

Acute Kidney Injury and Extrarenal Organ Dysfunction

New Concepts and Experimental Evidence

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ABSTRACT

Acute kidney injury (AKI) is a frequent complication in the intensive care unit with limited therapeutic modalities. Although survival from isolated AKI has improved with recent advancements in renal replacement therapy, mortality from AKI complicated by multiorgan dysfunction has remained unchanged and is estimated to be approximately 50%. Hence, defining and better understanding the pathophysiology of distant organ dysfunction associated with AKI is clinically important because it may lead to new treatment strategies. In animal models, it has become increasingly clear that AKI is not an isolated event but results in remote organ dysfunction involving the heart, lungs, liver, intestines, and brain through an inflammatory mechanism that involves neutrophil migration, cytokine expression, and increased oxidative stress. The purpose of this brief review is to summarize the human and basic science evidence for AKI and its detrimental effects on distant organs.

ACUTE kidney injury (AKI) frequently occurs in the critically ill with 5%–20% of patients experiencing an episode during their intensive care unit stay.¹ AKI in the intensive care unit is rarely an isolated event and frequently occurs within a broader spectrum of disease including sepsis and respiratory insufficiency, and often progresses into mul-

tiorgan dysfunction syndrome.² Despite recent advancements in renal replacement therapy, mortality among patients who sustain AKI complicated by multiorgan dysfunction appears to have remained unchanged and is estimated at approximately 50%.³ Recent clinical evidence suggests that AKI is not only an indicator for severity of illness, but that it also leads to earlier onset of multiorgan dysfunction with profound effects on mortality rates.^{4,5} Therefore, understanding the specific extrarenal effects of AKI in propagating or exacerbating multiorgan dysfunction is vital because it may identify therapeutic interventions to decrease mortality after AKI (fig. 1). The goals of this brief review are to assess the clinical evidence associating AKI with multiorgan dysfunction and present recent progress in understanding the mechanism using animal models of renal injury.

Clinical Relevance of AKI

Until recently, the lack of a standard definition for AKI resulted in large variations in reported incidence and mortality.⁶ In 2004, the Acute Dialysis Quality Initiative Group (ADQI) proposed the RIFLE criteria, which aimed to provide a uniform diagnosis and staging of patients with “acute renal failure” based on changes in serum creatinine, glomerular filtration rate, or urine output.⁷ Subsequent studies, including a prospective observational study by Lassnigg *et al.*, showed that a subtle change in creatinine as small as 0.3 mg/dl was associated with increased mortality.⁸ Consequently, the Acute Kidney Injury Network proposed the term “acute kidney injury” to supplant the usage of “acute renal failure” in recognition that clinically significant kidney injury occurs over a wide spectrum of severity.⁹

Simultaneous with these developments, new evidence in both basic science and clinical research began to transform the viewpoint of AKI as a single organ failure into one in which the kidneys play an active role in the evolution of multiorgan dysfunction. In the first prospective multicenter study that epidemiologically characterized AKI, Liano *et al.* found an “attributable mortality” rate of 56% among intensive care patients who sustain AKI that could not be ex-

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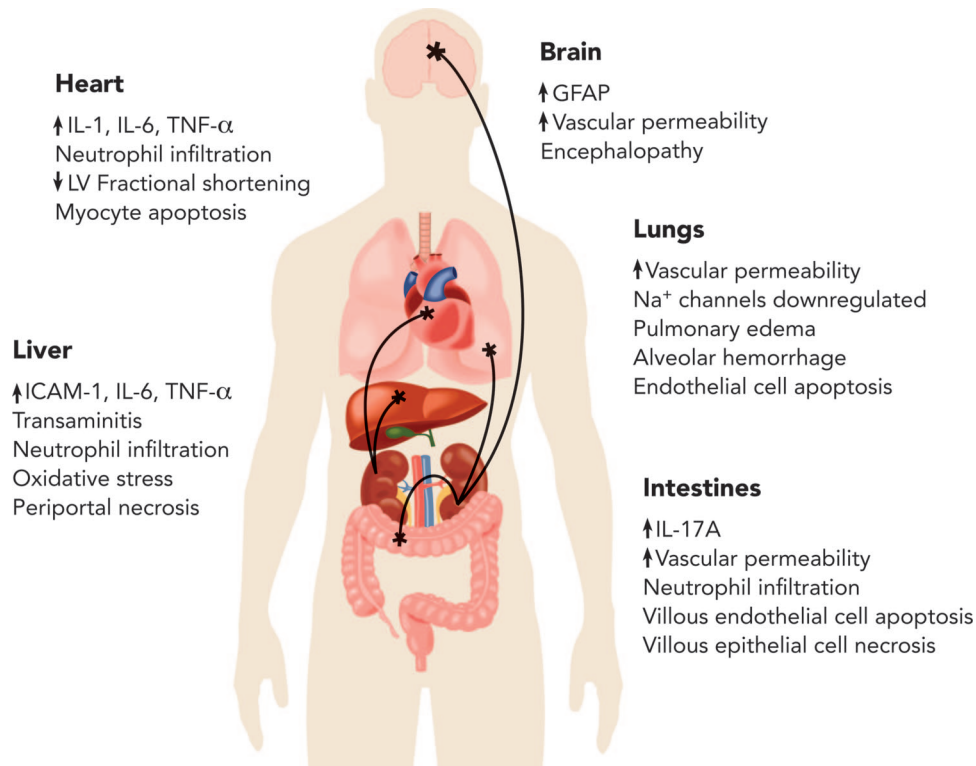


Fig. 1. Deleterious effects of acute kidney injury (AKI) on distant organs. AKI results in remote organ injury to the heart, lungs, liver, intestines, and brain and leads to an increase in cytokines, leukocyte trafficking, organ dysfunction, apoptosis, and necrosis. GFAP = glial fibrillary acidic protein; ICAM-1 = intercellular adhesion molecule-1; IL = interleukin; LV = left ventricular; TNF- α = tumor necrosis factor- α .

plained by other comorbid conditions and was thus attributed specifically to the effects of kidney injury.¹⁰ In addition, Levy *et al.* found increased mortality after AKI despite controlling for severity of illness by comparing patients with similar comorbid conditions and physiologic severity score, and by multivariate analysis.⁵ Furthermore, renal failure preceded other conditions such as sepsis, respiratory failure, mental status changes, and bleeding, suggesting that AKI occurs early in the course of multiorgan failure. More recently, a larger multicenter case-controlled study confirmed these results with a mortality rate that was doubled among patients requiring renal replacement therapy compared with control patients.¹¹ Although there may be residual “unmeasured” severity of illness, these studies make a compelling argument that patients in whom AKI develops are at increased risk of death due to kidney injury itself apart from severity of illness.

Why does AKI lead to earlier onset of multiorgan dysfunction and worsened mortality? Pulmonary insufficiency is perhaps one of the most clinically apparent and studied distant organ effects of kidney injury. AKI was found to delay recovery of injured lungs, with increased difficulty weaning from mechanical ventilation (41 days in AKI group *vs.* 21 days in non-AKI group).¹² Difficulty weaning from mechanical ventilation was also present in the nonoliguric AKI subgroup, suggesting that kidney injury apart from volume status increases mortality. Volume status, management of

which is made more difficult by compromised kidney function, also has an effect on mortality. Payen *et al.* found in an observational cohort study that positive fluid balance was associated with increased mortality.¹³ However, the Veterans Administration/National Institutes of Health Acute Renal Failure Trial Network study, a multicenter, randomized trial, demonstrated that intensive renal replacement therapy did not decrease mortality or multiorgan failure compared with less intensive therapy.¹⁴

Animal Models of AKI

The scope of clinical studies in this nascent area of research remains limited because of inherent difficulties in studying a complex disease process whose occurrence is closely interrelated with comorbid conditions. Animal models of renal injury have been instrumental in defining the pathophysiology of remote organ dysfunction after AKI by reducing the complexity and experimental limitations associated with human studies while allowing for isolation of variables to gain mechanistic understanding. Of the various animal models, renal ischemia reperfusion and nephrectomy are the most commonly studied because they are simple, reproducible, and can easily achieve a graded injury response. Renal ischemia reperfusion involves transient occlusion of the renal artery and has clinical relevance in suprarenal aortic aneurysm repair,¹⁵ partial nephrectomy,¹⁶ renal transplantation,¹⁷ contrast-in-

Table 1. Limitations of Animal Models of Kidney Injury

Model	Clinically Relevant	Simple	Reproducible	Graded Response
Ischemia-reperfusion injury	±	+	+	+
Nephrectomy	±	+	+	+
Nephrotoxic				
Radiocontrast	+	—	—	—
Gentamicin	+	—	+	—
Septic				
Endotoxin	+	+	+	—
Bacterial infusion	+	+	—	—
Cecal perforation	+	+	—	—
Combined insult	+	—	—	—

+ indicates presence of given quality. ± indicates partial presence of given quality.

duced nephropathy,¹⁸ shock, and cardiac arrest. The postreperfusion syndrome is a distinct feature with the injured renal tubules serving as a major source of cytokines and chemokines. In addition, reduction in renal blood flow up to 50% persists after reperfusion¹⁹ because of an imbalance between vasoactive mediators and endothelial dysfunction, leading to interstitial edema and leukocyte trafficking.²⁰ In contrast, unilateral and bilateral nephrectomies are of interest as they demonstrate the effects of decreased or absent renal function that is a fundamental characteristic of AKI, but without the effects of the reperfusion syndrome.

Other models of kidney injury, including nephrotoxic injury and sepsis, are less studied especially with regard to remote organ effects (table 1). Although these models are clinically relevant, they do not reliably induce AKI in mice, limiting their empirical usefulness. For example, studies of contrast-induced nephropathy often require previous exposure to combined renal insults such as ischemia and nephrotoxic drugs, as it is difficult to induce nephrotoxic injury with contrast medium alone.²¹ Similarly, nephrotoxic studies of gentamicin are often conducted in the presence of other insults such as gram-negative sepsis.^{22,23}

Animal models of kidney injury have limitations due to interspecies differences. In humans, hypotension and shock lead to hypoperfusion of the kidneys, which often results in ischemic tubular necrosis. However, severe and prolonged hypotension in rats does not typically induce renal injury and is therefore not suitable for use as a “single insult” animal model.²² In contrast, renal ischemia reperfusion in humans leads to subtle and focal histologic changes but similar insult in rats results in diffuse and extensive necrosis of the proximal tubules.^{24,25} Finally, the use of “single insult” models of AKI including renal ischemia reperfusion and nephrectomy fail to reflect the multifactorial causes of AKI that is thought to occur in the clinical setting.

Despite these challenges and limitations, animal models of AKI have been instrumental in demonstrating that AKI is not an isolated event and that it results in remote organ dysfunction to the lungs (table 2), heart, liver, intestines, and brain (table 3) through a proinflammatory mechanism that involves neutrophil migration, cytokine expression, and in-

creased oxidative stress^{26,27} (fig. 2). Neutrophil extravasation into target end organs is characteristic of the innate immune response in acute inflammation²⁸ and is associated with up-regulated cytokine expression,²⁹ which directly leads to end organ injury that is often assessed by increase in vascular permeability. This is demonstrated by injection of Evans blue dye, which has a high binding affinity for albumin, which remains predominantly intravascular but extravasates with disruption of vascular integrity.³⁰ Furthermore, activated neutrophils at sites of inflammation augment this injury by producing reactive oxygen species and depleting antioxidant capacity.

Pulmonary Dysfunction and AKI

The remote effects of AKI in the lungs are due to two distinct mechanisms: uncontrolled inflammatory cascade leading to increased membrane permeability, and down-regulation of sodium-potassium pump and water channels.³¹ Increased concentrations of tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6) (fig. 3) originating from either injured renal tubule cells after renal ischemia reperfusion or extrarenal cells (*e.g.*, T lymphocytes)^{32,33} after nephrectomy play key roles in inducing the acute phase response³⁴ and injury to distal organs including the lungs, heart, and liver by promoting an injurious inflammatory response.³⁵ TNF- α and IL-6 have also been shown to increase vascular permeability, leukocyte trafficking, and edema.^{36,37}

Increased proinflammatory cytokines directly mediate pulmonary injury after AKI. IL-6 deficient mice and wild-type mice administered neutralizing antibody for IL-6 were protected against pulmonary injury after renal ischemia reperfusion or bilateral nephrectomy with findings of decreased neutrophil infiltration, microvascular permeability, myeloperoxidase activity, and pulmonary edema.³¹ Conversely, when IL-6 is administered directly to wild-type mice, pulmonary injury ensues as demonstrated by increased myeloperoxidase activity.

The uncontrolled inflammatory response after AKI leads to increased pulmonary vascular permeability, as demonstrated by extravasation of Evans blue dye.³⁸ Impaired vas-

Table 2. Summary of Experimental Studies on Pulmonary Effects of AKI

Reference	AK Model	Animal	Findings
Kramer <i>et al.</i> ³⁸	IRI	Rat	CNI-1493, a macrophage pacifant, attenuated increase in pulmonary vascular permeability.
Rabb <i>et al.</i> ⁶⁸	IRI, BNx	Rat	Both IRI and BNx lead to down-regulated pulmonary ENaC, Na, K-ATPase and aquaporin-5.
Deng <i>et al.</i> ⁶⁹	IRI	Mouse	Rapid lung injury after AKI was attenuated by administration of α -MSH, an anti-inflammatory cytokine, with decreased TNF- α and ICAM-1 mRNA in lung tissue.
Kim <i>et al.</i> ⁷⁰	IRI, BNx	Rat	Both IRI and BNx resulted in acute lung injury with increased pulmonary vascular permeability and histology consistent with ARDS.
Zarbock <i>et al.</i> ⁷¹	IRI, BNx	Mouse	Injury from acid-induced acute lung injury was attenuated by uremia from both IRI and BNx. This effect was mediated by impaired pulmonary recruitment of uremic neutrophils.
Hassoun <i>et al.</i> ⁷²	IRI, BNx	Mouse	IRI but not BNx resulted in neutrophil infiltration and focal hemorrhage on lung histology and increased protein in bronchoalveolar lavage. IRI induces transcriptional changes in the lungs distinct from BNx.
Hoke <i>et al.</i> ⁷³	IRI, BNx	Mouse	Both IRI and BNx resulted in increased IL-6 and IL-1 β with pulmonary vascular congestion and neutrophil infiltration on histology. Administration of IL-10, an antiinflammatory cytokine, was protective with decreased cytokines and lung injury on histology.
Hassoun <i>et al.</i> ⁴¹	IRI	Mouse	Treatment with Z-VAD-FMK, a caspase inhibitor, attenuated lung microvascular changes.
Klein <i>et al.</i> ³¹	IRI, BNx	Mouse	Increase in lung myeloperoxidase, KC and vascular permeability after both IRI and BNx were attenuated in IL-6 deficient mice and mice treated with IL-6 neutralizing antibodies.
Awad <i>et al.</i> ⁷⁴	IRI	Mouse	Unilateral IRI resulted in increased marginated neutrophils in the lungs.

AKI = acute kidney injury; ARDS = acute respiratory distress syndrome; α -MSH = α -melanocyte stimulating hormone; BNx = bilateral nephrectomy; ENaC = epithelial sodium channel; ICAM-1 = intercellular adhesion molecule-1; IL = interleukin; IRI = ischemia-reperfusion injury; KC = keratinocyte-derived chemokine; mRNA = messenger RNA; TNF- α = tumor necrosis factor- α .

cular integrity results in accumulation of fluid within interstitial lung tissue, leading to pulmonary edema and compromised lung mechanics.³⁹ Extravasation of fluid into alveoli also inactivates surfactant, causing further compromise in lung compliance. Impaired vascular permeability appears to be mediated by macrophages as CNI-1493, a macrophage pacifant, attenuated increase in vascular permeability.³⁸

The intrinsic compensatory mechanism for interstitial lung edema is dependent on active sodium-potassium pump with passive diffusion of water across aquaporin channels.⁴⁰ However, ischemic AKI not only causes interstitial pulmonary edema, but it also down-regulates both sodium potassium pump and aquaporin, effectively nullifying this compensatory mechanism.^{38,41} Furthermore, animal models of reduced aquaporin activity demonstrate a predisposition for ventilator induced lung injury.⁴²

Histologic changes seen in the lungs after renal ischemia reperfusion, but not bilateral nephrectomy, include enhanced pulmonary endothelial and epithelial cell apoptosis.⁴¹ In addition, pulmonary edema, alveolar hemor-

rhage, and leukocyte trafficking were identified. However, in a later study, Klein *et al.* identified septal edema and neutrophil infiltration after both ischemic AKI and bilateral nephrectomy.³¹

Gastrointestinal Dysfunction and AKI

The liver and small intestines are interconnected by the portal circulation and work in tandem to propagate multiorgan dysfunction after AKI. The intestines have important immunologic and barrier functions that prevent the large concentration of intraluminal proinflammatory antigens such as Toll-like receptor ligands, cytokines, and bacterial antigens from entering the bloodstream *via* the portal circulation.^{43,44} Thus, loss of intestinal barrier integrity may initiate or propagate hepatic injury, which has severe clinical implications as the liver plays a vital metabolic role in critical illness including protein synthesis, drug metabolism, and detoxification.

Renal ischemia reperfusion and bilateral nephrectomy result in uncontrolled expression of interleukin-17A (IL-17A)

Table 3. Summary of Experimental Studies on Gastrointestinal, Brain, and Heart Effects of AKI

Organ	Reference	AKI Model	Species	Findings
Gastrointestinal	Miyazawa <i>et al.</i> ⁷⁵	IRI	Mouse	Neutrophil and T cell infiltration of liver, spleen and contralateral kidney. T cells in liver demonstrated cytotoxicity against both tumor cells and syngeneic thymocytes.
	Serteser <i>et al.</i> ⁴⁸	IRI	Mouse	Increased TNF- α concentrations and oxidative stress with increased hepatic myeloperoxidase concentrations and decreased superoxide dismutase, catalase and glutathione concentrations.
	Golab <i>et al.</i> ⁴⁷	IRI, BNx	Rat	Both IRI and BNx resulted in increased hepatic concentrations of TNF- α and oxidative stress with histologic evidence of hepatocyte injury. Glutathione administration before IRI is protective.
	Kim <i>et al.</i> ⁴⁹	IRI	Mouse	Volatile anesthetics reduced hepatic and intestinal injury after renal IRI via induction of sphingosine kinase-1/sphingosine-1-phosphate pathway.
	Park <i>et al.</i> ⁴⁵	IRI, BNx	Mouse	Both IRI and BNx resulted in endothelial apoptosis and disruption of vascular permeability in the intestines and periportal necrosis and neutrophil infiltration of the liver. Injury is mediated by IL-6, IL-17A, and TNF- α .
Brain	Adachi <i>et al.</i> ⁶⁷	IRI	Rat	Impaired motor activity after AKI with suppression of the central dopaminergic system in the presence of uremia.
	Liu <i>et al.</i> ⁷⁶	IRI	Mouse	AKI resulted in increased neuronal pyknosis, microgliosis, and glial fibrillary acidic protein. Extravasation of Evans blue dye into the brain suggests disrupted blood-brain barrier.
Heart	Kelly <i>et al.</i> ⁶¹	IRI	Mouse	Increased concentrations of TNF- α , IL-1, and ICAM-1 mRNA found in heart with increased myeloperoxidase activity. Impaired cardiac function demonstrated by echocardiography. Treatment with anti-TNF- α antibody attenuated apoptosis of cardiomyocytes.
	Tracz <i>et al.</i> ⁶²	IRI	Mouse	HO-1 ^{-/-} knockout mice demonstrated increased IL-6 mRNA in heart and lungs after AKI. IL-6 neutralizing antibody attenuated renal dysfunction and mortality.
	Nath <i>et al.</i> ⁷⁷	IRI	Mouse	Transgenic sickle mice had increased vascular congestion in heart and lungs after IRI.
	Takaoka <i>et al.</i> ⁷⁸	IRI	Rabbit	Brief IRI delayed decrease in myocardial ATP after myocardial ischemia and promoted recovery. SPT, an adenosine receptor inhibitor, attenuated the benefit of remote preconditioning.
	Pell <i>et al.</i> ⁷⁹	IRI	Rabbit	Remote preconditioning was abolished by nonselective adenosine receptor antagonist SPT and K _{ATP} channel blocker 5-HD.
	Gho <i>et al.</i> ⁶⁴	IRI	Rat	Brief IRI with hypothermia provided myocardial protection with decreased infarction relative to area at risk.

AKI = acute kidney injury; ATP = adenosine triphosphate; BNx = bilateral nephrectomy; HO-1^{-/-} = heme oxygenase; IL = interleukin; ICAM-1 = intercellular adhesion molecule-1; IRI = ischemia-reperfusion injury; mRNA = messenger RNA; 5-HD = sodium 5-hydroxydecanoate; SPT = 8-sulphophenyl-theophylline; TNF- α = tumor necrosis factor- α .

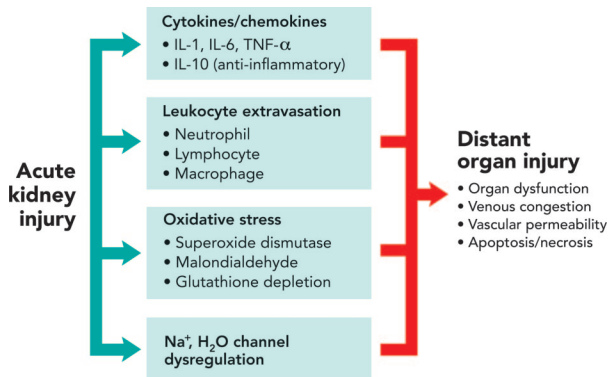


Fig. 2. Global mechanism of distal organ injury. Acute kidney injury leads to distant organ injury through a combination of proinflammatory and oxidative stress-mediated mechanisms. Serum and distal organ cytokine levels increase in conjunction with leukocyte trafficking and increased oxidative stress. In addition, sodium-water channel dysregulation in the lungs aggravates pulmonary edema. IL = interleukin; TNF- α = tumor necrosis factor- α .

in the small intestines.⁴⁵ IL-17A is a pro-inflammatory cytokine that has an important role in the allergic response by recruiting neutrophils, activating T cells, and inducing expression of other cytokines and chemokines such as TNF- α and IL-6. Indeed, AKI in mice resulted in a significant influx of neutrophils, macrophages (fig. 4), and T-lymphocytes in the small intestinal epithelium and vasculature after AKI in mice.^{45,46} This proinflammatory process leads to disruption of intestinal barrier integrity as demonstrated by extravasation of Evans blue dye and results in further exacerbation of the inflammatory cascade from penetration of intraluminal antigens into the portal circulation. Histologic changes to the villous lining of the intestines are consistent with loss of intestinal barrier integrity and include apoptosis of the villous endothelium, necrosis of villous epithelium, congestion of villous capillaries, and blunting of intestinal villi. Increased apoptosis within the

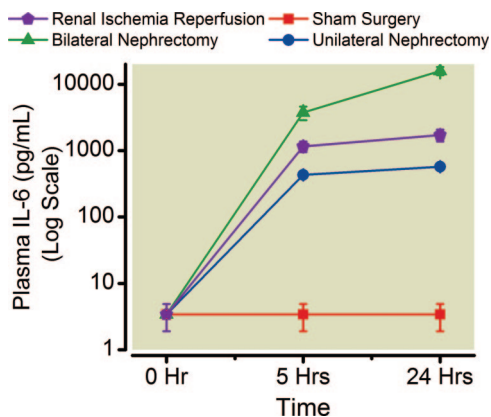


Fig. 3. Plasma interleukin-6 (IL-6) increases after acute kidney injury. Plasma IL-6 measured with mouse-specific enzyme-linked immunosorbent assay (in log scale) increased at 5 h and 24 h after unilateral nephrectomy, bilateral nephrectomy, or 30-min renal ischemia reperfusion.

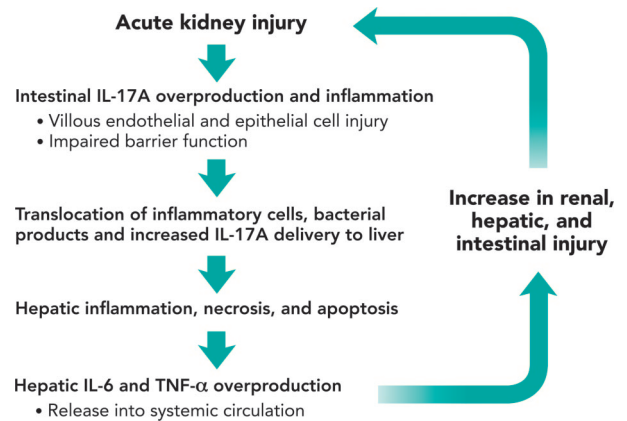


Fig. 4. Proposed mechanism of acute kidney injury (AKI)-induced liver dysfunction. AKI increases small intestinal expression of interleukin-17A (IL-17A) and causes small intestinal injury (impaired vascular permeability, villous endothelial apoptosis and epithelial necrosis, leukocyte infiltration with subsequent cytokine flow into the liver). These events result in hepatic injury (inflammation, apoptosis and necrosis) and increased generation and release of tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6) into systemic circulation causing further multiorgan injury.

villi was confirmed with terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) staining, particularly among perivascular endothelial cells.

IL-17A generated in the intestines drain into the portal circulation and subsequently causes increased hepatic expression of TNF- α and IL-6, as demonstrated by increased TNF- α and IL-6 messenger RNA in liver tissue (fig. 5).⁴⁵ This is followed by hepatic injury, as demonstrated by increased aspartate transaminase and alanine transaminase concentrations. Liver histology after AKI due to either renal ischemia reperfusion or nephrectomy demonstrates hepatic injury with neutrophil infiltration, hepatocyte vacuolization, and periportal necrosis (fig. 6).^{45,46} Remarkably, mice deficient in IL-17A, TNF- α , or IL-6, or mice treated with IL-17A, TNF- α , or IL-6 neutralizing antibodies were protected from liver injury after AKI, suggesting that small intestine generation of IL-17A and hepatic expression of TNF- α and IL-6 after AKI directly potentiates liver injury.

Increased oxidative stress and production of reactive oxygen species in the liver are also thought to play a key role in triggering and maintaining the inflammatory response. Malondialdehyde, an index of lipid peroxidation, was found to be increased in the liver after both renal ischemia reperfusion and bilateral nephrectomy.⁴⁶ In addition, hepatic glutathione, an important endogenous free radical scavenger with protective effects on the liver, was decreased. Administration of glutathione before renal ischemia reperfusion decreased histologic evidence of liver injury, decreased malondialdehyde concentrations, and reduced transaminitis. In addition, renal ischemia reperfusion leads to decreased concentrations of antioxidant enzymes including myeloperoxidase, superoxide dismutase, and catalase.⁴⁷

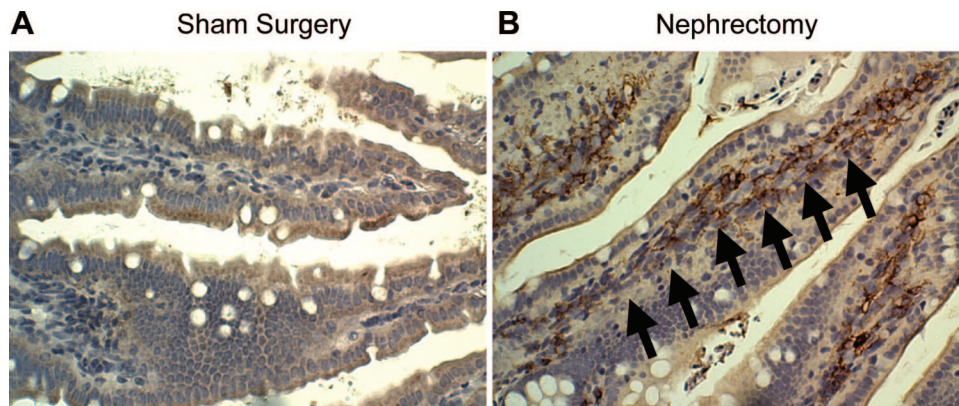


Fig. 5. Increased small intestinal macrophage infiltration after acute kidney injury (AKI). Representative photomicrograph ($\times 400$) of macrophages (dark brown stain indicated by arrows) in small intestinal tissue harvested from mice subjected to sham surgery (A) or bilateral nephrectomy (B) 5 h prior.

A two-hit model of combined kidney-liver ischemia reperfusion demonstrated that mice subjected to ischemic, unilateral, or bilateral nephrectomy AKI in addition to hepatic ischemia reperfusion had significantly worsened liver injury compared with mice subjected to sham kidney surgery with hepatic ischemia reperfusion.⁴⁵ This finding may provide an explanation for worsened clinical outcomes when AKI is combined with hepatic complications.⁴

Finally, antiinflammatory agents may play a vital role in protection against AKI-induced intestinal as well as hepatic injury. Isoflurane, a volatile anesthetic with potent antiinflammatory effects, was protective in mice against renal ischemia reperfusion with reduced intestinal and hepatic injury

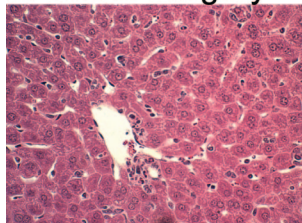
in mice compared to pentobarbital, which has minimal antiinflammatory effects.⁴⁸ This was shown to be mediated directly *via* sphingosine-1-phosphate, a G-protein coupled lysophospholipid ligand well known for its ability to promote cell growth and survival, and inhibition of apoptosis.

Cardiac Dysfunction and AKI

Cardiorenal syndrome is characterized by the combination of heart and kidney failure, with one of the organs usually being the primary organ of failure.⁴⁹ In particular, cardiorenal syndrome type 3 defines heart failure that occurs after AKI. Several mechanisms have been suggested for cardiac dysfunction after AKI, including fluid overload contributing to pulmonary edema, acidemia causing pulmonary vasoconstriction, untreated uremia resulting in pericarditis and decreased myocardial contractility, and hyperkalemia giving rise to arrhythmias.^{50,51} Even in the absence of these conditions, which are often treatable, cardiac dysfunction may still occur in the setting of AKI.

There is increasing basic science and clinical evidence that inflammatory cytokines have negative consequences on cardiac outcome. The Framingham study found that patients with increased TNF- α and IL-6 concentrations were at increased risk for developing congestive heart failure.⁵² Patients with increased C-reactive protein concentrations greater than 5 mg/dl also have a 2.8-fold increased risk of developing congestive heart failure. Furthermore, patients with increased concentrations of all three markers had even higher risk of congestive heart failure (hazards ratio 4.07). Among patients with symptomatic heart failure, increased concentrations of TNF- α correlate directly with worsening severity of disease, higher New York Heart Association class, and are prognostic of worsened clinical outcomes.^{53–56} Patients with congestive heart failure exhibit many features observed in chronic inflammatory conditions. Indeed, patients with severe congestive heart failure have increased concentrations of TNF- α that correlated significantly with features of cachexia.^{57–58}

A Sham Surgery



B Renal Ischemia Reperfusion

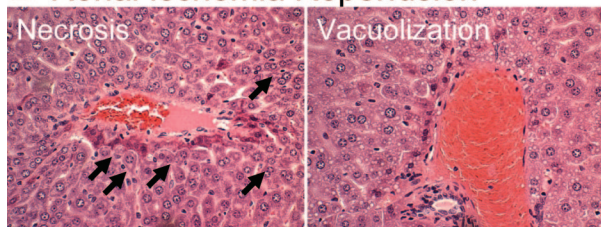


Fig. 6. Hepatic injury after acute kidney injury (AKI). Hepatic injury with increased hepatic necrosis and vacuolization after renal ischemia reperfusion. Representative photomicrograph of liver ($\times 400$, hematoxylin and eosin staining) of mice subjected to sham surgery (A) or to 30 min of renal ischemia and 24 h of reperfusion (B). Ischemic AKI rapidly caused nuclear and cytoplasmic degenerative changes, periportal venous hepatocyte necrosis (arrows), and marked hepatic vacuolization and congestion.

The role of cytokines in the pathogenesis of congestive heart failure is further strengthened by experimental studies suggesting that TNF- α and IL-6, acting concomitantly with neurohormones that lead to salt and water retention, are involved with progressive left ventricular dysfunction, pulmonary edema, left ventricular remodeling, myocyte hypertrophy, and apoptosis.⁵⁴ Transgenic mice that overexpress TNF- α were found to have left ventricular dilatation and hypertrophy that led to premature death. In addition, these mice were found to have bilateral pleural effusion, myocyte apoptosis, and transmural myocarditis. Transgenic mice that overexpress both IL-6 and its receptor, IL-6R were also found to have ventricular hypertrophy.⁵⁹

Cytokine-mediated cardiac dysfunction secondary to AKI has been demonstrated in animal models. Renal ischemia reperfusion in rats resulted in increased TNF- α , IL-1, and intercellular adhesion molecule messenger RNA and myeloperoxidase activity in the heart.⁶⁰ Within 48 h after renal ischemia reperfusion, significant increases in left ventricular end diastolic diameter, left ventricular end systolic diameter, and decreased fractional shortening were demonstrated by echocardiography. Renal ischemia reperfusion, but not bilateral nephrectomy, resulted in myocardial apoptosis. TNF- α was directly implicated in cardiac dysfunction after AKI as administration of TNF- α blocking antibody significantly decreased cardiomyocyte apoptosis. More recently, heme oxygenase-1, an isoform of an enzyme that catalyzes the degradation of heme and is inducible by oxidative stress and hypoxia, was demonstrated to exert cytoprotective effects.⁶¹ Heme oxygenase-1 knockout (HO-1^{-/-}) mice were found to have exacerbated decrease in glomerular filtration rate with marked induction of IL-6 messenger RNA and increased mortality in response to renal ischemia reperfusion.

In contrast with more significant renal injury, mild renal ischemia reperfusion has been found to provide protection against subsequent myocardial ischemia. Research into remote ischemic preconditioning began after observations that occlusion of a specific coronary artery provided myocardial protection beyond its area of perfusion.^{62,63} Gho *et al.* first demonstrated that mice subjected to renal ischemia for 15 min under hypothermic conditions (30°C) were found to have decreased ischemic myocardial area after coronary artery occlusion.⁶⁴ Several potential mechanisms have been proposed. The ability of hexamethonium, a ganglionic blocker, to abolish remote ischemic preconditioning effects suggests the possibility of a neuronal pathway. In addition, transfusion of blood from a rabbit subjected to combined heart and kidney ischemia reperfusion into an otherwise untreated rabbit was found to provide cardioprotection, providing basis for a humoral mechanism. Finally, myocardial ischemic protection may be due to an antiinflammatory and antiapoptotic systemic response.^{64,65} However, remote ischemic preconditioning is not specific to the kidneys and has

also been demonstrated in ischemia reperfusion of skeletal muscle, brain and liver.

Cerebral Dysfunction and AKI

In animal models of AKI, neurotransmitters have recently been demonstrated to play a role in uremic encephalopathy. Decreased dopamine turnover in the striatum, mesencephalon, and hypothalamus were noted 48 h after bilateral renal ischemia reperfusion, but it is not certain whether this effect is directly caused by AKI or uremia.⁶⁶ In addition, cerebral inflammation and functional changes were demonstrated after AKI. In mice, renal ischemia reperfusion was found to result in increased neuronal pyknosis and microgliosis in the hippocampus, which plays a substantial role in learning, memory, anxiety, and depression.⁶⁷ Pyknosis, the irreversible condensation of chromatin in the nucleus, is found in cells undergoing necrosis or apoptosis. Microglial cells, the resident macrophages in the central nervous system, are key mediators of the neuroinflammatory cascade. Furthermore, increased glial fibrillary acidic protein, a marker for cellular inflammation, was noted. Extravasation of Evans blue dye into the brain suggests disruption of the blood-brain barrier in mice after renal ischemia reperfusion. This finding is of clinical importance as disruption of the blood-brain barrier not only results in cerebral edema, but also allows metabolites and toxins that are normally impermeable to the blood brain barrier to produce central nervous system changes. In behavioral testing, mice subjected to renal ischemia reperfusion or bilateral nephrectomy had moderate to severe declines in locomotor activity.⁶⁷

Conclusions

Recent clinical studies demonstrate earlier onset of multiorgan failure and increased mortality after AKI that cannot be explained by increased severity of comorbid conditions alone. In animal models of renal ischemia reperfusion or bilateral nephrectomy, it is increasingly clear that AKI is not an isolated event and that it engenders distant organ injury to the lungs, heart, liver and brain through a mechanism that involves neutrophil migration, increased cytokine concentrations, and oxidative stress. However, therapeutic options for treatment of renal failure, especially when complicated by multiorgan failure, continue to be limited with poor efficacy. Hence, understanding the mechanism behind AKI-induced distal organ injury is important as it may reveal new therapeutic targets.

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