CHAPTER 113

Cardiorenal Syndrome Type 3

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OBJECTIVES

This chapter will:

1. Identify mechanisms of cardiac dysfunction during acute kidney injury.
2. Understand issues applying data from animal models to human kidney injury events.
3. Appreciate short-term mortality and long-term increase in cardiovascular events associated with kidney failure episodes.

Cardiorenal syndrome type 3 (CRS-3) refers to the impact of acute kidney injury (AKI) on cardiac function. AKI is very common among hospitalized patients worldwide, with reported rates largely dependent on the setting (intensive care unit [ICU] vs. community hospital) and the cause of hospitalization. In developed countries, 1% to 2% of hospitalized adults develop AKI, an incidence that increases to 15% to 20% of those with acute myocardial infarction, and 50% to 60% of ICU patients admitted for sepsis.[1,2] In its most severe form, AKI can cause obvious changes in cardiac function: hyperkalemia leading to arrhythmias, fluid overload leading to congestive heart failure/pulmonary edema, and acidosis leading to impaired contractility and impaired response of peripheral vessels to catecholamines. However, subtle changes in the setting of mild episodes of renal injury have long-term effects on cardiovascular prognosis. Separate from altered fluid balance and electrolyte abnormalities, AKI events frequently are associated with alterations in inflammatory markers that may contribute to cardiac inflammation, hypertrophy, and atherosclerosis. Given the frequency of AKI events and the potential long-term impact, we need to improve our understanding and identify potential therapeutic targets to lessen the long-term injury related to AKI events.

The data presented in this chapter are broken down into animal models and lessons learned from human studies. The animal models have the advantage of being able to isolate the impact of a single event (i.e., 30 minutes of ischemia) on an otherwise pristine cardiac background. The animal data have provided significant insight into the impact of individual components that occur during the AKI event, particularly related to cytokines, intracellular

signaling, mitochondrial changes, and fluid/electrolyte balance. Although this has been important in elucidating the pathways involved, it also has shown us that the different types of renal injury lead to cardiac injury in different ways. For example, ischemic renal events followed by reperfusion injury lead to a significantly higher level of cytokines with different impact on cardiac function than bilateral nephrectomy models, in which the primary players are volume overload, electrolyte disturbances, and uremic toxins. Also, it is not clear that information garnered from animal models can be applied directly to humans. The majority of studies on renal-cardiac cross-talk comes from rodent models. However, mouse biology is different from humans (mouse biology is even different within different mouse strains). Studying CRS-3 in multiple different species, particularly pigs, whose kidneys and immune systems more closely resemble ours, will be necessary before progressing to therapeutic trials in humans.[3] Aside from interspecies differences in biology, the human "models" frequently occur within the setting of a complex medical background. The same factors predisposing to AKI overlap with factors predisposing cardiac complications. Preexisting endothelial dysfunction in a hypertensive patient with diabetes could predispose to changes in vascular distribution of blood flow related to increased cytokine levels after renal ischemia reperfusion injury. In another example, age is a risk factor for AKI, as well as susceptibility of cardiac events through underlying vascular disease and preexisting ventricular wall thickening/stiffness. With this background and reduced functional reserve, the elderly patient may not be able to tolerate cardiac changes or volume expansion associated with renal injury that could be asymptomatic in a younger population.

These caveats aside, a lot of progress has been made in the past 10 years regarding CRS-3. The better models are understood, the more complex the picture is becoming. Despite biologic differences, there is already strong evidence for similarities in types of cardiac injury related to AKI. As longer-term follow-up in human studies becomes available, it is becoming clear that many of the causes of acute cardiac dysfunction during the renal insults contribute to long-lasting changes in myocardial structure and function that affect survival. Keeping that in mind, in the sections below we discuss experimental evidence of AKI-associated acute cardiac dysfunction, as well as any suggestion that the involved pathway may contribute to long-term structural changes. Understanding these studies should lead to novel investigations in the treatment of AKI and prevention of cardiac complications from the injury. In the future, the treating nephrologist will be responsible for the medical management of associated electrolyte disorders, volume overload, and acidosis associated with AKI described elsewhere in this text book, as well as several therapeutic options to reduce AKI severity and prevent the short- and long-term cardiac effects. Fig. 113.1 summarizes many of the pathways discussed below.[4]

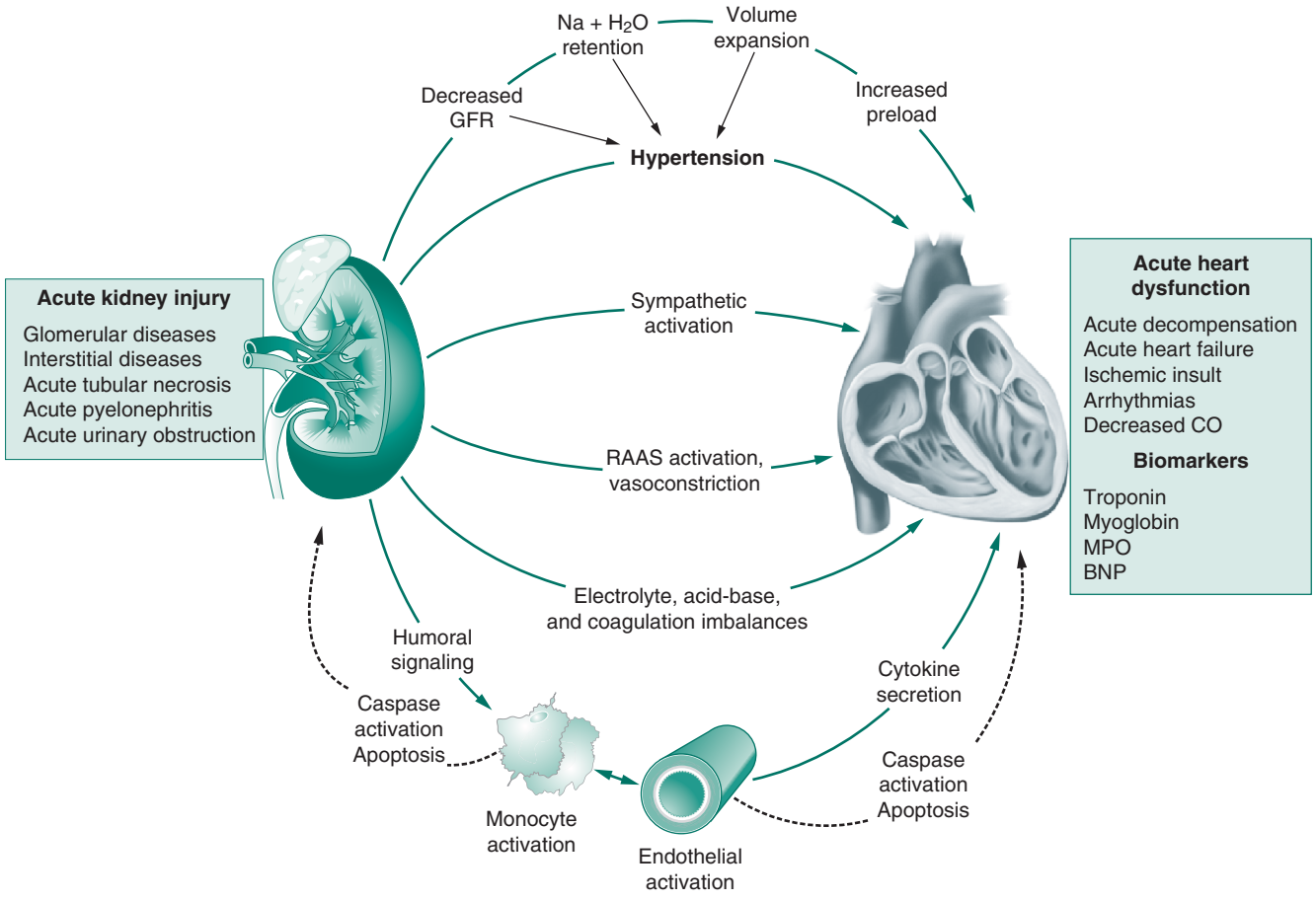

FIGURE 113.1 Cardiorenal syndrome type 3. *BNP,* B-type natriuretic peptide; *MPO,* myeloperoxidase. (Figure by Rob Flewell with permission.[4])

ANIMAL MODELS

Cytokines and Cardiotoxicity

After ischemia, cellular injury triggers the onset of inflammation through the activation of nonspecific adaptive immunity pathways. These pathways lead to the recruitment of inflammatory cells to the kidney and activation of renal parenchymal, epithelial, and dendritic cells. Other types of renal injury, particularly contrast agents and medications, can activate similar pathways and lead to similar inflammatory response.[5–7] Activation of renal tubular cells, interstitial cells, infiltrating immune cells, and resident dendritic cells leads to secretion of chemokines and proinflammatory cytokines. These cytokines and activated inflammatory cells may spill over into the circulation and affect extrarenal tissues. This leads to measurable increase of cytokine levels in the systemic circulation, although the degree likely relates to the severity and type of injury. Although renal limited injury is sufficient to cause an increase in cytokine levels in the blood, in some studies these levels are confounded by a systemic exposure to the mechanism of injury (i.e., sepsis models of AKI, where there is systemic exposure to the causal agent as opposed to pure contrast nephropathy). Increases have been noted in many different cytokines, particularly IFN-γ, TNF-α, IL-1β, IL-6, IL-18.[8]

Many of these cytokines also are elevated after cardiac ischemia and are accepted contributors to heart failure progression. In cardiac disease, cytokines are produced by the myocytes or surrounding tissues to function in an autocrine or paracrine function.[9] Isolated cardiac myocytes, whole perfused animal heart models, and systemic perfusion of cytokines have been used to delineate the different impact of cytokines on cellular function, with the important caveat that local production and effect may be modified by the surrounding cellular milieu. IL-1β has been shown to depress myocardial contractility in vitro and in vivo, an effect that is likely mediated through the induction of IL-18 expression.[10] In addition, IL-18 has been shown to induce myocardial hypertrophy and fibrosis. Tumor necrosis factor-alpha (TNF-α) is elevated in the setting of AKI and also has been shown separately to have direct depressant effects on the myocardium through reducing sensitivity of the β-adrenergic receptor to catecholamines, altering calcium signaling, as well as ultimately inducing apoptosis.[11] Inhibition of TNF-α led to decreased cardiac apoptosis in rat models.[12]

The very same cytokines that are expressed in response to acute injury are appreciated increasingly to initiate a repair process that can lead to long-term fibrosis rather than recovery. TGF-β is just one example of a well-known factor associated with acute repair mechanisms and as a mediator of the development of fibrosis after AKI. A more recently described peptide, tumor necrosis factor–like weak inducer of apoptosis (TWEAK), also has been shown to be elevated in the setting of AKI. TWEAK signals by binding to the fibroblast growth factor-inducible-14 (FN14) receptor on renal epithelial cells and fibroblasts. In animal models of AKI, blockade of TWEAK leads to reductions in cellular injury, cytokines levels, and inflammatory infiltrates.[13] TWEAK-FN14 signaling also is implicated in cardiac remodeling in the setting of heart failure, contributing to hypertrophy and fibrosis, as well as atherosclerosis.[14] Blocking TWEAK signaling is being studied for several autoimmune diseases and cancers. It is possible that TWEAK blockade could be a strategy to reduce renal injury in the setting of AKI as well as its distant cardiac effects.

In addition to acting directly on cardiac tissue, cytokines increase adhesion molecule expression on vascular endothelial cells leading to the infiltration of immune cells into heart tissue. In humans, cellular infiltrates after myocardial infarction and abnormal control of inflammatory response are associated with ventricular remodeling and heart failure progression.[15] In experimental models, 30 minutes of renal ischemia leads to abrupt increases in IL-1 and TNF-α in the systemic circulation, with concomitant detection in cardiac tissues. The increase in cardiac IL-1 and TNF-α activity also correlates with increased ICAM-1 expression on endothelial cells and leukocyte infiltration into the myocardium. This study was unable to isolate the impact of cellular infiltrates from the cytokines signaling. However, the downstream effects of the combination were clear. Cardiac tissues showed apoptosis as detected by TUNEL stain, dilated LV size on echocardiogram, and decreased fractional shortening. Interestingly, these changes were not found in sham-operated animals, or animals that underwent bilateral nephrectomy, which suggests that it is the inflammatory response to ischemia reperfusion injury with subsequent changes in cytokines that are the source of these changes.[11]

Neuroendocrine Activation

Neuroendocrine activation is characteristic in acute kidney injury. Activation of sympathetic nervous system (SNS) occurs in heart failure and kidney injury. Upregulation of renin-angiotensin-aldosterone axis (RAAS) and SNS plays an important role in CRS-3.

Angiotensin II, which is a central product with activation of RAAS, affects cardiac function by more than one mechanism. Angiotensin II is a potent vasoconstrictor of renal efferent vasculature and systemic vasculature. It stimulates the release of norepinephrine from sympathetic nerve terminals leading to increased venous tone, increased systemic vascular resistance, and thereby causing increase in preload and afterload. Increased vasoconstriction can exacerbate the effects of myocardial ischemia by limiting adequate oxygen delivery.

In an experimental animal study, Kingma et al. were able to demonstrate not only impaired coronary vasoresponsiveness but also elevated oxygen consumption at rest in dogs with acute renal failure. These data imply possible increased susceptibility to myocardial ischemia in acute renal failure.[16] In addition to vasoconstriction, angiotensin II increases sodium reabsorption in the proximal tubule, and by stimulating aldosterone release, influences distal renal tubular sodium and water retention as well. Experimental studies also have shown the potential direct role of angiotensin II in myocardial structure and function by causing cardiac hypertrophy, fibrosis, remodeling, and apoptosis.[17,18] In vitro, angiotensin II can induce cellular hypertrophy, reprogramming, or even necrosis of cardiac myocytes, as well as upregulation of fibrosis associated genes in cardiac fibroblasts.

Animal experiments have shown that within 48 hours of acute kidney injury, functional changes can occur in the myocardium via neuroendocrine activation, acute sodium, and fluid retention and accumulation of uremic and inflammatory toxins.[19] In a synergistic manner, these effects of angiotensin II starting from molecular to systemic level, RAAS participates in the pathophysiology of the acute manifestations and long-term cardiovascular outcomes from injury.

Mitochondrial Abnormalities

The cardiac myocyte requires a continuous supply of ATP to continue muscle contraction and maintenance of the electrochemical gradients that coordinate contraction and signal transduction. The majority of ATP in the myocyte is provided by the metabolism of glucose and fatty acids in the mitochondria. In the setting of ischemia, reduction in energy as well as reactive oxygen species produced by mitochondria contribute to cardiac dysfunction. It is now increasingly recognized that alterations in mitochondrial function, membrane integrity, and release of cytochrome C actively contribute to cellular apoptosis.[20] Mitochondrial function is modulated by signals from the surrounding environment in various cardiovascular conditions, and in experimental conditions, preventing mitochondrial signals can reduce cellular injury and apoptosis.[21]

In 2015 Sumida et al. published new findings on the impact of ischemic renal injury on cardiac mitochondrial function, using a mouse model with 30 minutes of bilateral arterial clamping to induce renal ischemia.[22] Functionally, they noted reduced fractional shortening of cardiac muscle at 72 hours and histologically found increased apoptosis and caspase-3 expression. Studying cardiac tissues after only 24 hours, they found that the heart tissue had significantly fragmented mitochondrial membranes and release of cytochrome C compared with sham-operated mice. Tissue extracts showed increased levels mitochondrial regulatory protein, dynamin related protein-1 (Drp1), which has been shown to lead to mitochondrial fission, but no changes in other mitochondrial regulatory proteins. Interestingly, and potentially therapeutically, an inhibitor of Drp1, mitochondrial division inhibitor-1(mdivi-1), given 6 hours after renal ischemia, was able to prevent mitochondrial changes and cardiac apoptosis. This prevention in cardiac injury occurred despite similar degrees of elevation in blood urea nitrogen (BUN), creatinine, and cytokine expressions.

Metabolic Acidosis

The intracellular pH is maintained normally between 6.9 and 7.2, whereas the interstitial compartment is approximately 7.3. Development of metabolic acidosis is one of the most common abnormalities in renal failure and a common indication for initiating renal replacement therapy (RRT) in critically ill patients. Depending on the model used, a reduction in pH has been associated with reduction in myocardial contractility, arrhythmogenesis, and on vascular smooth muscle cell tone/systemic vascular resistance.

Many of the in vitro and animal studies on the impact of acidemia on cardiac function have focused on pH values as low as 6 to 6.5 range, values seen in the setting of myocardial ischemia but beyond what typically is seen in renal failure. These studies have shown that increasing hydrogen concentrations alter multiple ion channel functions, affecting the coordinated flux of Na+, K+, and Ca++.[23–25] Alterations in the control of ion flow is likely responsible for the proarrhythmic state that accompanies restoration of perfusion (postacidosis arrhythmias).[26] Acidosis also reduces myocardial contractility, an effect that is likely related to changes in intracellular calcium management and contractile protein sensitivity to calcium.[27]

This degree of acidemia is beyond what is seen typically in patients with AKI, so the applicability of these findings outside of myocardial ischemia can be questioned. Models investigating AKI specifically are hampered by our inability to separate the impact of acidosis from other physiologic perturbations, such as fluid retention and electrolyte disorders. It also appears that acidosis from alterations in pulmonary function (hypercarbia) may affect the circulation differently from pure metabolic acidoses. To isolate the physiologic impact of different types of acidemia on cardiac function and systemic hemodynamics, Stengl et al. studied mechanically ventilated pigs during respiratory and metabolic acidosis.[28] In each scenario, the pH was reduced gradually to 7.1 from either hypoventilation or infusion of HCl. In both settings, the stroke volume was reduced while end diastolic volumes were unchanged (consistent with in vitro data in the same study showing reduced contractile force of isolated pig myocytes). Cardiac output was maintained in each case by a concomitant increase in cardiac output. Respiratory acidosis was associated with a reduction in systemic vascular resistance, an effect that was not seen in the metabolic acidosis group. Total renal blood flow and the fraction of renal blood flow compared with total cardiac output were no different. Finally, despite the impact of severe acidosis on myocardial ion channel function, they were not able to detect any changes electrocardiographically nor did any animal experience arrhythmia at a pH of 7.1.

FGF23, Klotho, and Phosphorus

In the setting of chronic kidney disease, FGF23 is produced normally by osteocytes to increase phosphorus excretion by the kidney. However, extrarenal effects of FGF23 also are being recognized. By binding to the FGF receptor 4, FGF23 stimulates cardiac hypertrophy, independent of blood pressure, an effect that is blocked partially by soluble Klotho.[29] The impact of these interactions in acute kidney injury still are being delineated. In animal models of AKI, levels of FGF23 are increased within 24 hours, even in animals kept on a low-phosphorus diet.[30] Klotho normally counteracts the extrarenal effects of FGF23, and low levels in chronic kidney disease models (animals and humans) correlate with the degree of vascular calcifications and cardiac hypertrophy. In the setting of AKI, Klotho levels are reduced.[31] Phosphorus levels frequently are elevated in the setting of chronic renal failure, and its elevation is associated with the formation of left ventricular hypertrophy. In the setting of AKI in the ICU, however, some patients actually have low levels, replacement of which may improve cardiac contractility. As yet, the data supporting a role for FGF23, Klotho, and phosphorus are based mostly on experience in animal models of chronic renal failure and human studies. Given the long-term impact of episodes of AKI on cardiac function, it is possible that the balance of increased FGF23 levels with low Klotho increases signaling through the FGF receptor 4, leading to long-term structural changes.

Uremia Toxins

There is overwhelming evidence that uremic toxins are associated with cardiovascular toxicity in chronic kidney disease. Independent of changes in acid-base disorders, and electrolytes, the data are limited on effects of acute uremia on cardiac function. Hundreds of protein metabolites accumulate in AKI, although much of the research has focused on just a few compounds such as urea, creatinine, methylguanidine, guanidinosuccinic acid, phenol, p-cresol, and indoxyl sulfate. Acute accumulation of urea with a combination of these other compounds seems to be act a

myocardial depressant factor.[32,33] Phenol has been shown to have a negative inotropic effect on mammalian cardiac muscle in concentrations often found in the circulation of patients with renal failure.[34] Another in vitro study was able to demonstrate reduced inotropy of the mouse heart cells when cultured with serum derived from uremic patients.[35] Creatinine has chloride channel–blocking properties and reduces the contractility of cultured myocardial cells. The biochemical basis of uremic pericarditis is unclear, but its alleviation with dialysis favors a strong association.

Renal Biomarkers and Cardiac Function

An exciting area of renal research is the discovery of new markers of renal injury that identify patients at earlier time points than serum changes in creatinine or cystatin C. These are released by the kidney in response to injury. It is now recognized that several of them are more than just markers; they have distant effects on diverse cell types as well.

Neutrophil gelatinase-associated lipocalin (NGAL) has been studied extensively in the setting of AKI. It is expressed normally in the epithelial tissues of the kidney, lung, stomach, and colon, where its role regulating iron availability may have bacteriostatic effects. In AKI, it may have direct effects on the renal tubular cells, regulating replication and aiding renal recovery. Expression of NGAL can be induced in other tissues in response to inflammation by tumor necrosis factor-alpha (TNF-α) and interferon gamma (IFN-γ). Cardiac myocytes have been shown to express NGAL in the setting of myocardial infarction, myocarditis, and acute heart failure decompensation thought to be related to inflammation and signaling through Toll-like receptors.[36,37]

Ongoing research suggests that elevated levels also may have a direct effect on cardiac myocytes, although the exact mechanism still has to be identified. Iron overload and iron deficiency have been associated with cardiomyopathies. Intracardiac synthesis of NGAL has the potential to alter the availability of iron for cardiac metabolic use. Extracellularly, NGAL binds to matrix metalloproteinase-9, preventing its inactivation, leading to increased activity and increased degradation of collagen. NGAL also may have a role in the inflammation noted in the kidney and cardiac tissues. NGAL has been shown to induce polarization of macrophages to an inflammatory type M1 phenotype. During studies of atherogenesis, it was shown that increasing levels of NGAL in cell culture leads to increased expression of IL-6, IL-8, and monocyte chemoattractant protein-1 (MCP-1) by cardiac myocytes and smooth muscle cells.[38] Thus NGAL can be induced in response to inflammation and promote further inflammation. How strong of a role NGAL plays in cardiac dysfunction and whether that is related to iron availability, metabolism, inflammation, or collagen metabolism, remains to be determined.[39]

Galectin-3 is found in a wide range of tissues, including the heart and kidneys, and when secreted into the interstitial space, interacts with surface receptors to initiate transmembrane signaling. Normal hearts do not express galectin-3, but it is rapidly increased in response to injury and is overexpressed before heart failure and fibrosis develop. It is thought that at the site of injury, galectin-3 is released into the interstitial space, activating fibroblasts, reducing matrix metalloprotease activity and attracting macrophages, leading to progressive fibrosis.[40] In animal models, overexpression of galectin-3 leads to cardiac and renal fibrosis. Galectin-3 also plays a role in cardiac remodeling during chronic heart failure progression, and serum levels of galectin-3 predict mortality and heart failure progression. In the setting of experimental AKI, galectin-3 levels are increased within hours and continue to be elevated even 7 days later. The suggestion is that increased galectin-3 levels from ischemia renal injury will lead to increased presence in cardiac tissue, contributing to fibrosis in response to acute cardiac injury.[41]

Kidney injury molecule-1 (KIM-1) is a transmembrane glycoprotein that is expressed in the proximal tubule and whose expression is increased in the setting of tubular injury. KIM-1 has been shown to be rapidly increased in the setting of renal injury during cardiac catheterization, cardiopulmonary bypass surgery, and in acute heart failure decompensation.[42] KIM-1 is predictive of future hospitalization and mortality independent of serum creatinine. However, a direct link between KIM-1 upregulation and cardiac injury has yet to be established.

HUMAN STUDIES

There are limited data to explain the pathophysiology of acute renal failure leading to acute cardiac dysfunction in human subjects. AKI is thought to have direct and indirect mechanisms of cardiac injury. Direct mechanisms involve cytokines, pro- and antiinflammatory factors, myocyte apoptosis, and leukocyte infiltration. Indirect mechanisms include uremia, acidemia, hypertension, electrolyte imbalance, and fluid and salt retention.[43]

Many cytokines are hypothesized to be involved in the cardiorenal cross-talk. As described in the mouse renal ischemia reperfusion injury models, TNF-α, interleukin-1 (IL-1), and IL-6 are associated with depressed cardiac function. Inhibition of TNF-α led to decreased cardiac apoptosis in rat models.[12] Increased levels of TNF-α and IL-6 also have been associated with progression and mortality of CHF in humans.[44] The RENEWAL trial, which combined data from the RENAISSANCE and RECOVER trials, studied etanercept versus placebo in CHF patients.[45] Both studies showed no difference in the primary end points of heart failure hospitalizations or death between patients who received etanercept versus placebo.[46] These findings led to the premature termination of the trials. The ATTACH trial studied the possible benefit of infliximab, a chimeric monoclonal antibody to TNF-α. This trial also showed no difference in mortality or heart failure exacerbations between infliximab and placebo groups.[47] NGAL has shown promise to be an early biomarker of AKI. In a study of pediatric patients undergoing cardiopulmonary bypass, urinary NGAL levels peaked about 4 to 6 hours postbypass and reliably predicted AKI in those patients.[48]

Although animal studies have shown changes in left ventricular end-diastolic pressure (LVEDP) and fractional shortening after renal ischemia reperfusion injury, there are currently few studies demonstrating similar findings in humans. Ganda et al. studied LV size after starting dialysis in chronic kidney disease (CKD) patients with known heart failure with reduced ejection fraction. They found that starting hemodialysis resulted in 16% reduction in heart failure hospitalization and left ventricle (LV) myocardial ischemia. There was no difference in LV fractional shortening.[49] Olsson et al. compared LV ejection fraction and LV end diastolic diameter with transthoracic echocardiography (TTE) in patients with and without AKI after valvular heart surgery. They found that there was no acute change in myocardial structure or function in the AKI group compared with those who did not get AKI postoperatively.[50]

SHORT-TERM OUTCOMES

Cardiovascular Events in Acute Kidney Injury (CHF, Infarction, Arrhythmia)

AKI causes many physiologic changes that affect the heart, including electrolyte imbalance, fluid overload, and acidosis. Hyperkalemia increases activity of potassium ion channel leading to shortened repolarization time. ECG classically shows "peaked" T waves. Progressive worsening of hyperkalemia causes widened QRS, prolonged PR, and even intraventricular/fascicular/ bundle branch blocks. Calcium plays an important role in the relaxation and contraction of the cardiac myocardium. Hypercalcemia can cause shortened QT intervals. Hypermagnesemia can interfere with AV nodal and intraventricular conduction, leading to heart block or cardiac arrest.[41]

Fluid retention in AKI is common with reduced sodium and fluid excretion related to altered angiotensin, aldosterone, sympathetic nervous system activation, and impaired renal function (as well as the common practice to give additional fluid in the setting of AKI to rule out volume depletion). Fluid overload has been associated with poor respiratory status, increased preload and afterload, and poor postsurgical healing. Observational studies have shown an association between fluid overload, AKI, and worse outcomes in critically ill patients.[51] Wiedemann et al. studied conservative fluid management versus liberal fluid management in patients with acute lung injury. Although there was no difference in 60-day mortality, the conservative strategy showed decreased mechanical ventilation duration and without increased end-organ damage including need for dialysis.[52] The Fluid and Catheter Treatment Trial (FACTT) was a large multicenter, randomized trial studying conservative versus liberal fluid management in patients with acute lung injury. They also found that a positive fluid balance was associated with increased mortality and post-AKI diuretic treatment was associated with improved 60-day patient survival.[53]

In CRS-3, it is thought that fluid overload in the setting of AKI can cause acute or acute-on-chronic decompensated heart failure. The pathophysiology of fluid overload in acute decompensated heart failure (ADHF) is also not clear. Despite the common teaching that there is "fluid overload," other groups suggest that it may be a redistribution of fluids rather than increased fluids causing pulmonary edema and worsening heart failure.[54] Aside from alterations in left ventricular end-diastolic pressure, alterations in pulmonary capillary permeability allow fluid to leak to the pulmonary interstitium. This would explain why some patients have pulmonary edema without other signs of congestive heart failure.[55] Colombo et al. proposed that this fluid "redistribution" may be due to vascular endothelial activation. In comparison of venous cells of healthy patients to those with decompensated heart failure, there was an increase in nitro-tyrosine formation, COX-2, and inducible nitric oxide synthase (iNOS) expression, which is believed to be part of the inflammatory response.[56] In some patients, decreased oncotic pressure resulting from hypoalbuminemia in addition to increased hydrostatic pressure in congestive heart failure also may contribute the pulmonary edema.[55]

Acidosis also is thought to play a role in cardiac dysfunction. In animal studies, it has been shown that acidosis may decrease contractility via changes in β-receptor expression.[57] Metabolic acidosis in the setting of AKI can lead to increased work of breathing and worsening respiratory status.

Because AKI leads to worse outcomes in surgical and medical ICU patients, one could hypothesize that early RRT should improve patient outcomes. Recent studies have compared early versus late initiation of RRT in a critical care population with AKI. Gaudry et al. was a large multicenter study that compared early versus late RRT initiation in ICU patients, which showed no difference in 60-day mortality.[58] On the contrary, the ELAIN trial was a single-center study that showed reduced 90-day mortality, duration of RRT, and length of stay in the early RRT group. The ELAIN trial also studied levels of inflammatory markers pre- and post-RRT. The early RRT group had significantly lower levels of IL-6 and IL-8, while IL-10, IL-18, and macrophage migration inhibition factor (MIF) did not differ; reduced mortality may be due to reduced inflammatory markers.[59]

Sepsis is another inflammatory response thought to contribute to renal failure. In comparison of ICU patients who had AKI in the setting of sepsis versus other causes (e.g., nephrotoxins, postsurgical state, cardiogenic shock, hypovolemia), those with septic AKI had more severe AKI and longer duration of mechanical ventilation. Despite this, they were also the group that had more renal recovery.[60] In sepsis, rising nitric oxide synthase causes arterial vasodilatation. This in turn activates the RAAS and sympathetic nervous system to increase cardiac output and induce renal vasoconstriction to maintain perfusion.[61] Anti-TNF therapy in septic patients was not associated with better outcomes.

Long-Term Impact After AKI

Mortality After Acute Kidney Injury Event

AKI after cardiac surgery results in significantly higher mortality, hospital costs, and use of mechanical ventilation in ICU patients.[62] AKI also is associated with worse long-term outcomes.

Odutayo et al. published a meta-analysis looking at AKI and long-term cardiovascular outcomes. There was a 58% increased risk of CHF, 86% increased risk of cardiovascular mortality, 38% increased risk of major cardiovascular events, 40% increased risk of acute MI, and 15% increased risk of stroke in patients who had AKI.[63] This emphasizes the importance of understanding and preventing AKI, especially in patients with known cardiac disease. Tsai et al. performed multivariable regression analyses on almost 70,000 patients who had AKI after percutaneous coronary interventions. In this study they found that AKI in this setting led to increased incidence of bleeding, myocardial infarction, and death.[64] A retrospective cohort study further differentiated between early versus late AKI after cardiac surgery and long-term outcomes. They concluded that one third of patients who underwent cardiac surgery developed AKI within 30 days. Similar to aforementioned studies, there was increased risk of myocardial infarction, stroke, and heart failure despite early or late-onset AKI.[65] Patients who had AKI after abdominal surgery also had long-term worse renal outcomes and mortality. Baseline characteristics associated with worse outcomes in these postsurgical patients included diabetes, hypertension, cardiac disease, and lower eGFR.[66]

Renal failure may also have a long-term effect on myocardial structure. Inflammation seen in CKD is hypothesized to interfere with collagen type I balance, which is considered a major cause of myocardial fibrosis. In early kidney disease, this can be due to fluid overload, hypertension, inflammation, and rise in cytokines. As CKD progresses, factors

including anemia, hyperparathyroidism, and vitamin D deficiency, which may accelerate fibrosis.[67] Ganda et al. studied LV size after starting dialysis in CKD patients with known heart failure with reduced EF. They found that start HD resulted in 16% reduction in heart failure hospitalization and left ventricular myocardial infarction. There was no difference in LV fractional shortening.[49] Olsson et al. compared left ventricular ejection fraction and left ventricular end-diastololic volume (LVEDV) with TTE in patients with and without AKI after valvular heart surgery. They found that there was no acute change in myocardial structure in the AKI group compared with those who did not get AKI postoperatively.[50]

Given the poor outcomes in patients who have had AKI or CKD, many studies are evaluating whether AKI leads to increased atherosclerosis. As discussed before, AKI is thought to cause an inflammatory response resulting in extrarenal disease. In CKD there is depression of phagocytes and dendritic cells, with increased cytokines triggering proinflammatory monocytes and macrophages.[68] This activation of the immune system is thought to cause many adverse effects, including increased atherogenesis. Unfortunately, most of these studies have been in animal models and are not always consistent. Patients with kidney disease often are complicated by their comorbidities, including hypertension, diabetes, and cardiac disease. These confound many findings regarding specificity of markers.[41]

CONCLUSION

As the earlier discussion suggests, our understanding of the impact from acute kidney injury is in the preliminary stages. Mechanistic studies from animal models have provided numerous pathways to investigate for potential therapies. Future interventions may focus specifically on reduction of AKI severity, with less cellular injury leading to lower levels of uremic toxins, fluid overload, and inflammatory markers, with potential benefits on cardiac outcomes. Other interventions likely will focus on the overlapping pathways that lead to renal and cardiac fibrosis, those signals that convert AKI events into long-term renal and cardiac dysfunction. Given how quickly chronic cardiac and renal injury begins to develop after an AKI event, much of this research will have to include biomarker studies of renal injury to allow earlier detention and intervention in the appropriate set of patients. For an intervention to be worthwhile, it may be sufficient for an intervention to reduce the severity of renal injury, such as peak creatinine or peak levels of an injury marker such as NGAL. This type of outcome can be known within days of the event, making studies much easier. A truly successful intervention would reduce both short-term and long-term complications, requiring more expensive studies with longer durations. This highlights the need for improved biomarkers that predict long-term outcomes.

It is an exciting time for research into CRS-3 with many different therapeutic options to pursue and many more pathways to be studied. Within the next decade, there will be several more successful interventions to reduce the severity of acute kidney injury and its subsequent effects.

Key Points

1. Acute kidney injury leads to acute alterations in cardiac function through multiple traditional mechanisms, such as fluid overload, electrolyte abnormalities, and acidosis.
2. Recently, multiple humoral mechanisms have been identified through which AKI can lead to acute and chronic myocardial dysfunction.
3. Current interventions to limit acute kidney injury have not shown impressive effects on cardiac function. Hopefully, future studies with additional interventions on these newly identified humoral pathways will improve short- and long-term outcomes.

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