Cardiorenal Syndrome in Acute Kidney Injury

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Summary: Varying degrees of cardiac and kidney dysfunction commonly are observed in hospitalized patients. As a demonstration of the significant interplay between the heart and kidneys, dysfunction or injury of one organ often contributes to dysfunction or injury of the other. The term cardiorenal syndrome (CRS) was proposed to describe this complex organ cross-talk. Type 3 CRS, also known as *acute renocardiac syndrome*, is a subtype of CRS that occurs when acute kidney injury contributes to or precipitates the development of acute cardiac dysfunction. Acute kidney injury may directly or indirectly produce acute cardiac dysfunction by way of volume overload, metabolic acidosis, electrolyte disorders such as hyperkalemia and hypocalcemia, and other mechanisms. In this review, we examine the definition, epidemiology, pathophysiology, and treatment options for CRS with an emphasis on type 3 CRS.

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Cardiac and kidney dysfunction commonly are found in hospitalized patients.[1] As a result of the complex interplay between the heart and kidneys, dysfunction of one organ often results in dysfunction of the other.[2] The term *cardiorenal syndrome* (CRS) was proposed as early as the 1940s to describe the complex bidirectional interactions between the heart and kidneys.[3] Although CRS often is thought of as cardiac dysfunction leading to kidney injury, it now is well established that kidney injury can lead to negative effects on both the heart and the circulatory system.[4]

A formal classification system for CRS was proposed in a Consensus Conference by the Acute Dialysis Quality Initiative Group[5] in 2008 (Table 1). This classification first divides CRS into two main groups: cardiorenal syndrome (types 1 and 2) and renocardiac syndrome (types 3 and 4), based on which organ dysfunction is primary versus secondary. The classification is subdivided further to denote whether the primary organ dysfunction is acute (types 1 and 3) or chronic (types 2 and 4) in onset. Finally, type 5 CRS describes a systemic disease, such as diabetes mellitus or sepsis, that results in both heart and kidney dysfunction simultaneously.

In this review, we focus on type 3 CRS, or acute renocardiac syndrome, in which acute kidney injury (AKI) leads to acute cardiac dysfunction. We examine the epidemiology of type 3 CRS, explore the pathophysiology and associated evidence, and discuss the clinical evaluation and treatment of the patient with type 3 CRS.

DEFINITIONS AND EPIDEMIOLOGY OF TYPE 3 CRS

AKI describes an acute decrease in kidney function, and can result in extracellular volume overload, electrolyte disturbances, and metabolic acidosis. There are multiple definitions of AKI based on urine output and serum creatinine (SCr). The Kidney Disease: Improving Global Outcomes; Acute Kidney Injury Network; and Risk, Injury, Failure, Loss, End-Stage Renal Disease consensus definitions provide diagnostic and staging criteria based on the increase in SCr and decrease in urine output.[6-8] Designed primarily for epidemiologic studies, these definitions have significant limitations regarding their utility in the clinical diagnosis and treatment of AKI. For example, kidney injury that precedes a frank decrease in kidney function manifested by a decrease in glomerular filtration rate has been associated with poor renal and overall outcomes and is not captured by the current diagnostic criteria.[9] Furthermore, there is an emerging paradigm of AKI as a continuum beginning with an acute kidney stress resulting in kidney damage with subsequent development of AKI with frank dysfunction. This is followed by multiple potential recovery patterns, resulting in outcomes ranging from full recovery to organ failure (Fig. 1).[10]

Although current AKI diagnostic and staging criteria may underestimate the true burden of AKI, the incidence of AKI is increasing in hospitalized patients, particularly among those requiring intensive care unit (ICU) level of care. In some studies, the incidence of AKI is reported to be as high as 70% of ICU patients, with 5% to 25% of

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Table 1. Classification of Cardiorenal Syndromes

General definition
CRS is a pathophysiologic disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ induces acute or chronic dysfunction in the other organ
CRS type 1 (CRS-1): acute cardiorenal syndrome
Abrupt worsening of cardiac function leading to acute kidney injury
CRS type 2 (CRS-2): chronic cardiorenal syndrome
Chronic abnormalities in cardiac function causing progressive and permanent chronic kidney disease
CRS type 3 (CRS-3): acute renocardiac syndrome
Abrupt worsening of renal function causing acute cardiac disorders
CRS type 4 (CRS-4): chronic renocardiac syndrome
Chronic kidney disease contributing to decreased cardiac function, cardiac hypertrophy, and/or increased risk of adverse cardiovascular events
CRS type 5 (CRS-5): secondary cardiorenal syndrome
Systemic condition (eg, diabetes mellitus, sepsis) causing cardiac and renal dysfunction

those developing severe AKI that requires renal replacement therapy (RRT). The clinical significance of this observation is highlighted by mortality rates associated with AKI ranging from 50% to 80%.[11]

In type 3 CRS, AKI resulting from many potential insults leads to acute cardiac dysfunction via multiple pathways, including fluid overload leading to congestive heart failure and pulmonary edema, hyperkalemia and other electrolyte abnormalities leading to arrhythmias, and metabolic acidosis leading to impaired cardiac contractility and response to catecholamines. In addition, AKI is associated with a proinflammatory immune response contributing to cardiac inflammation, hypertrophy, and atherosclerosis. Although it is clear that the incidence of AKI is increasing in many populations, the epidemiology of type 3 CRS is more difficult to characterize. Currently, the epidemiology of type 3 CRS remains poorly understood for a variety of reasons, including heterogeneous definitions of AKI, variability in the risk factors for AKI and acute cardiac events in various populations, difficulty determining the temporal relationship between AKI and cardiac events, and failure to capture cardiac outcomes in many studies of AKI.[12]

PATHOPHYSIOLOGY OF TYPE 3 CRS: FROM IN VITRO TO IN VIVO EVIDENCE

AKI is thought to have both direct and indirect effects on cardiac structure and function. Proposed direct mechanisms include activation of the immune system, sympathetic nervous system (SNS), and renin-angiotensin-aldosterone

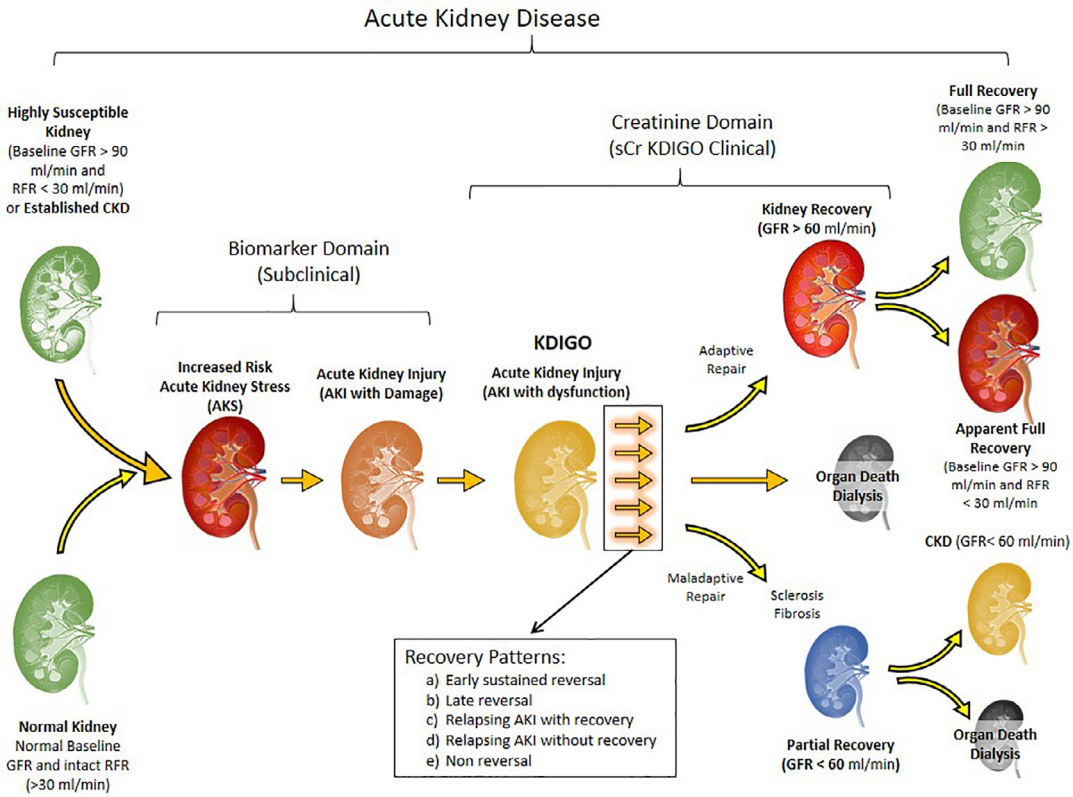

Figure 1. AKI as a continuum of injury with multiple potential outcomes. AKI is a continuum of injury initiated by multiple potential insults. A period of subclinical kidney injury precedes a frank decrease in GFR manifested by an increase in serum creatinine concentration and/or decrease in urine output. The subsequent recovery phase includes potential outcomes ranging from full recovery to organ death. Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; RFR, renal functional reserve.

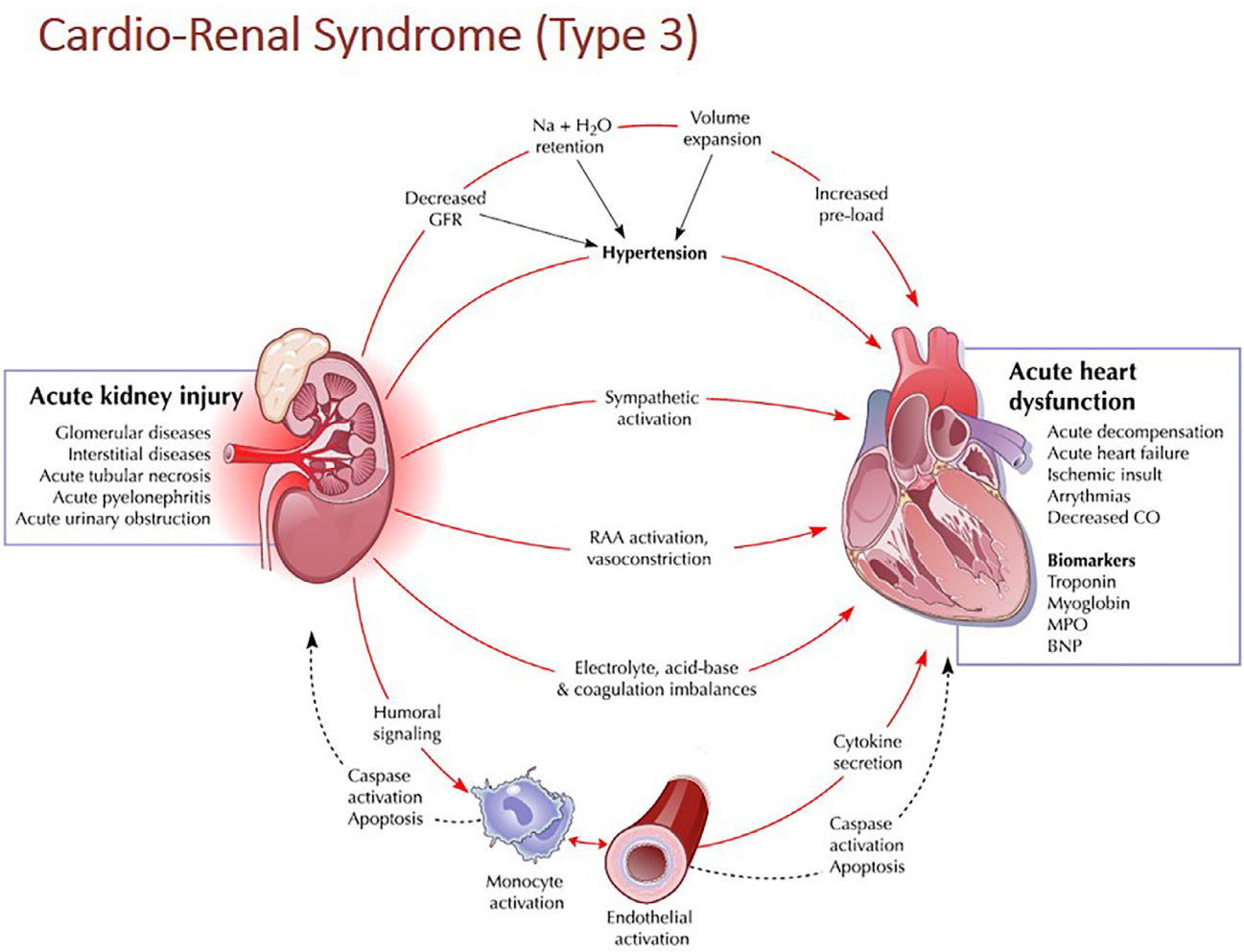

Figure 2. Pathophysiologic pathways in type 3 CRS. AKI is the initial insult in type 3 CRS and can result from many potential etiologies. AKI is thought to have both direct and indirect effects on cardiac structure and function leading to acute cardiac injury. Direct mechanisms include RAA and SNS activation. Indirect mechanisms include volume overload, electrolyte disturbances, and acidemia. Acute cardiac injury can take multiple forms including acute heart failure, cardiac ischemia, and arrhythmia. Abbreviations: BNP, brain natriuretic peptide; GFR, glomerular filtration rate; MPO, myeloperoxidase; RAA, renin-angiotensin-aldosterone. Reprinted from Ronco et al[69] with permission.

system (RAAS), as well as mitochondrial dysfunction. Indirect mechanisms include acidemia, uremia, hyperkalemia, and volume overload. Overall, the pathophysiologic mechanisms of type 3 CRS remain poorly understood. Much of the pathophysiologic data regarding AKI and cardiac dysfunction are provided by in vitro studies and animal models that have the advantage of allowing for a clear temporal delineation of AKI and subsequent cardiac effects. In addition, animal models allow for more detailed measurements of the effects of AKI on pathways of interest, including cytokine release, changes in intracellular signaling and mitochondrial function, fluid balance, acid/base alterations, and electrolyte disturbances. To date, mechanistic data on type 3 CRS in human beings is lacking, in large part owing to the factors discussed earlier. The potential pathophysiologic pathways involved in type 3 CRS are summarized in Figure 2 and discussed further later.

Inflammation

Inflammation likely plays a key role in the cross-talk between the kidneys and heart. In animal models of renal ischemic injury, cellular injury triggers nonspecific adaptive immunity pathways with consequent activation and recruitment of inflammatory cells into the kidneys.[13-15] This activation of immune cells leads to secretion of chemokines and proinflammatory cytokines into the circulation, with potential wide-reaching effects. In particular, increased serum levels of interferon γ, tumor necrosis factor α (TNF-α), interleukin 1β (IL1β), IL6, and IL18 have been observed in animal models of AKI, specifically ischemia-reperfusion injury (IRI) and cisplatin-induced AKI models.[16] The negative impact of proinflammatory cytokines on myocardial function also has been shown in both in vitro and animal models. Exogenously administered IL1β has been shown to depress myocardial contractility

in an experimental mouse model, an effect that likely is mediated through the induction of IL18 based on the observation of increased plasma levels.[17] In addition, TNF-α and IL1 messenger RNA expression is increased in heart tissue in a rat model of ischemic AKI. This increase in myocardial proinflammatory cytokines was associated with functional changes in the heart, manifested by decreased left ventricular fractional shortening and increased left ventricular end-diastolic and end-systolic diameter on echocardiogram. In addition, the local inflammation was associated with myocardial apoptosis, which was attenuated with pharmacologic inhibition of TNF-α.[18]

Many of the proinflammatory cytokines associated with acute cardiac injury also are integral in a maladaptive repair process that results in cardiac fibrosis. A more recently described peptide, tumor necrosis factor−like weak inducer of apoptosis (TWEAK), has been shown to be increased in circulation in the setting of AKI in both animal models and human beings.[19,20] In animal models of AKI, pharmacologic inhibition of TWEAK is associated with a reduction in renal tubular cell injury, proinflammatory cytokine levels, and inflammatory infiltrates.[21] TWEAK-cytokine signaling also is implicated in cardiac remodeling in the setting of heart failure, contributing to hypertrophy and fibrosis, as well as atherosclerosis.[22] Antagonism of TWEAK using recently developed anti-TWEAK and anti-Fn14 antibodies represents a potential therapeutic strategy to reduce renal injury in the setting of AKI as well as its distant cardiac effects.[21]

Cytokines also can increase the expression of adhesion molecules on vascular endothelial cells, which facilitates the infiltration of immune cells into cardiac tissue. In patients with acute coronary syndrome, myocardial immune cell infiltrates after myocardial infarction are associated with abnormal ventricular remodeling and heart failure progression.[22] In experimental animal models of cardiac ischemia, an increase in myocardial IL1 and TNF-α levels correlates with increased intercellular adhesion molecule 1 expression on endothelial cells and leukocyte infiltration into the myocardium.[22] Although yet to be shown in AKI, this cytokine-mediated mechanism of cardiac injury may contribute to cardiac dysfunction in type 3 CRS.

Observational studies in human beings have found that proinflammatory cytokines increased in AKI are associated with depressed cardiac function. Specifically, increased circulating levels of TNF-α and IL6 have been associated with progression of heart failure and increased mortality in human beings.[23] Two randomized control trials—Randomized Etanercept North American Strategy to Study Antagonism of Cytokines and Research into Etanercept: Cytokine Antagonism in Ventricular Dysfunction—randomized a total of 2048 heart failure patients to etanercept, a fusion protein directed against TNF, versus placebo, with the primary end points of death and heart failure−related hospitalization. Both trials were stopped prematurely because of a lack of efficacy, with no significant difference in primary end points between the groups.[24] The Anti-TNF Therapy Against Congestive Heart Failure trial randomized 150 patients with moderate-to-severe heart failure to high-dose (10 mg/kg) and low-dose (5 mg/kg) infliximab, a chimeric monoclonal antibody to TNF-α, versus placebo. Low-dose infliximab did not improve mortality or heart failure hospitalizations, and high-dose infliximab was associated with an increased risk of death and hospitalizations.[25]

Although animal studies have shown changes in left ventricular end-diastolic pressure and fractional shortening after renal IRI, there currently are few studies showing similar findings in human beings. Olsson et al[26] compared left ventricular ejection fraction and left ventricular end-diastolic diameter with transthoracic echocardiography 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 develop AKI postoperatively.

Neuroendocrine Activation

Activation of the SNS and up-regulation of RAAS occurs in AKI (Fig. 3), and activation of both the SNS and RAAS are associated strongly with cardiotoxic effects.[27] SNS activation in AKI not only further activates RAAS, but also has multiple direct negative effects on the heart, including increased myocardial oxygen demand, disrupted calcium homeostasis, myocyte apoptosis, and myocyte hypertrophy.[28,29] RAAS activation results in increased angiotensin II, which causes systemic vasoconstriction and extracellular volume expansion via increased sodium retention. In addition, angiotensin II contributes via multiple mechanisms to cardiac remodeling and hypertrophy.[30] In vitro studies have shown that angiotensin II can induce hypertrophy, cellular reprogramming, and necrosis of cardiac myocytes, as well as up-regulate fibrosis-associated genes in cardiac fibroblasts.[31,32] With a litany of clinical trial data showing mortality and morbidity benefit for pharmacologic inhibition of RAAS and SNS activation in human subjects with heart failure and myocardial infarction, use of angiotensin-converting enzyme inhibitors, angiotensin II−receptor blockers, and β-blockers has become standard of care.[27] Although there is strong evidence for a clinical benefit of RAAS inhibition in type 2 CRS,[33,34] currently there is a lack of evidence showing a benefit of RAAS and SNS inhibition in human beings in the setting of type 3 CRS. Furthermore, inhibition of RAAS in the setting of AKI introduces the potential for worsening kidney injury.

Mitochondrial Dysfunction

Mitochondrial dysfunction resulting from AKI is an emerging mechanism for cardiac injury in type 3 CRS.

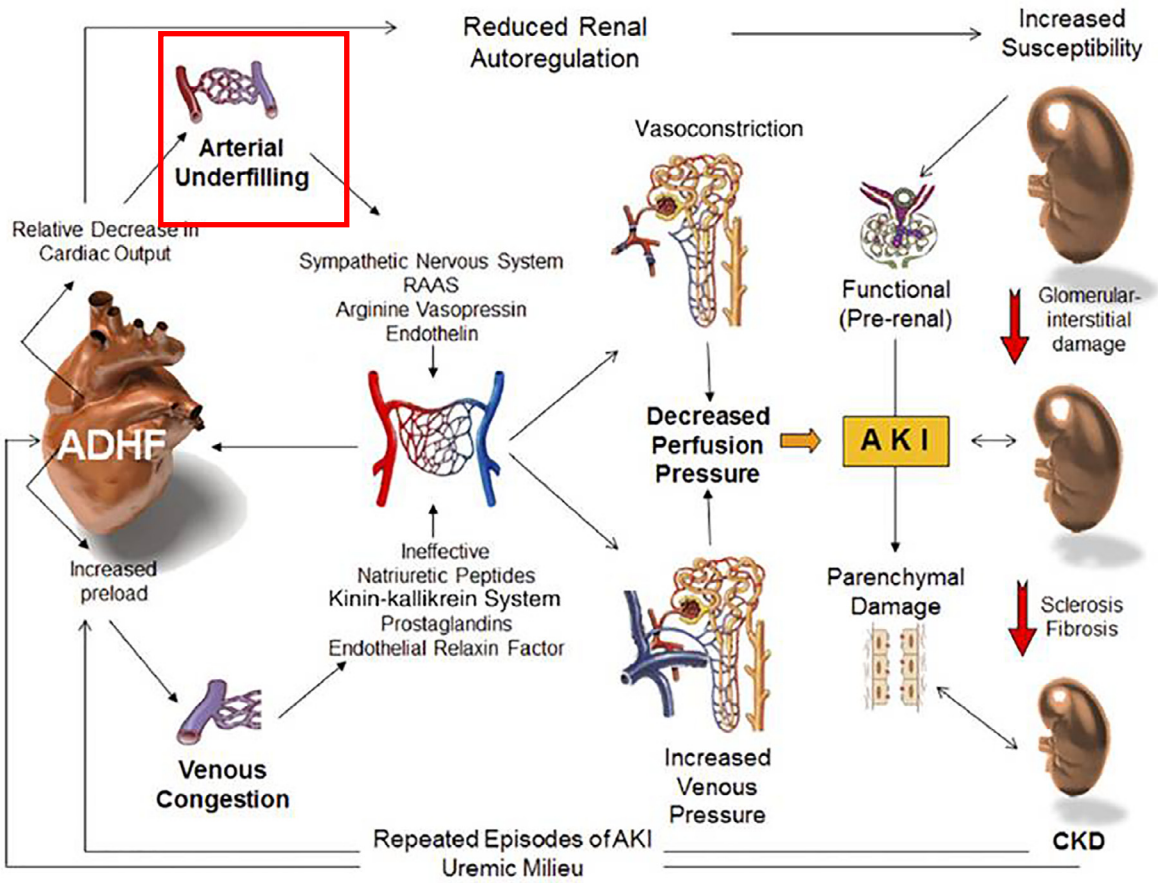

Figure 3. Complex interplay of sympathetic nervous system and renin-angiotensin-aldosterone system activation in type 3 CRS. Both AKI and acute heart failure are associated with increased RAAS and SNS activation. RAAS and SNS activation in AKI contributes to cardiotoxicity via multiple mechanisms. Similarly, RAAS and SNS activation associated with acute heart failure contributes to AKI via renal vasoconstriction and decreased perfusion pressure. In addition, venous congestion in acute heart failure contributes to AKI via increased renal venous pressure. Abbreviations: ADHF, acute decompensated heart failure; CKD, chronic kidney disease.

Cardiac myocytes require a continuous supply of adenosine triphosphatase to maintain myocardial contractility. Much of the requisite adenosine triphosphatase is supplied by metabolism of glucose and fatty acids in the mitochondria. In a mouse model of myocardial ischemia, ischemia induces mitochondrial dysfunction, resulting in a reduction in adenosine triphosphatase production and an increase in reactive oxygen species, which contributes to further cardiac dysfunction. In addition, mitochondrial dysfunction is associated with alterations in membrane integrity and release of cytochrome C, which contributes to cellular apoptosis.[35]

Interestingly, animal models of renal ischemia have shown evidence of mitochondrial dysfunction in the myocardium independent of direct myocardial ischemia. By using a mouse model with 30 minutes of bilateral renal arterial clamping to induce renal ischemia, Sumida et al[36] found reduced fractional shortening of cardiac muscle at 72 hours and increased myocyte apoptosis, as evidenced by increased caspase-3 protein expression. After only 24 hours after renal IRI, fragmented mitochondrial membranes and release of cytochrome C was shown in myocardial tissue. Tissue extracts also showed increased levels of a mitochondrial regulatory protein, dynamin related protein-1, which has been shown to lead to mitochondrial fission, but no changes in other mitochondrial regulatory proteins. Administration of an inhibitor of dynamin related protein-1, mitochondrial division inhibitor-1, administered 6 hours after renal IRI, prevented mitochondrial changes and cardiac myocyte apoptosis, suggesting a potential target for the prevention of cardiac injury after AKI.[36]

Metabolic Acidosis

Metabolic acidosis is a common complication of AKI and is a frequent indication for initiating RRT. Acidemia resulting from AKI has direct physiologic effects on cardiac function that result in a proarrythmic state and reduced contractility. In addition, acidemia results in systemic arteriolar vasodilation and impaired response to vasopressors in shock. In vitro studies with isolated cardiac myocytes

have shown that acidosis affects the flux of electrolytes essential to the myocyte action potential, including sodium, potassium, and calcium, which may contribute to the proarrythmic state. Acidosis reduces myocardial contractility via alterations in intracellular calcium handling and contractile protein sensitivity to calcium.[37] Furthermore, acidosis affects β-adrenergic−receptor expression, contributing to reduced contractility.[38]

To assess the physiologic impact of different types of acidemia on cardiac function and systemic hemodynamics, mechanically ventilated pigs with respiratory and metabolic acidosis were studied. The arterial pH was reduced gradually to 7.1 from either hypoventilation or infusion of hydrochloric acid. A reduction in stroke volume was shown with both mechanisms of acidosis, however, end-diastolic volume and cardiac output were maintained. Interestingly, respiratory acidosis was associated with a reduction in systemic vascular resistance, an effect not seen in the metabolic acidosis group. Despite in vitro evidence showing alterations in myocardial electrolyte flux with acidemia, there were no observed proarrythmic events in the setting of severe acidemia.[37,39]

The negative effects of acidemia on cardiac function have been shown in human beings as well. In critically ill patients with acute respiratory distress syndrome requiring mechanical ventilation, permissive hypercapnia resulting in an arterial pH of 7.2 was associated with a significant decrease in cardiac contractility. Correction of the acidemia to an arterial pH greater than 7.3 with infusion of tromethamine, a buffer that does not produce carbon dioxide, resulted in improvement in cardiac contractility.[40]

Uremia

Retention of uremic toxins is a hallmark of chronic kidney disease and AKI. To date, more than 100 potential uremic toxins have been identified and include small water-soluble compounds, larger middle molecules, and protein-bound molecules. Multiple uremic toxins have been associated with cardiovascular disease. In vitro studies of two small uremic compounds, asymmetric dimethylarginine and symmetric dimethylarginine, are associated with endothelial dysfunction, vascular damage, and proinflammatory pathways.[41,42] In addition, infusion of asymmetric dimethylarginine in healthy human subjects resulted in a decrease in cardiac output and an increase in systemic vascular resistance.[43] Several middle molecules, including β2-microglobulin, IL6, TNF-α, and fibroblast growth factor-23 (FGF-23), have been identified as predictors of cardiovascular disease as well. FGF-23 is a growth factor produced normally by osteocytes to increase phosphorus excretion by the kidney in addition to multiple extrarenal effects. FGF-23 has been shown to induce cardiac left ventricular hypertrophy independently of blood pressure,[44] and this effect is attenuated by administration of soluble Klotho,[45] which acts as a co-receptor for FGF-23 but also has cytoprotective and anti-oxidant properties. In animal models of AKI, FGF-23 levels are increased within 24 hours, even in animals kept on a low-phosphorus diet.[45] Studies in human beings have confirmed that plasma FGF-23 levels are increased dramatically in patients with AKI and are associated with adverse clinical outcomes including RRT and death.[46-49] Although Klotho normally counteracts the extrarenal effects of FGF-23, Klotho levels decrease in the setting of AKI, potentially exacerbating the cardiotoxic effects of FGF-23.[50,51] Although acute uremia in AKI is a plausible contributor to cardiac toxicity in type 3 CRS, it has yet to be shown definitively. Furthermore, the complex nature of uremic toxicity requires further investigation to determine its role in cardiac toxicity after AKI.

Hyperkalemia

Renal excretion of potassium is an essential mechanism for the maintenance of potassium homeostasis. Hyperkalemia is a potentially life-threatening complication of AKI, and an indication for RRT initiation. Hyperkalemia is associated with potentially fatal arrhythmias and cardiac toxicity. The early electrophysiologic signs of hyperkalemia are characterized by a narrowing and peaking of the T wave on electrocardiogram (ECG), which correlates with increased activity of potassium channels and faster repolarization. If hyperkalemia is progressive, there is a decrease of the cell-resting membrane potential, which prevents repolarization. In severe hyperkalemia (potassium, $\geq$7.0 mEq/L), the initial ECG pattern can evolve with marked QRS complex prolongation resulting in a slow sine-wave ventricular flutter pattern and subsequent asystole.[52] Of note, the ECG findings associated with severe hyperkalemia also may be absent, or the ECG may be atypical and nondiagnostic.[12]

Volume Overload

Volume overload is a common complication of AKI and is encountered frequently in critically ill patients with AKI. Among critically ill patients with AKI, extracellular fluid overload is associated independently with increased mortality, a lower likelihood of recovery of kidney function, and a higher likelihood for RRT initiation.[53] There is significant observational and experimental evidence that volume overload resulting from AKI also has direct negative effects on cardiac function. Volume overload is associated with myocardial interstitial edema, which has been shown to contribute to the development of myocardial fibrosis and reduced left ventricular compliance in animal models.[54,55] In addition, there is evidence that volume overload is temporally associated with the development of ventricular arrhythmias.[56]

DIAGNOSIS OF TYPE 3 CRS

Making the clinical diagnosis of type 3 CRS is challenging given the need to establish the occurrence of AKI before acute cardiac injury. Furthermore, type 3 CRS often occurs in the setting of critical illness, when determination of the sequence of insults may not be possible. Although the diagnosis of AKI is based on established criteria focused on an increase in SCr concentration and a decrease in urine output, acute cardiac dysfunction may manifest in multiple ways including arrhythmia, heart failure, and ischemia. When AKI is identified as the primary insult, there are many methods for identifying secondary acute cardiac injury. An ECG is the primary method for the diagnosis of arrhythmia. Ultrasound, chest radiography, and bioelectrical impedance analysis may aid in the diagnosis of volume overload in heart failure associated with type 3 CRS. In addition, there are multiple serum biomarkers of cardiac injury including cardiac troponins, pro−B-type natriuretic peptide (BNP), and multiple novel biomarkers that may facilitate the diagnosis of type 3 CRS.

Coupled with the clinical assessment of volume status, which includes evaluation for jugular venous distension, lung auscultation for evidence of pulmonary edema, and assessment of peripheral edema, ultrasound evaluation may provide important additional information about volume status in type 3 CRS. Ultrasound evaluation of the inferior vena cava diameter correlates with invasive hemodynamic monitoring,[57] and echocardiographic assessment of the cardiac index and inferior vena cava diameter also correlate with invasive hemodynamic assessment of cardiac function and volume status.[58] Evidence suggests that ultrasound in addition to traditional clinical assessment may be of clinical utility in the diagnosis of volume overload in type 3 CRS.

Chest radiography is a readily available, noninvasive, diagnostic tool that also may aid in the diagnosis of heart failure in type 3 CRS. A chest radiograph is able to show evidence of heart failure, including dilated upper-lobe vessels, cardiomegaly, interstitial edema, enlarged pulmonary artery, pleural effusion, prominent superior vena cava, and Kerley lines. A prospective study of emergency room physicians found chest radiographs showing heart failure were identified correctly 79% of the time, for a sensitivity of 59% and a specificity of 96%, suggesting physicians are able to identify heart failure when present, but may under-call it frequently. In addition, the technique for obtaining the chest radiograph (supine, anteroposterior, and posteroanterior) and patient rotation can affect the sensitivity and specificity for the diagnosis of heart failure.[59]

Bioelectrical impedance analysis (BIA) is a method of measuring electrical impedance of body tissues, which

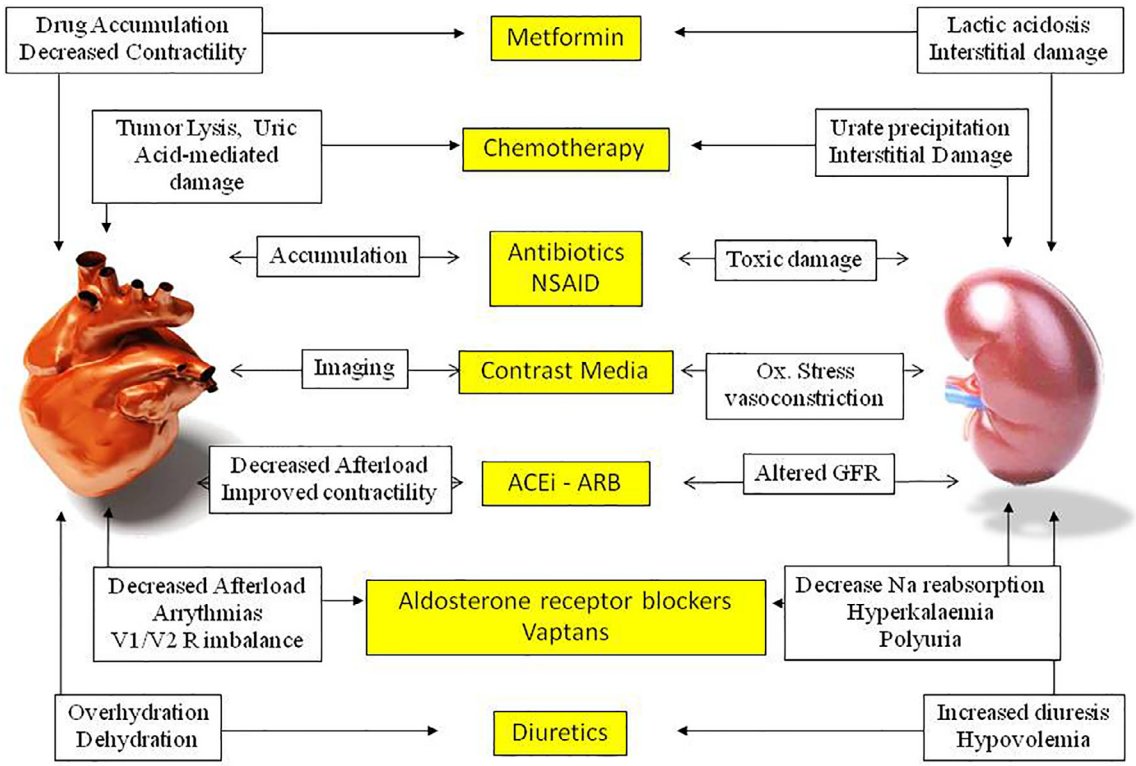

Figure 4. Medications associated with AKI. Many commonly prescribed medications contribute to AKI in type 3 CRS. In addition, many of these medications contribute via multiple mechanisms to cardiac toxicity precipitating acute cardiac injury. Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II−receptor blocker; GFR, glomerular filtration rate; NSAID, nonsteroidal anti-inflammatory drug; Ox, oxidative; V1-V2 R, vaptans 1 and 2 receptors.

then can be used to estimate total body water and volume status. BIA is a potentially attractive tool for evaluating volume status in the setting of type 3 CRS because it is quick, noninvasive, and inexpensive. Although clinical studies have shown a potential incremental benefit of BIA in the diagnosis of acute heart failure, clinical implementation of BIA remains limited. This is in large part owing to a lack of uniformity in the methods of impedance measurement and a lack of proven effect on clinical outcomes.[60]

There are multiple serum biomarkers with proven clinical utility for the diagnosis of acute cardiac injury, however, clinical data showing utility specifically in type 3 CRS are lacking. Cardiac troponins are biomarkers of ischemic cardiac injury that also are predictive of adverse cardiac events.[61] BNP is a hormone secreted by cardiac myocytes in response to increased stretch resulting from increased intracardiac pressures. BNP levels aid in the diagnosis of acute heart failure and also are predictive of future outcomes, including future cardiac events, hospitalizations, and mortality.[62] Finally, because of the significant role that inflammation plays in type 3 CRS, measurement of cytokines such as TNF-α, IL1, and IL6 may have early diagnostic utility.[63]

THERAPEUTIC APPROACH

Effective treatment of type 3 CRS is dependent on the etiology and severity of AKI, as well as the type of acute cardiac injury. It is essential to identify the etiology of AKI and address any potential reversible causes. Examples of reversible causes of AKI include obstructive uropathy with urologic intervention, prerenal azotemia with fluid resuscitation, or acute glomerulonephritis with immunosuppression. It also is important to identify and stop medications that may contribute directly to AKI (Fig. 4). If no quickly reversible etiology is identified and the AKI is severe with complications such as severe acidemia, hyperkalemia, or volume overload, RRT may be indicated.

While addressing the primary AKI, treatment of the resulting acute cardiac injury must occur simultaneously. In the case of arrhythmia, a cardiology consultation with appropriate antiarrythmic medication should be instituted, and for acute coronary syndrome, a cardiology consultation with appropriate medical and/or interventional management should be pursued. In the case of heart failure and fluid overload resulting from AKI, removal of excess fluid is the cornerstone of therapy. Fluid overload is associated with higher mortality in ICU patients and is associated with adverse effects in almost all organ systems.[64] In the setting of nonoliguric AKI and fluid overload, management with loop diuretics is a mainstay of therapy. However, among clinicians there is some hesitancy to administer loop diuretics in the setting of AKI because of concern for worsening AKI related to hypovolemia. Although definitive evidence does not exist identifying the optimal fluid balance strategy after AKI, there is observational evidence suggesting an association between a positive fluid balance after AKI and higher mortality in ICU patients.[53,65] Furthermore, post-AKI diuretic therapy has been associated with improved survival in ICU patients,[66] and a modest increase in serum creatinine with diuresis for volume overload in heart failure is associated with a higher survival rate.[67] In the case of critically ill patients with oliguric AKI requiring RRT and with volume overload, observational evidence suggests an association between negative daily fluid balance with RRT and improved outcomes.[68]

SUMMARY

Type 3 CRS is defined as AKI that contributes to or precipitates the development of acute cardiac injury. Although the epidemiology of type 3 CRS currently is poorly described, the increasing incidence of AKI suggests that type 3 CRS will be encountered increasingly by clinicians in the future. Our understanding of the complex mechanisms linking AKI and subsequent acute cardiac injury is presently evolving. Multidisciplinary research focused on improving our understanding of the epidemiology and pathophysiology of type 3 CRS is essential to facilitate improvements in diagnosis, as well as the development of targeted and effective therapies.

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