great implications for ICU patients and remains the cornerstone to prevent lung injury and improve outcomes [77]. The knowledge from these studies may as well provide a pathway toward what would be the best use of lung protective strategies in the OR to reduce post-operative pulmonary complications. Although few clinical studies focus on the general surgical patient population, increasing evidence suggests that low tidal ventilation [78,79] and low driving pressures [80] could potentially

prevent the occurrence of major respiratory dysfunctions. A few years ago, the original definition of VILI was extended to include dynamic work during ventilation, such as respiratory rate and flow, which distributes energy to the lung causing injurious strain [81,82]. Cressoni and colleagues introduced the concept of mechanical power, which combines the lung damaging static (transpulmonary driving pressure, tidal volume) and dynamic (respiratory rate, flow) components into one variable, and is defined as energy per breath times respiratory rate (J/min) [81]. These studies were the first to indicate that a power threshold, rather than focusing on individual parameter limits, should be taken into account to minimize VILI in healthy and diseased lungs [81]. Although the concept of mechanical force is promising, the current mathematical equation has limitations and lacks an appropriate representation of the PEEP and aerated lung tissue [83,84]. Improved modeling will be critical for large multicenter trials relating mechanical power to the risk of VILI to define a 'safe' mechanical power threshold for clinical practice and ventilator settings [84-86].

ARDS is one of the most serious pulmonary complications characterized by hypoxemia, non-cardiogenic pulmonary edema, and excessive lung inflammation with high mortality rates ranging from 27-46% [87,88]. According to the Berlin definition proposed in 2012, ARDS is categorized in mild ($PaO_2/FiO_2 \leq 300$ mmHg), moderate ($PaO_2/FiO_2 \leq 200$ mmHg), or severe ARDS ($PaO_2/FiO_2 \leq 100$ mmHg) with a significant mortality increase across the severity categories [88,89]. The incidence in the general surgical population is low (0.2%), however, several factors such as pneumonia, extrapulmonary sepsis, aspiration, high risk surgeries, imbalanced ventilator and fluid management, significantly propagate the risk to develop lung failure after surgery [90]. Excessive inflammatory activation and degradation of the alveolar-capillary barrier resulting in pulmonary edema formation, are considered central processes in the pathogenesis of acute lung injury [75,91]. Improvements in outcomes of ARDS patients are primarily attributable to advances in supportive care on specialized ICUs (e.g. limiting fluid overload [92], early prone positioning[93], extracorporeal membrane oxygenation? [94]) and evolving lung-protective mechanical ventilation concepts (low tidal volume and plateau pressure [77], 'open lung' approach (controversial) [95,96], low driving pressures [97], and low mechanical power? [81]). However, despite intense research over four decades and more than 20 large multicenter clinical trials, no specific pharmacological therapies have proven effective in the treatment of ARDS [98]. Therefore, the paradigm has shifted to earlier interventions to prevent ARDS. The **L**ung **I**njury **P**rediction **S**core (LIPS) and the **C**hecklist for **L**ung **I**njury **P**revention (CLIP) have been suggested to standardize early recognition and initiate good practices for ARDS patients [99,100]. Knowledge of ARDS risk factors provides the rationale for Phase III clinical trials from the **P**revention & **E**arly **T**reatment of **A**cute **L**ung Injury (PETAL) Network and the **L**ung **I**njury **P**revention **S**tudy (LIPS) Group. Unfortunately, most of the trials published until now remain negative and did not provide any substantial breakthroughs for ARDS prevention and therapy. Ongoing study efforts continue to focus on basic physiological concepts and attenuation of the immune response. Adding to the list of negative studies last year, PETAL investigators reevaluated the benefits of early neuromuscular blockade to reduce patient–ventilator dyssynchrony and the work of breathing for patients with moderate-severe ARDS [101]. Equally disappointing were the results obtained from studies addressing the potential of antioxidants and immune-modulators, such as statins [102], Vitamin C [103], and Vitamin D [104]. Linking platelet immune

functions to ARDS is increasingly recognized as a potential therapeutic intervention. However, despite repeated demonstration that the inhibition of platelet signaling attenuates lung inflammation in preclinical studies [105], the use of aspirin compared with placebo was not successful to reduce the risk of ARDS at 7 days in a multicenter trial randomizing 390 patients (LIPS-A trial) [106].

One of the lessons of the many failed trials is that ARDS represents a heterogeneous syndrome, and it is unlikely that one therapeutic strategy is suitable for all patients. Thus, identifying subgroups of patients that could benefit from specific interventions may provide a more promising approach for ARDS prevention, treatment, and trial design [107,108].

d) Acute kidney injury

Acute kidney injury (AKI), defined by a rapid decline of kidney function within a few hours or days, is a morbid complication of the surgical patient and is associated with poor outcomes and increased mortality [11]. Traditionally, the concept of acute renal failure focused on severe, and relatively rare total loss of kidney function, thereby overlooking mild and moderate stages of renal impairment that occur more frequently [109]. However, all severity levels can be associated with adverse outcomes and in particular, the milder forms remain underdiagnosed [110,111]. To streamline research and clinical practice, the consensus definition of AKI has been revised with the intention to standardize assessment of kidney injury, define different severity categories and predict patient prognosis [Risk, Injury, Failure, Loss, End Stage Renal Disease (RIFLE) criteria, 2004; Acute Kidney Injury Network (AKIN) criteria, 2007; Kidney Disease: Improving Global Outcomes (KDIGO) criteria, 2012]. Since the release of the KDIGO criteria, the incidence of documented AKI in hospitalized patients is progressively increasing [112] underscoring the clinical importance of renal injury. Yet, the epidemiological change is not only attributable to the new criteria, but also indicates a real rise of AKI cases most likely reflecting the aging population, increasing comorbidities, and more complex surgeries [113,114]. The incidence of AKI is considered rare in the general surgical population [115], but recent studies identified particular patient groups at high risk of renal injury. To this point, an incidence of 8.5% after gastric bypass surgery [116] is reported, 26% for trauma patients [117], 7-39% for patients undergoing major abdominal surgery [34], 19-46% for cardiac surgical patients [32], 48% after orthotopic liver transplantation [118], and rates as high as 75% for patients undergoing ruptured abdominal aortic aneurysm repair [33].

Renal hypoperfusion and inflammation are considered major contributors to cellular damage and tubular cell dysfunction in the kidneys [11]. Hemodynamic instability and hypovolemia often occur temporarily during the perioperative period, potentially altering both MAP and cardiac output, and subsequently impairing renal blood flow [119]. Initially, compensatory mechanisms involving the sympathetic nervous system, hormones, and the renin–angiotensin axis control the renal blood flow by regulating the diameter of the renal vasculature to maintain glomerular filtration. However, persistent hypoperfusion can exceed the auto-regulatory capacity of the kidney, leading to cellular hypoxia, tubular necrosis, and the release of danger signals (damage-associated molecular patterns, DAMPs) [120]. Combined with surgical injury, these ischemic episodes can trigger a systemic inflammatory response resulting in recruitment of immune cells, endothelial dysfunction and renal

microcirculatory alterations, thereby causing further tubular damage [121]. Nephrotoxic drugs, such as antimicrobial substances including aminoglycosides and amphotericin B, nonsteroidal anti-inflammatory medication, or iodinated contrast imaging agents, can further increase the susceptibility of the kidney to perioperative stressors [122].

With the limited understanding of the pathogenesis of AKI, therapeutic approaches and preventive efforts remain majorly based on physiological concepts. Hemodynamic optimization and avoidance of intravenous fluid over- or underload are well-established concepts in reno-protection [123-125]. Early detection, precise risk stratification, and supportive strategies can improve patient outcomes, however, the number of clinical trials remains inadequate [126]. Recent pharmacological approaches to attenuate inflammatory activity include perioperative aspirin and clonidine [127], rosuvastatin [128] or high-dose atorvastatin administration [129], short-term perioperative medication of oral spironolactone [130], or treatment with THR-184—a bone morphogenetic protein-7 agonist [131]. Unfortunately, all of the investigations failed to demonstrate outcome improvements in clinical trials. While renal replacement therapy continues to be the cornerstone of treatment for patients with severe kidney injury, the question of when (‘early vs. late’) and at which AKI stage to initiate extracorporeal organ support, remains at the center of intensive research efforts [132,133].

e) Intestinal dysfunction

For more than 30 years, the gut has been considered a central modulator in the development of multiple organ failure and sepsis [134]. Traditionally, distant organ dysfunction was attributed to direct translocation of indigenous bacteria and toxins through the intestinal wall into systemic circulation due to inflammatory mucosal hyperpermeability [13]. Critically ill patients in intensive care units frequently experience splanchnic hypoperfusion and intestinal barrier dysfunction [135]. During the perioperative period, the incidence of mesenteric ischemia is only well documented for cardiac (< 1%) [36] and aortic surgery patients (1.6-15.2%) [37]. Either as transient mesenteric ischemia triggering a gut-derived systemic inflammation or as mesenteric ischemic necrosis, bowel injury can be caused by an acute embolic or thrombotic obstruction of the mesenteric vasculature, or as non-occlusive mesenteric ischemia due to low flow situations, such as acute heart failure, cardiac arrhythmia or during high-dose administration of vasopressors [136,137]. Acute bowel ischemia is generally a devastating complication that requires early diagnosis and intervention to prevent bowel necrosis and patient death. Primarily, patients with several comorbidities and poor cardiovascular conditions are affected [36]. It is now recognized that not only the leakiness of the gut, but also the composition of bowel microbiome, has a significant impact on patient outcome [138]. Critical illness can cause acute changes of the microbiome, and vice versa, the gut bacteria impacts critical illness. Intestinal microbiota can directly influence the cytokine response to injury, and thus, has the potential to drive immune responses into either a protective or an injurious direction [139,140]. Several stressors during critical disease states, such as antibiotics, proton pump inhibitors, vasopressors and tissue hypoxia, can cause alterations of the gut microbiome leading to a detrimental immune profile and disease-exacerbating neutrophil subsets [141], which can trigger the development of organ failure [139,142].

f) Liver dysfunction

Acute liver dysfunction is defined as a sudden onset of jaundice, hepatic encephalopathy, and coagulopathy. Patients undergoing hepatectomy or cases with pre-existing liver disease have a particular high risk to develop liver failure after surgery [14,35]. In addition, liver injury can be precipitated by cardiogenic causes, such as myocardial infarction or sustained arrhythmia resulting in passive acute liver congestion, and congestive heart failure leading to 'cardiac cirrhosis' [143]. Portal hypertension, arteriovenous shunting and reduced splanchnic inflow can result in decreased hepatic arterial and venous perfusion at baseline, thereby increasing the susceptibility of the liver to ischemic injury. Intraoperative hypotension, hemorrhage, and vasoactive drugs, as well as mechanical compression of the liver by positive-pressure ventilation or pneumoperitoneum during laparoscopic surgery, further contribute to reduce liver circulation [144,145]. To a limited extent, the liver can increase oxygen extraction to compensate for the decrease in hepatic blood flow, however, impaired oxygen and substrate delivery to the remaining functional hepatocytes and liver sinusoidal endothelial cells is likely to precipitate acute hepatic decompensation. ATP depletion and mitochondrial dysfunction due to ischemia lead to the accumulation of toxic mediators, such as lactate and reactive oxygen species causing hepatic inflammation [146]. On the cellular level, resident liver macrophages (Kupffer cells) are critical for promoting liver resistance toward ischemia and reperfusion injury, for example through reprogramming via hypoxia-inducible transcription factors [147,148]. Importantly, HIF stabilization confers hepato-protection during acute liver damage and is essential for tissue recovery and repair [148]. Practice approaches to prevent or minimize acute hepatic failure in patients undergoing liver surgery include treating comorbid conditions, limiting the extent of surgery and increasing the volume of the future remnant liver by portal vein embolization [149]. Preclinical studies in rodents indicate that following hepatic injury platelets are recruited into the liver, and that increasing platelet counts improved liver regeneration and survival after hepatectomy [150,151]. Evidence is increasing that the induction of thrombocytosis either by splenectomy or platelet transfusion may promote regenerative processes after liver resection or transplantation [152,153]. To make use of the regenerative potential of platelets without increasing the risk of transfusion- or splenectomy-related side effects, further understanding of the underlying mechanisms by which platelets stimulate regenerative programs in hepatocytes and liver sinusoidal endothelial cells will be essential to develop targeted therapies for perioperative liver dysfunction [154].

Cellular mechanisms leading to organ dysfunction

Many pathways inducing cellular damage are similar for all organs systems and include a combination of ischemic tissue injury and a dysregulated inflammatory response. On the cellular level, tissue hypoxia and inflammation are closely linked: Inflammatory conditions are often characterized by hypoxia, and conditions of low oxygen levels are often characterized by the onset of tissue inflammation (Figure 3). Perioperative reduction of blood supply during episodes of low blood pressure or occlusive events limits substrate and oxygen availability, causing cell-type specific transcriptional reprogramming involving hypoxia-inducible factors (HIF). Injured cells release 'danger signals' and induce trafficking of leukocytes to the side of tissue damage, which is associated with a profound increase in

local oxygen demand. Activated immune cells release inflammatory mediators and cytotoxic molecules to pre-empt impending infection, but at the same time potentially cause collateral tissue injury. Cellular destruction can induce an amplification loop, in which leukocyte recruitment is maintained through sustained release of tissue injury signals. (Figure 4). If the immunological exacerbation is triggered by pathogen invasion, the clinical syndrome is defined as sepsis and causes infectious organ failure, which will be discussed elsewhere. In the following section, we will exemplify molecular pathways leading to organ dysfunction, and present potential therapeutic strategies to target these mechanistic networks to improve clinical outcomes.

a) Immunological activity and acute organ injury

Neutrophil recruitment to the site of infection is an essential early step in initiating innate immunity and effective bacterial clearance, yet excessive or inappropriate inflammation is associated with considerable collateral damage of the host tissues. Several complications that can be present during the perioperative period, such as acute myocardial infarction, stroke, reversal of cardiac arrest or organ transplant, are characterized by an initial tissue hypoperfusion followed by a sudden restoration of blood flow (ischemia-reperfusion) [155]. This sequence has been shown to cause an inflammatory activation sharing parallels with neutrophilic inflammation directed towards microorganisms [156]. Besides microbe-derived pathogen-associated molecular patterns (PAMPs), the host response is activated by damage-associated molecular patterns (DAMPs) released from injured or hypoxic cells [157]. Whereas PAMP-signaling has a clear role in pathogen defense, the purpose of neutrophil recruitment into damaged tissues without infection is less understood. Recently, Huang and Niethammer used an elegant approach in zebrafish to uncouple tissue damage- and microbe-induced signaling during bacterial infection. Interestingly, they showed that neutrophils ignore bacteria in the absence of DAMPs, providing evidence for the indispensability of danger signals for microbial defense [158].

Given the adverse clinical effects of excessive inflammation, Kang et al. suggest a blood-cleansing device for patients with sepsis, which may also be of interest for perioperative patients with a systemic inflammatory response. In that approach, DAMPs and PAMPS are continuously removed from the blood using magnetic beads coupled to mannose-binding ligand, and the cleansed blood is returned back to the individual (‘biospleen device’) [159]. However, this approach has so far only been studied in animal models. More advanced and of clinical use in Japan and parts of Western Europe, is direct hemoperfusion to remove circulating endotoxins via high affinity binding to polymyxin B immobilized to polystyrene-derived fibers. Despite evidence for improvements of hemodynamics, and oxygenation as well as renal function in pilot trials, polymyxin B hemoperfusion failed to improve survival at 28 days for patients with septic shock in a North American multicenter, randomized controlled trial in a cohort of 450 patients with septic shock and high endotoxin activity levels (Evaluating the Use of Polymyxin B Hemoperfusion in a Randomized Controlled trial of Adults Treated for Endotoxemia and Septic Shock, EUPHRATES trial) [160]. Results from these studies indicate that filter-based approaches need to be designed more selectively in the future to specifically eliminate pro- over anti-inflammatory mediators.

Although it was established more than 25 years ago that dysregulated inflammatory activity and oxidative stress can result in damage of cellular structures and cell death [161], to date, no biological response modifier has proven effective for the treatment of acute organ injury. Clinical trials investigating broad-spectrum immuno-modulatory agents to block the excessive inflammatory response of multiple cell types, such as corticosteroids, keep yielding conflicting data about their benefit. Recent medium to large randomized-controlled trials in patients with severe acquired pneumonia, sepsis, and kidney injury only added to this controversy, and still lack a clear rationale for the use of corticosteroids either to prevent or treat organ failure [162-164]. Equally disappointing were the results from two multicenter trials attempting to take advantage of the anti-inflammatory and antioxidant properties of vitamin C or statins in patients with sepsis-associated lung failure [102,103]. One of the lessons of many failed trials of immunomodulatory treatment for organ dysfunction is that ubiquitous immune modulators are not for every patient, suggesting that an individualized and context-dependent fine-tuning of the inflammatory response is more likely to improve outcomes.

Currently, selective inhibition of particular drivers of inflammation is coming into the focus of clinical investigations. Upon exposure to DAMPs and PAMPs, cytokines and chemokines (including TNFα, IL-6, IL-1β and IL-8) as well as complement peptides are released, which activate the endothelium and stimulate leukocyte adhesion and transmigration [15]. Numerous *in vitro* and genetic mouse experiments contributed to the current understanding of pro- and anti-inflammatory signaling. Although neutralizing compounds, such as inhibitory antibodies, were shown to reduce inflammatory markers and improve outcomes in experimental animal models, only a few small trials exist indicating potential benefits of such approaches as a therapy for organ injury. For example, specific inhibition of TNF-Receptor 1 signaling could dampen inflammation in ARDS patients, as suggested by a pilot study in healthy volunteers [165]. In small patient cohorts, the inhibition of the IL-6 receptor by Tocilizumab [166,167], and targeting the interleukin-1β innate immunity pathway with canakinumab [168], were shown to have protective effects on myocardial injury. In a cohort of 80 stroke patients in a single-center, randomized placebo-controlled phase 2 trial, subcutaneous IL-1 Receptor antagonist reduced plasma inflammatory markers in patients with ischemic stroke [169].

Although neutrophils are generally considered to exacerbate tissue injury through the release of proteases and oxidants, recent work has implicated that neutrophils may also exhibit anti-inflammatory and reparative characteristics [170,171]. They can actively contribute to host protection, for example neutrophils have been shown to shuttle micro-vesicles containing immuno-modulating microRNAs to damaged epithelial cells in models of acute lung [172]. Currently, evidence is increasing for a role of neutrophils in terminating and resolving inflammation. Cessation of leukocyte influx, apoptosis, and subsequent efferocytosis are fundamental events in all organs during the resolution of inflammation [173]. Neutrophil-derived proteases, such as matrix-metalloprotease 9, can proteolytically degrade DAMPs including HMGB1 and Hsp90 and thus, could dampen danger signaling and recruitment of additional immune cells by clearing immunogenic molecules [174]. In a model of acute liver injury, it has just recently been demonstrated that reactive oxygen species can induce a reparative phenotype of macrophages that drives liver repair, suggesting that neutrophils can

coordinate the surrounding cells and initiate resolution programs [175]. Accordingly, neutrophils orchestrate post-myocardial infarction healing by inducing macrophage efferocytosis via neutrophil gelatinase-associated lipocalin (NGAL) [176].

Given that the net output of inflammatory activity can either resolve inflammation, or drive a detrimental amplification loop that can result in excessive, systemic inflammation and collateral tissue damage (Figure 4), balanced fine tuning of leukocytes and particular immune-modulators at different phases of inflammation might provide future strategies for organ protection.

b) Linking hypoxia signaling to organ protection

Only recently, William Kaelin, Peter Ratcliffe, and Gregg Semenza were awarded the Nobel Prize in Physiology or Medicine 2019 for their exceptional discoveries of fundamental pathways by which cells respond to hypoxia. Perioperative hemodynamic changes, hypovolemia, and hemostatic abnormalities can result in insufficient organ perfusion and limit cellular oxygen availability. The adaptive response to reduced oxygen levels is primarily mediated by hypoxia-inducible transcription factors (HIFs), which orchestrate transcriptional programs that regulate tissue metabolism and maintain homeostasis in conditions of low oxygen [177,178].

HIFs are basic helix-loop-helix transcription factors composed of two subunits, HIF-α and HIF-β. The stability of HIFs is controlled by oxygen-dependent prolyl hydroxylases (PHDs) and von Hippel–Lindau (VHL), an E3 ubiquitin ligase [178]. Under normoxic conditions, HIF-α subunits are hydroxylated by PHDs at two conserved proline residues, inducing their polyubiquitination by VHL and subsequent degradation at the proteasome [179]. Factor-inhibiting HIF (FIH), an oxygen-dependent asparaginyl hydroxylase, also regulates hypoxia signaling through hydroxylation of asparaginyl residues of HIF-α subunit, which prevents the association of HIFs with transcription coactivators [180]. Under hypoxic conditions, PHDs and FIHs are inactive due to the low availability of oxygen as one of their essential substrates. Consequently, the degradation of the HIF-α subunit is blocked and combines with HIF-β, resulting in a functional heterodimeric transcription factor. Following dimerization, HIF translocates into the nucleus and binds to hypoxia-responsive elements (HREs) in target gene promotors (Figure 5). Several lines of evidence suggest that besides the traditional oxygen-dependent HIF activation, pro-inflammatory factors such as bacterial products or citric acid cycle intermediates, can stabilize HIFs directly [181,182]. In models of acute sepsis, lipopolysaccharide (LPS) has been shown to increase HIF-1α stability and decrease PHDs via toll-like receptor 4 under normoxia [181]. Other studies show, that hypoxia increases the activity of pro-inflammatory transcription factor NFκB (nuclear-factor-κ-light-chain enhancer of activated B cells) through PHD-dependent hydroxylation of its negative regulator IκB kinase-β [183].

Although hypoxia can generate cytotoxic metabolites that induce pro-inflammatory responses and break down tissue barriers, there are many examples in which stabilization of HIFs induces tissue-protective responses [184]. HIF-elicited transcriptional programs have been shown to dampen organ injury in a variety of inflammatory disease models through the production of anti-inflammatory mediators, such as adenosine [185-188]. Activated immune

cells and damaged epithelia release adenosine triphosphate (ATP) or adenosine diphosphate (ADP) from the intracellular compartment. Hypoxia can induce the expression of a cascade of nucleotide converting enzymes, including ectonucleoside triphosphate diphosphohydrolase 1 (CD39) and ecto-5' nucleotidase (CD73), both in a HIF-dependent and independent manner [188]. The signaling molecule adenosine is the end product of the hydrolysis from adenosine monophosphate (AMP) to adenosine and phosphate by CD73 [189]. The increase of extracellular adenosine activates protective down-stream signaling via purinergic receptors such as A_{2A} and A_{2B} adenosine receptors (AR), which themselves are known HIF targets [190,191]. For example, HIF-dependent adenosine signaling contributes to cardio-protection during myocardial ischemia-reperfusion injury as demonstrated by larger infarct sizes in mice with a genetic deletion of CD39 and CD73, which could be reversed by the administration of AMP or apyrase to CD39-deficient mice or 5'-nucleotidase application to CD73 knockout mice, respectively [192-194]. In line with these findings, a protective role of extracellular adenosine during acute lung injury has been suggested. HIF-1α transcriptionally upregulates the immunosuppressive A_{2B} adenosine receptor, and thereby attenuates pulmonary edema, inflammation, and gas exchange [195]. Finally, extracellular adenosine levels are regulated by equilibrative nucleoside transporters (ENTs), which terminate purinergic signaling by adenosine re-uptake [190,196]. In hypoxic conditions, HIF-dependent transcriptional ENT repression is an innate mechanism to increase extracellular adenosine. Accordingly, pharmacological blockade of ENTs using dipyridamole or nitrobenzylthioinosine, can attenuate ventilator-induced lung injury as well as bacterial gram-negative lung inflammation [190,197].

The understanding that inflammatory lesions are profoundly hypoxic and that the enhancement of adenosine signaling by HIFs is an essential endogenous organprotective response, provides a strong rationale for using pharmacological HIF activators to attenuate organ injury. Remote ischemic preconditioning (RIPC), defined as repeated, short periods of ischemia and reperfusion applied to an extremity (e.g. the arm or the leg) to protect remote tissues during and after prolonged ischemia, was one of the first approaches to make use of this favorable, adaptive response [198]. Several preclinical and clinical studies support the concept of RIPC for tissue protection in various target organs, including the heart, kidney, lung, and the brain [199-202]. Despite promising results from a multicenter, randomized double-blind trial enrolling 240 patients at high risk for acute kidney injury by Zarbock and colleagues [200], the evidence for RIPC is still inconclusive as demonstrated by two other large clinical studies by Meybohm et al., and Hausenloy et al. [203,204]. These conflicting results may reflect the challenges to choose the optimum type, duration, and timing of the ischemic intervention according to patient-related factors such as skeletal muscle mass, hepatic function, and comorbidities. A propofol-based anesthetic technique may as well make a contribution to these findings in that RIPC effectivity has been shown to be reduced by propofol in a preclinical study [205].

Although the molecular mechanisms involved in RIPC remain incompletely understood, there is increasing evidence that HIFs are activated in RIPC leading to the secretion of HIF-dependent cytoprotective molecules in peripheral tissues to protect remote organs, such as IL-10 release from the ischemic limb musculature for cardioprotection [194,199]. By using pharmacological HIF activators, HIF-dependent gene expression programs that mimic

protective endogenous pathways could be turned on, which may exhibit a more reliable mode of action and allow for dosage titration to overcome the variability of RIPC effects. Normoxic HIF stabilization can be elicited pharmacologically by several classes of compounds, which are mainly PHD inhibitors [206]. Blocking the catalytic activity of PHDs efficiently stabilizes HIF1 by preventing its proteasomal degradation (Figure 5). Both, transgenic PHD knockout models and administration of PHD inhibitors, indicated a protective role for HIF activation in various disease models, including acute lung injury, stroke, myocardial ischemia/reperfusion injury, acute kidney dysfunction, liver damage and organ transplantation [194,207-211]. Several companies have developed orally available small-molecule inhibitors [roxadustat (FG-4592), vadadustat (AKB-6548), daprodustat (GSK1278863), desidustat (ZYAN1) and molidustat (BAY 85-3934)], which have been established in numerous phase-2 clinical trials as a treatment of anemia and chronic kidney disease (CKD) by increasing endogenous erythropoietin and improving iron metabolism [212-215]. Vadadustat, daprodustat, and roxadustat advanced to phase III clinical trials. Meanwhile, roxadustat is the first small-molecule PHD inhibitor approved by China for the treatment of anemia in patients with dialysis-dependent CKD [216]. Until now, no major side effects have been reported in these trials. However, given the complexity of HIF target genes, unknown effects of different inhibitor affinities to PHD isoforms, and a potential to interfere with signaling pathways that involve proline-hydroxylation of non-HIF signaling molecules—in particular long-term effects during chronic application—remains an area of investigation [217]. Nevertheless, current results from basic research on hypoxia pathways together with clinical trials, provide a strong rationale for implementing HIF activators in the context of perioperative organ injury and encourage novel clinical investigations, particularly as these compounds would be used for short-term organ protection, rather than for long-term use.

Conclusions and future directions

Perioperative organ injury is primarily caused by a dysregulated inflammatory response or insufficient tissue perfusion, and represents a major risk factor for morbidity and mortality in surgical patients. Progressive barrier dysfunction, edema, and subsequent bacterial translocation can transition single-organ injury to multi-organ failure and sepsis.

Patient-centered, multidisciplinary care protocols can contribute to achieve early recovery after surgical procedures by maintaining pre-operative organ function and reducing surgical stress responses, while supportive care on specialized ICUs and extracorporeal organ replacement strategies remain the cornerstone of treating organ failure. However, only few other therapeutic approaches have proven effective in the management of organ dysfunction.

Understanding the molecular basis of inflammatory and oxygen sensing pathways has proven great implications for the field of perioperative medicine. It is now appreciated that inflammatory activation and the initiation of resolution programs overlay in a manner that will determine whether organ injury is repaired or progresses to loss of organ function. Inflamed lesions are often profoundly hypoxic and it is important to emphasize that although hypoxia is a proinflammatory stimulus, stabilization of HIF transcription factors can promote an anti-inflammatory and tissue-protective response. A significant challenge that

remains is the movement of this knowledge into clinical practice. The protective effects of remote ischemic preconditioning in various organs has been shown to require the stabilization of HIFs. Recent positive trials of the HIF activator roxadustat [215,218] and vadadustat [219] for renal anemia hopefully give rise to clinical investigations of these compounds for perioperative kidney, cardiac or lung protection in surgical patients soon. Indeed, prophylactic pre-conditioning using HIF activators could represent an innovative therapeutic approach for organ protection. Unfortunately, from our experience it is currently challenging to receive support from pharmaceutical companies for trials in the field of perioperative medicine, as these enterprises prioritize to introduce HIF activators for the treatment of renal anemia. Due to the fact that potential side-effects reported in trials for organ protection could jeopardize marketing of these drugs, the pharmaceutical partners remain hesitant in providing orally available HIF activators for other clinical applications. We hope that such barriers will be overcome in the near future once these compounds have received FDA approval in the USA, to advance these pathways closer to being preventive approaches or treatments for perioperative organ injury.

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Abbreviations

ADP	Adenosine Diphosphate
AKI	Acute Kidney Injury
AKIN	Acute Kidney Injury Network
ALT	Alanine aminotransferase
AMP	Adenosine Monophosphate
Ang-2	Angiopoetin-2
AR	Adenosine Receptor
ARDS	Acute Respiratory Distress Syndrome
ATP	Adenosine Triphosphate
CC-16	Club cell protein 16
CK-18	Cytokeratin 18
CKD	Chronic Kidney Disease
CK-MB	Creatine kinase myocardial band
CLIP	Checklist for Lung Injury Prevention
DAMPs	damage-associated molecular patterns

ENT	Equilibrative Nucleoside Transporter
EUPHRATES	Evaluating the Use of Polymyxin B Hemoperfusion in a Randomized Controlled trial of Adults Treated for Endotoxemia and Septic Shock
FIH	Factor-inhibiting HIF
GABA	γ-aminobutyric acid
GFAP	Glial fibrillary acidic protein
α-GST	α-Glutathione S-transferase
GPBB	Glycogen phosphorylase isoenzyme BB
hFABP	Heart-type fatty acid binding protein
HIF	Hypoxia-inducible factor
HRE	Hypoxia-responsive elements
ICAM	Intercellular adhesion molecule-1
ICU	Intensive Care Unit
I-FABP	Intestinal fatty acid-binding protein
KDIGO	Kidney Disease: Improving Global Outcomes
KIM-1	Kidney Injury Molecule-1
L-FABP	liver-type fatty acid-binding protein
LIPS	Lung Injury Prevention Score
LIPS-A	Lung Injury Prevention Score with Aspirin
LPS	Lipopolysaccharide
MAP	Mean Arterial Pressure
MI	Myocardial Infarction
NFκB	Nuclear-factor-κ-light-chain enhancer of activated B cells
NGAL	neutrophil gelatinase-associated lipocalin
NSE	Neuron specific enolase
PAMPs	pathogen-associated molecular patterns
PEEP	Positive End Expiratory Pressure
PETAL	Prevention & Early Treatment of Acute Lung Injury
PHD	Prolyl Hydroxylase

PMI	Perioperative Myocardial Ischemia
PPR	Pattern Recognition Receptor
RAGE	Receptor for advanced glycation endproducts
RIFLE	Risk, Injury, Failure, Loss, End Stage
RIPC	Remote Ischemic Preconditioning
UCHL-1	Ubiquitin carboxy-terminal hydrolase L1
VHL	von Hippel–Lindau
VILI	Ventilator-induced lung injury
vWF	von Willebrand factor

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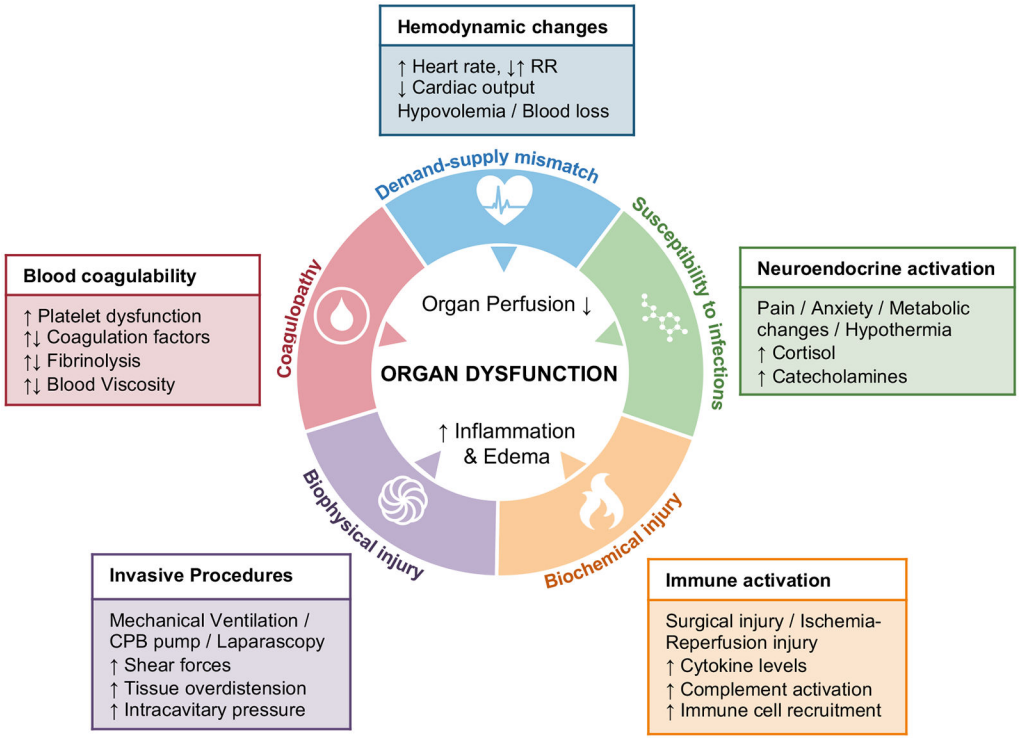
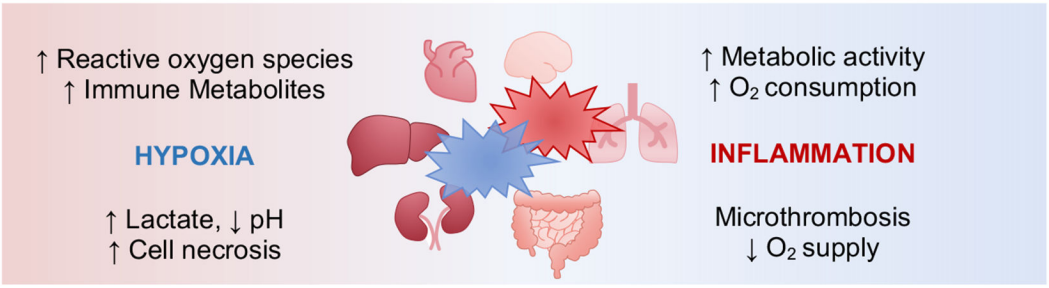


Figure 1: Pathophysiological mechanisms of perioperative organ injury.

Inflammation and ischemia are the pathophysiological hallmarks of perioperative single or multiple organ failure [155]. During the perioperative period, organ perfusion can be significantly impacted by hemodynamic changes (blue) resulting from a demand-supply mismatch and/or hemostatic abnormalities (red) including either coagulopathic bleeding, or clotting. Neuroendocrine activation as part of the physiological stress response to the surgical insult can alter the immunological profile and contribute to increased susceptibility to infection (green). The surgical insult can trigger an uncontrolled inflammatory response with excessive release of inflammatory mediators and cytotoxic molecules, causing biochemical tissue damage, barrier dysfunction and edema (yellow). Concomitant activation of immune cells in a sterile environment can result in collateral tissue damage and organ dysfunction. Mechanical forces, such as mechanical ventilation, surgery on use of cardiopulmonary bypass pump or laparoscopy can cause tissue over distension and shear stress. Exposure to artificial surfaces and membrane oxygenators can contribute to immune cell activation and amplify collateral tissue damage (purple).



Inflammation in Hypoxic Conditions	Hypoxia in Inflammatory Conditions
Pulmonary edema	Acute lung injury
Vascular occlusion	• Hypoxemia
• Myocardial Infarction	Pathogen Infection/Sepsis
• Stroke	• ↑ Metabolic activity > ↑ O_2 consumption
Organ Transplant	• Microthrombosis > ↓ O_2 supply
Tissue Ischemia	Anemia of Inflammation
• Hypotension	• ↓ O_2 availability
• Vasopressors	

Figure 2: Simplified overview of the cellular sources and time-course of biomarker release after surgery.

Surgery (‘Trigger’) causes localized organ injury and triggers the release of danger signals, thereby activating the coagulation and complement system, and the immune response including stimulation of inflammatory and tissue cells (‘Activation’). During and after the operation, cellular damage and immunological activity lead to the release of various mediators in a timely coordinated manner, which relate to the course of the response to the surgical insult (‘Mediators and Biomarker’). These molecules are considered as biomarkers and have been suggested to have predictive values before tissue injury for specific organs becomes irreversible. The normalization of biomarker levels over time indicates recovery from tissue damage, whereas biomarker persistence points toward a significant and potentially permanent impact on organ function (‘Outcome’).

(Ang, Angiopoetin, C3 and C5, complement component 3 and 5; CRP, C-reactive protein; ICAM, Intercellular adhesion molecule 1; IL, Interleukin; MIP, Macrophage inflammatory protein; PCT, Procalcitonin; PAI-1, Plasminogen activator inhibitor 1; SAA, Serum Amyloid; TF, Tissue Factor; TNFα, Tumor-necrosis factor α; TNF-R, Tumor necrosis factor receptor; VCAM, vascular cell adhesion molecule-1)

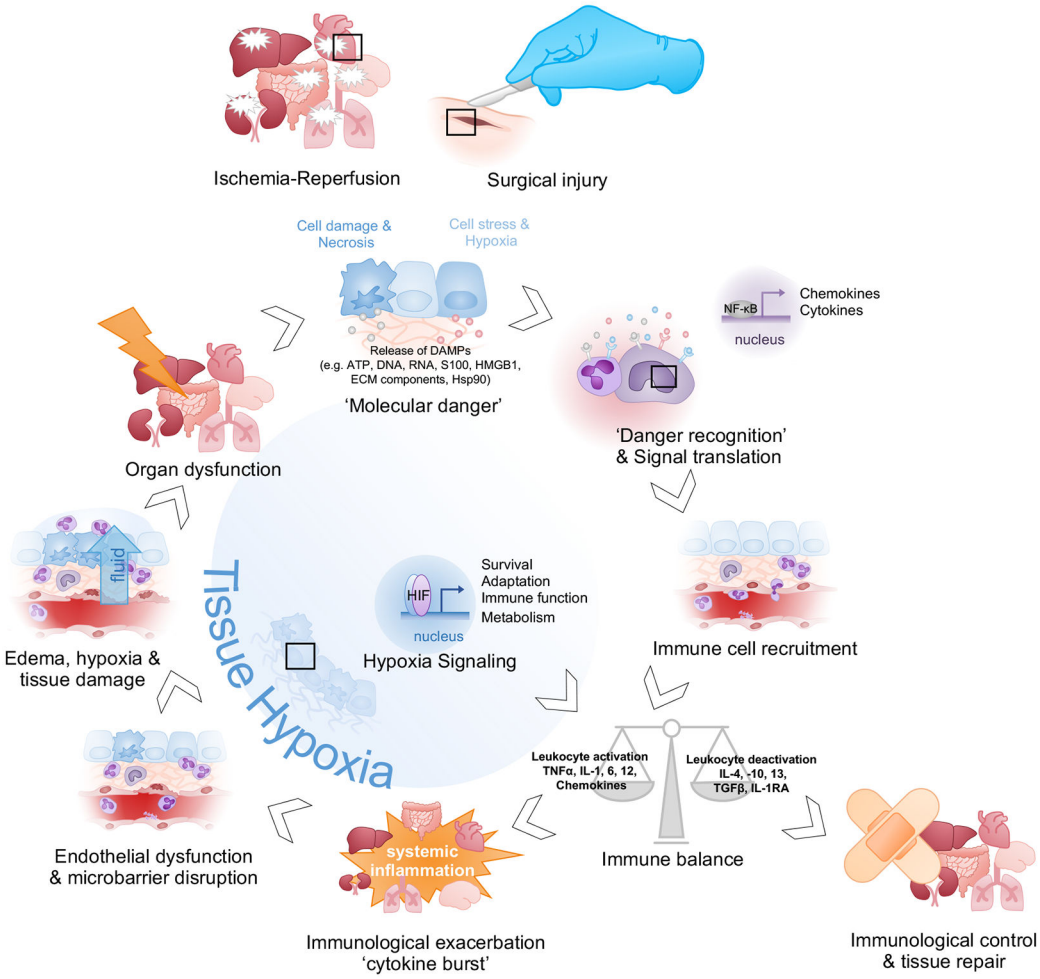


Figure 3: Links between Hypoxia and Inflammation.

Inflammed tissue (red) lesions are profoundly hypoxic, and hypoxia (blue) is a proinflammatory stimulus. Limited cellular oxygen availability results in the accumulation of cytotoxic metabolites, causing tissue damage and necrosis. Inflammation causes localized hypoxia by increased metabolic activity and oxygen (O_2) consumption by immune and tissue cells. In addition, activated endothelial cells promote platelet aggregation and microthrombosis, thereby reducing oxygen supply. Examples for clinical condition primarily characterized by tissue hypoxia that causes inflammatory changes are summarized in the left panel, and perioperative inflammatory manifestations leading to tissue hypoxia on the right.

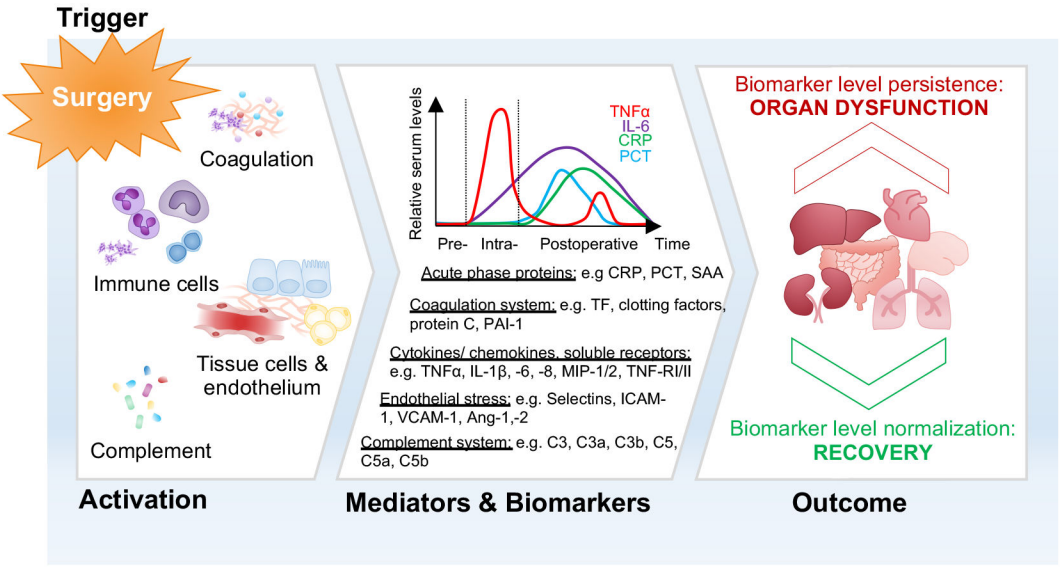


Figure 4: Cellular mechanisms leading to organ dysfunction.

Ischemia-reperfusion or surgical injury leads to local cellular damage, hypoxia and necrosis, and leads to the release of endogenous danger signals (DAMPs) from injured tissues (‘Molecular Danger’). DAMPs bind to pattern-recognition receptors (PRRs) on immune, endothelial, and epithelial cells and induce pro-inflammatory cytokine release and upregulation of adhesion molecules on the endothelium (‘Danger Recognition and Signal translation’). Activated leukocytes traffic to the site of injury and release cytokines, chemokines, and cytotoxic molecules to pre-empt impending infection (‘Immune cell recruitment’). The net inflammatory activity (‘Immune balance’) can either drive resolution and tissue repair (‘Immunological control’) or induce uncontrolled, systemic inflammation (‘Immunological exacerbation’). Cytotoxic molecules and reactive species from immune cells damage endothelial cells, leading to plasma leakage and subsequent tissue edema (‘Endothelial Dysfunction & Microbarrier disruption’). Tissue swelling and sustained inflammatory activity cause hypoxia and cellular damage (‘Edema, hypoxia & tissue damage’), leading to organ injury (‘Organ dysfunction’). Persistent cellular destruction can induce an amplification loop, in which leukocyte recruitment is maintained through sustained release of signals of tissue injury (‘Molecular Danger’). Nevertheless, although hypoxia can generate cytotoxic metabolites that induce proinflammatory responses and break down tissue barriers, there are many examples in which stabilization of HIFs induces tissue-protective responses (‘Hypoxia Signaling’).

(ATP, adenosine triphosphate; ECM, extracellular matrix; IL, interleukin; IL1-RA, interleukin-1 receptor antagonist; NF-κB, nuclear factor kappa B; HMGB-1, high-mobility group protein box 1; Hsp90, heat-shock protein 90; PRR, pattern-recognition receptor; S100, S100 protein; TGFβ, transforming growth factor β; TNFα, tumor necrosis factor α;)

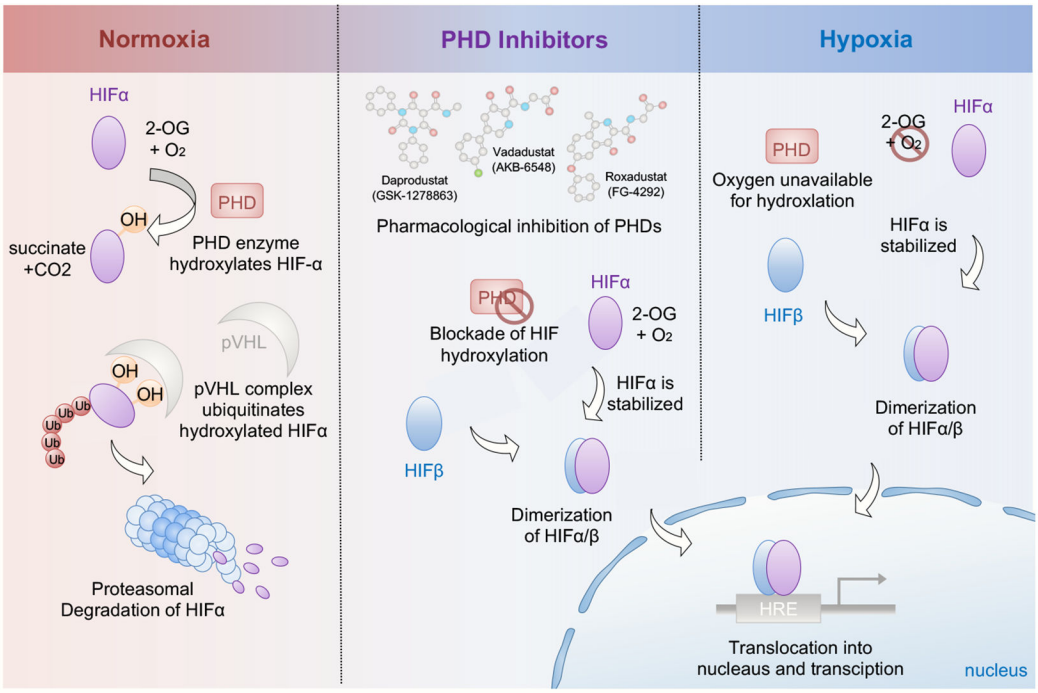


Figure 5: Regulation of Hypoxia-inducible factor (HIF) during normoxia and hypoxia.

Insufficient organ perfusion, respiratory system failure, and anemia can lead to cellular hypoxia. In normoxic conditions, the proline residues of HIFα subunits are constantly hydroxylated by oxygen-dependent prolyl-4-hydroxylases (PHDs). Von Hippel–Lindau protein (pVHL), an E3 ubiquitin ligase, recognizes hydroxylated HIFα and targets it for proteasomal degradation (left panel, light red). When oxygen levels drop (right panel, light blue), molecular O_2 as an essential co-substrate for PHDs is unavailable, thereby inhibiting hydroxylase activity. Small PHD-inhibitors, such as roxadustat, vadadustat and daprodustat, block the function of PHDs and can mimic cellular hypoxia (middle). Subsequently, HIFα escapes the PHD-dependent hydroxylation under hypoxic conditions, dimerizes with the HIFβ subunit and translocates into the nucleus. Binding of the HIF-α:HIF-β transcription factor complex to the hypoxia-responsive elements (HREs) in the promoter regions activates target gene expression.

(HIF, hypoxia-inducible factor; 2-OG, 2-oxoglutarate; O_2, oxygen, CO_2, carbon dioxide, OH, hydroxyl group; PHD, prolyl hydroxylase domain protein; pVHL, von Hippel–Lindau tumor suppressor; Ub, ubiquitin; HRE, hypoxia-responsive element; p300/CBP, p300/CREB-binding protein)

Table 1:

Overview of risk factors and biomarkers related to perioperative organ dysfunction.

Organ Dysfunction	Top Surgeries associated with Perioperative Organ Injury	(Ref.)	Major Risk Factors for Organ Dysfunction (general surgical population)			Markers of Organ Injury (selection)		
			Preoperative	Intraoperative	Postoperative	Biomarker	Time to peak	Cellular Source
Stroke	Aortic/ Cardiac surgery Carotid endarterectomy Resection of head & neck tumors	(19-22)	Carotid stenosis History of stroke or TIA Abrupt discontinuation of anticoagulation Coronary artery disease Arrhythmias	Hyper-/ Hypotension Arrhythmias, CHF, MI Manipulation of aortic athero-sclerotic lesions Surgical complexity & duration Bypass time	Arrhythmias, CHF, MI Hypercoagubility Dehydration Hemorrhage	Copeptin GFAP * NSE S100B UCHL-1 *	rapid rapid early early rapid	Hypothalamus Astrocytes Neurons Astrocytes, Glia Neurons
Delirium	Hip fracture repair Aortic/ Cardiac surgery Vascular surgery	(23-25)	Advancing Age Multiple comorbidities Cognitive impairment (dementia) Substance abuse Premedication with Benzodiazepines	Hypotension Deep anesthetic levels Anticholinergics Surgical complexity & duration Bypass time	Insufficient pain control Opioid-based analgesic regimens Benzodiazepine sedation Prolonged mechanical ventilation Infection, Sepsis	N/A		
Myocardial infarction (Noncardiac surgery)	Vascular surgery Intraperitoneal surgery Orthopedic surgery	(26-28)	Unstable or severe angina Recent MI Decompensated CHF Significant Arrhythmias Peripheral artery disease Renal insufficiency	Tachyarrhythmia Hypo-/ Hypertension Blood loss, transfusion Hypercoagubility Surgical complexity & duration	Hypo-/ Hypertension Arrhythmias Hypercoagubility Insufficient pain control Hypothermia	CK-MB GPBB hFABP Myoglobin Troponin *	early rapid rapid rapid early	Myocard, Muscle Cardiomyocytes, Brain Cardiomyocytes, Kidney Myocard, Muscle Cardiomyocytes
Pulmonary complications	Aortic/ Cardiac surgery Thoracic surgery Upper abdominal surgery	(29-31)	Chronic lung disease Major Trauma/ Severe Burns Aspiration Pneumectomy Obesity	Mechanical Ventilation Massive transfusion Fluid overload Surgical complexity & duration Cardiopulmonary Bypass	Pneumonia, Sepsis Prolonged mechanical ventilation Chest tubes Aspiration Nasogastric tubes	Ang-1/2 sICAM sRAGE SP-D vWF	early early early early early	Endothelial cells Endothelial cells Alveolar Type I cells Alveolar Type II cells Endothelial cells
Acute kidney injury	Aortic-/ Cardiac surgery Major abdominal surgery Trauma surgery	(32-34)	Hypertension Chronic kidney disease Coronary artery disease Peripheral artery disease Chronic lung disease	Hypovolemia/ Fluid overload Anemia, transfusion Intraabdominal pressure Surgical complexity & duration Cross-clamp/ Bypass time Hypotension	Nephrotoxic substances Infection, Sepsis Rhabdomyolysis Hypovolemia/ Fluid overload Hypotension	Cystatin-C KIM-1 * L-FABP NGAL TIMP2xIGFBP7 *	functional early rapid rapid early	GFR Marker Proximal tubule Tubular epithelium Tubular epithelium, PMN Various
Liver Dysfunction	Hepatectomy	(14,35)	Cirrhosis Steatosis Cholestasis Arrhythmias, CHF, MI Renal insufficiency	Blood loss, transfusion Fluid overload Major liver volume resection	Intraabdominal Infection, Sepsis Biliary obstruction Portal vein thrombosis	ALT * CK-18 α-GST miR-122 *	early N/A early N/A	Hepatocytes Hepatocytes Hepato-/ Enterocytes Hepatocytes

Organ Dysfunction	Top Surgeries associated with Perioperative Organ Injury	(Ref.)	Major Risk Factors for Organ Dysfunction (general surgical population)			Markers of Organ Injury (selection)		
			Preoperative	Intraoperative	Postoperative	Biomarker	Time to peak	Cellular Source
				Intraabdominal pressure Arrhythmias, CHF, MI	Hemorrhage Ascites			
Bowel injury	Aortic-/ Cardiac surgery	(36,37)	Peripheral artery disease Arrhythmias, CHF, MI Chronic lung disease Coronary artery disease	Blood loss, transfusion Cross-clamp/ Bypass time Hypotension, Hypovolemia	Prolonged mechanical ventilation Vasopressors Infection, Sepsis Hypercoagubility Renal failure	Citrulline * I-FABP α-GST	N/A early early	Enterocytes Enterocytes Hepato-/ Enterocytes

* indicates high specificity of biomarker, grey background indicates prognostic potential of biomarker.

(CHF, Congestive heart failure; MI, myocardial infarction; Ang1/2, Angiopoetin 1,2; ALT, Alanine aminotransferase; CK-18, Cytokeratin 18; CK-MB, Creatine kinase myocardial band; GFAP, Glial fibrillary acidic protein; GPBB, Glycogen phosphorylase isoenzyme BB; α-GST, α-Glutathione S-transferase; hFABP, Heart-type fatty acid binding protein; sICAM, soluble Intercellular adhesion molecule-1; IGFBP7, Insulin Like Growth Factor Binding Protein 7; I-FABP, Intestinal-type fatty acid-binding protein; KIM-1, Kidney Injury Molecule-1; L-FABP, liver-type fatty acid-binding protein; NSE, Neuron-specific enolase; NGAL, Neutrophil gelatinase-associated lipocalin; sRAGE, soluble Receptor for advanced glycation endproducts; SP-D, Surfactant protein D; vWF, von Willebrand factor; TIMP2, Tissue inhibitor of metalloproteinases 2; UCHL-1, Ubiquitin carboxy-terminal hydrolase L1)