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Review Article

Anesthetics attenuate ischemia–reperfusion induced renal injury: Effects and mechanisms

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ABSTRACT

Acute kidney injury (AKI) secondary to ischemia–reperfusion injury (IRI) is a major cause of patient morbidity and mortality in the perioperative period. It can lead to new onset of chronic kidney disease and accelerate its progression. Patients with risk factors undergoing cardiac, vascular, and liver transplantation surgeries, which may inevitably involve IRI, are more susceptible to AKI. Anesthetic agents have been postulated to possess renoprotective properties. Thus, exploring the utilization of selective perioperative anesthetic agents with renoprotective properties may be a promising avenue to reduce the risk of AKI. This review discusses the effects and mechanisms of dexmedetomidine, inhalational and intravenous anesthetics, and xenon-mediated renoprotection. Although the renoprotective effects of these agents obtained in the laboratory are promising, much work especially via clinical trials is required to determine the translational value from the bench to the bedside.

1. Introduction

Acute kidney injury (AKI) secondary to ischemia–reperfusion injury (IRI) is a key contributor to morbidity and mortality in the perioperative period, presenting a major health care and economic burden.[1–4] It also leads to new onset of chronic kidney disease (CKD) while concomitantly expediting its progression. The term AKI that is used throughout this review has gained recognition to replace the previously used term, acute renal failure (ARF), in order to achieve two main objectives: first, to establish a conventional terminology that enables comparison of data more efficiently; and second, to illustrate the wide range of disease states the term incorporates.[5,6] Delayed graft function, which can be defined as a patient needing dialysis within 7 days of renal transplantation,[7] is an unfortunate extension of AKI in the transplant process that is associated with a higher incidence of acute rejection and poorer long-term graft survival.[8] In this review, we discuss the epidemiology, cause, and mechanisms of AKI together with dexmedetomidine, inhalational and intravenous anesthetics, and xenon gas-mediated renoprotection and their potential clinical applications.

2. Epidemiology of AKI

The Risk, Injury, Failure, Loss, and End-stage renal disease classification (RIFLE) is now used as a valuable criteria for diagnosis and monitoring prognosis of AKI (Table 1).[6] A meta-analysis identified that the overall mortality rate from AKI remained unchanged at 50% for the past 5 decades.[9] Approximately 1% of surgical patients develop AKI, however, perioperative AKI mortality can be as high as 83% in cardiac surgery.[10] In a large retrospective study of 2672 patients undergoing coronary artery bypass grafting (CABG), perioperative AKI was found to be associated with a 14-fold increase in mortality.[11] It is also linked to vascular intervention[12] and surgery,[13] as well as urology, kidney, and liver transplantation.[14] A prospective multicenter cohort study of 29,269 intensive care unit (ICU) patients demonstrated an incidence of 5.7% and mortality of 60.3%.[15] Its high incidence is comparable with acute lung injury and severe sepsis.[16] In addition, AKI significantly prolonged the length of hospitalization by up to 50%.[17] As a consequence of advancing techniques, the surgical population is steadily ageing with increasing comorbidities, causing AKI to become a worsening problem, which continues to be a substantial burden on the health care system.[18] Moreover, there is evidence to suggest that AKI can not only predispose but compound the effects of an existing diagnosis of CKD to increase the risk of end-stage renal disease amongst the elderly.[19]

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Table 1
The Risk, Injury, Failure, Loss, and End-stage renal disease (RIFLE) classification for acute renal injury—a hierarchical classification to categorize the risk, diagnosis of ARF, and ESKD.

	GFR criteria	Urine output criteria	
Risk	Increased SCr ×1.5 from baseline Decreased GFR >25%	<0.5 mL/kg/h over 6 h	High sensitivity
Injury	Increased SCr ×2 from baseline Decreased GFR >50%	<0.5 mL/kg/h over 12 h	
Failure	Increased SCr ×3 from baseline Decreased GFR 75%	<0.3 mL/kg/h over 24 h	High specificity
Loss	Persistent ARF = complete loss of kidney function >4 weeks		
ESKD	>3 months		

ARF = acute renal failure; ESKD = end-stage kidney disease; GFR = glomerular filtration rate; SCr = serum creatinine.

3. Causes of AKI and risk factors

Causes of AKI have traditionally been classified as prerenal (occurring in 30–60% of cases), intrinsic renal (20–40%), or postrenal (10%).[5] Prerenal causes are associated with hypoperfusion and acute tubular necrosis (ATN), which is linked to trauma, hemorrhage, cardiogenic shock, sepsis, systemic inflammatory response syndrome (SIRS), and IRI in surgical patients. IRI is a major cause of perioperative AKI, involving the inevitable temporary cessation and restoration of blood supply during surgeries such as cardiopulmonary bypass, renal artery angioplasty, and liver and kidney transplantation.[5] The short-term hypoxia is detrimental to the kidneys. Up to 50% of donor kidneys are involved in short-term hypoxia in renal transplantation, further diminishing the donor rate and leading to a 10% failure rate of primary grafts in those transplanted. The resurgence of blood flow may commence the recovery of the injured tissues from the ischemic phase yet also paradoxically induce further damage. Patients with high risk factors, such as advanced age, hypertension, diabetes, decreased cardiac function, and pre-existing renal disease[20] undergoing cardiac,[21] vascular, and liver transplantation surgeries, which inevitably involve IRI, are more susceptible to AKI and higher mortality.[22]

4. Mechanisms of IRI-induced AKI

IRI is defined as "the cellular damage after reperfusion of previously viable ischemic tissues".[23] Its pathogenesis is a multifactorial interplay between biochemical, cellular, vascular endothelial, and tissue-specific factors, with inflammation being a common feature.[24] Renal hypoperfusion triggers vasoconstriction, alteration of the ultrafiltration coefficient, tubular obstruction, and vascular congestion.[25] However, recent experimental work has challenged this established "decreased perfusion paradigm". It has been postulated that intrarenal circulation changes such as modification in efferent arteriolar function and intrarenal shunting may be more likely drivers of AKI than changes in global blood flow.[26]

Hypoxia as a result of ischemia and subsequent reperfusion is associated with increased reactive oxygen species (ROS) production and dysfunction of the antioxidant system, resulting in tubular cell injury and death.[27] Inflammatory cytokines and chemokines are secreted, initiating the innate immune response. There is induction of toll-like receptors, activation of polymorphonuclear cells, with neutrophil infiltration following expression of adhesion molecules[27] causing microvascular plugging and promoting local tissue destruction. Complement activation via the alternative pathway is also involved.[28] Local inflammation causes ATN, which accounts for 75% of AKI. The necrotic debris acts as a danger signal and stimulates further inflammatory response in a vicious cycle. The molecular mechanisms of AKI are summarized in Fig. 1.

5. The renoprotective effects of anesthetics

There is a distinct lack of effective strategies to obviate the number of surgical cases of patients developing AKI. Therefore, formulating effective strategies to prevent and treat AKI, which especially occur during the perioperative period, are urgently needed. Utilization of selective perioperative anesthetic agents with renoprotective properties may be a promising avenue. The most recent publications in this regard are shown in Table 2 and the details of these publications are discussed below.

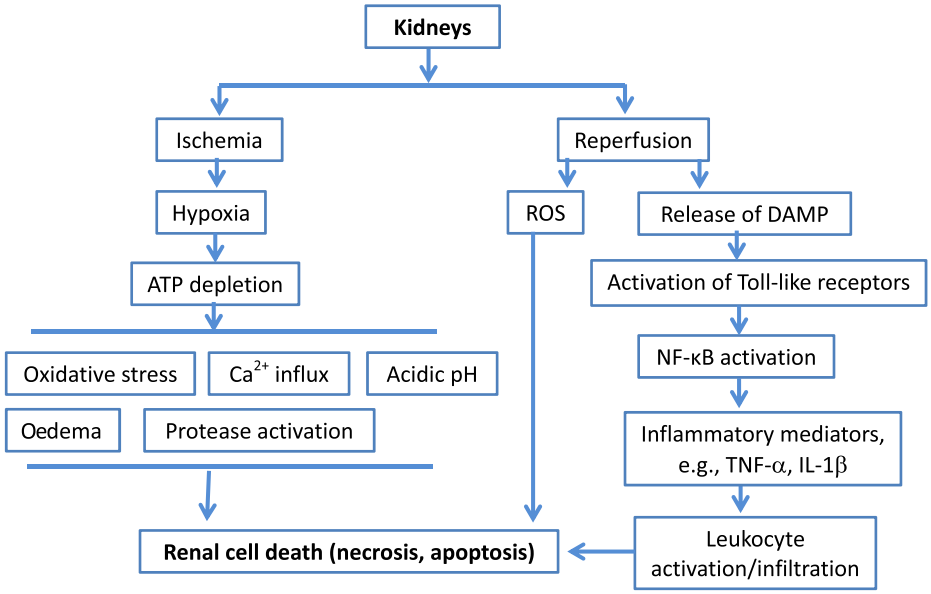

Fig. 1. Putative molecular mechanisms of ischemia–reperfusion injury (IRI). DAMP = damage-associated molecular pattern; IL-1β = interleukin-1β; NF-κB = nuclear factor-κB; ROS = reactive oxygen species; TNF-α = tumor necrosis factor-α.