The Complex Association Between Cardiac Disease and Kidney Dysfunction: Cardiorenal Syndrome, Contrast-Induced Nephropathy, and Cardiac Surgery-Associated Acute Kidney Injury

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The heart supplies oxygen-rich blood to tissues and organs, and the kidneys need to be well perfused by the heart in order to function properly in their role of maintaining fluid and salt homeostasis; therefore, it is not surprising that there is an intricate relationship between these two organs. Many studies have examined the pathophysiology and treatment options for renal failure and heart failure as separate entities, but fewer studies have investigated them jointly. Furthermore, between the many subtypes of cardiorenal syndrome, the ambiguity of contrast-induced versus cardiac-induced nephropathy after invasive cardiac procedures, and the prevalence of concomitant cardiac and renal disease, there is a need for a broad collective review of cardiac and renal disease. This article examines the pathophysiology behind cardiorenal syndrome, contrast-induced nephropathy after invasive cardiac procedures, and acute kidney injury after cardiac surgery, together with the data supporting currently available prevention and treatment options.

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KEY WORDS

Cardiorenal syndrome • Contrast-induced nephropathy • Acute kidney injury

Cardiorenal syndrome (CRS) is a term used to describe an interdependent relationship between the heart and the kidneys based on their neurohormonal relationship. Both organs have an integral role in fluid balance and sodium homeostasis; therefore, it makes logical sense that when one is diseased, the other organ will become affected. Unfortunately, the nomenclature throughout the literature is still poorly defined. In 2008, Ronco and colleagues[1] proposed a classification scheme that illustrates the pathways by which CRS can occur. The five subtypes are as follows: type I (acute CRS) describes the situation when acutely decompensated heart failure (or cardiogenic shock) leads to acute kidney injury (AKI); type II (chronic CRS) describes chronic cardiac function abnormalities that cause progressive chronic kidney disease that may eventually lead to permanent failure; type III (acute renocardiac syndrome) describes AKI or failure that leads to acute cardiac dysfunction; type IV (chronic renocardiac syndrome) describes chronic kidney disease that leads to cardiac dysfunction and/or increased risk of cardiovascular events; and type V (secondary CRS) describes systemic disease that causes simultaneous deterioration of both cardiac and renal function.[1] As one can deduce from this scheme, the pathophysiology of CRS is multifactorial and complex, and the precise interactions between the kidneys and the heart that lead to CRS still need to be further elucidated.

CRS has reached increased significance in the past decade, not because it is a new phenomenon, but because patients with both heart failure and chronic kidney disease are living longer and thus it is more prevalent. Renal dysfunction is a common comorbidity in patients with congestive heart failure (CHF). The Acute Decompensated Heart Failure National Registry (ADHERE) reports that almost one-third of over 100,000 patients admitted with decompensated heart failure also had concomitant renal dysfunction,[2] and these patients had a higher incidence of adverse cardiovascular events. A meta-analysis from 2006 shows that patients with end-stage renal disease are more likely to die from cardiovascular causes than from renal failure itself.[3] Left ventricular hypertrophy, which leads to increased myocardial oxygen demand and eventually to ischemic events, is increased in all stages of renal failure.[4] Whether the inciting event is secondary to disease of the kidney or an intrinsic cardiac disease, it is clear that the relationship exists and further exploration of the underlying causes is necessary in order to develop more effective treatments.

Although there is a consensus that CRS is becoming more prevalent and that it is a cause of increased morbidity and mortality, the underlying biology is less clear. It is unclear whether the pathophysiology is specific to the type of CRS, whether it is caused by primary cardiac or kidney disease, or instead due to a systemic disease unrelated to the heart or kidneys. The neurohormonal axis, including the renin-angiotensin-aldosterone system (RAAS), arginine vasopressin (AVP), and the sympathetic nervous system (SNS), plays a vital role in fluid and sodium homeostasis, as well as in hemodynamic stability. Historically, it was believed that heart failure triggered renal dysfunction. Conventional belief was that low ejection fraction and decreased cardiac output led to renal failure by causing decreased renal blood flow that in turn activated the RAAS, leading to fluid retention and elevated preload.[5] However, the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial found that there was no correlation between baseline renal function and cardiac index, and that improvement in cardiac output did not itself improve renal function.[6] Additional studies since the ESCAPE trial have shown that patients with acute decompensated heart failure and normal ejection fraction still have worsening renal function.[7] Therefore, the evidence suggests that the pathophysiology of CRS is most likely related to volume overload and elevated cardiac filling pressures, rather than depressed cardiac output.

In a normal healthy heart, myocardial stretch and dilation cause release of natriuretic peptides. Elevated left atrial pressure activates baroreceptors and stimulates a positive feedback loop that decreases AVP release from the posterior pituitary, as well as decreasing the renal SNS stimulation. These pathways interact to increase water and sodium excretion in order to maintain total body fluid balance and composition.[8,9] When this system is disrupted (eg, by heart failure) the kidneys continue (inappropriately) to retain sodium and water despite having increased total body fluid.[10]

The paradox of concomitant venous congestion and relative arterial hypovolemia makes CRS difficult to treat effectively. Although the venous reflexes serve to promote sodium and fluid

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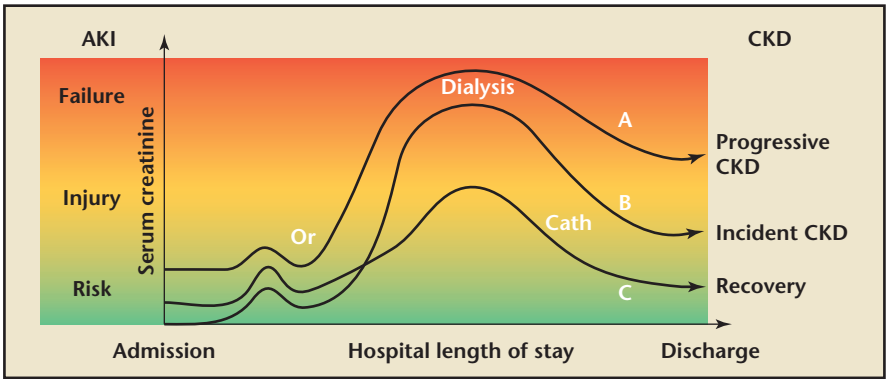

Figure 1. The two hit model of contrast nephropathy-cardiac surgery-associated AKI. **(A)** This patient is admitted with an elevated serum creatinine. His catheterization leads to a small increase (RIFLE-R), but his operation is complex and he worsens to RIFLE-F and undergoes continuous venovenous hemofiltration (CVVH). He recovers but has progressive CKD at hospital discharge. **(B)** This patient has a normal serum creatinine on admission, and also has a small bump following his catheterization. He also undergoes complex surgery and has a profound worsening of his renal function (to RIFLE-F) and also undergoes CVVH. He survives but his renal function does not recover to normal and he leaves with new (incident) CKD. **(C)** This patient is admitted with elevated serum creatinine, and has a similar increase to the other patients after the catheterization. His operation is primary CABG, however, and he only sustains a rise in creatinine to RIFLE-I. He does not require CVVH and his renal function returns to baseline prior to discharge. AKI, acute kidney injury; CABG, coronary artery bypass graft; CKD, chronic kidney disease; CVVH, continuous venovenous hemofiltration; RIFLE, Risk, Injury, Failure, Loss, End-stage renal disease.

excretion, they are overwhelmed by the SNS- and RAAS-mediated arterial reflexes. In both heart and renal failure, the RAAS is chronically activated by reduced perfusion pressure leading to elevated levels of angiotensin II, which itself causes arterial vasoconstriction, as well as stimulating the release of aldosterone and activating the SNS. These mechanisms together cause vasoconstriction of the kidney's afferent arterioles, increased absorption of sodium from the kidneys overall, with decreased sodium delivery to the distal tubules and collecting ducts, which is the site of action of aldosterone. The SNS is activated not only by angiotensin II but also by the baroreceptors in the aorta and aortic arch, and thus provides a positive feedback action on the RAAS resulting in further stimulation of aldosterone. The result is increased afterload and decreased stroke volume, decreased renal blood flow and glomerular filtration rate, and increased absorption of sodium and water from the kidneys. This further exacerbates the volume-overload state. The condition is further aggravated by the fact that both angiotensin II and aldosterone accelerate myocardial fibrosis and remodeling.[11] Angiotensin II also exerts its deleterious effects by activating nicotinamide adenine dinucleotide phosphate-oxidase within vascular smooth muscle cells, cardiac myocytes, and renal tubular epithelial cells, generating reactive oxygen species (ROS) and promoting vascular inflammation.[12] ROS disturb endothelial nitric oxide (NO) release and reduce the bioavailability of NO, in turn disrupting natriuresis and the balance of vasodilation and vasoconstriction causing hypertension and elevated afterload.[12] Oxidative stress from ROS shifts cytokine production toward proinflammatory mediators, leading to cellular damage and stimulating cardiac and renal fibrosis.[13] Adenosine is generated by the breakdown of adenosine triphosphate and adenosine diphosphate in the renal tubules and is released locally in the kidney under stress. This promotes vasoconstriction and enhances sodium reabsorption, which leads to further water and sodium retention.[14]

The SNS is acutely activated to maintain cardiac output, but chronic activation leads to a reduction in beta-adrenoceptor density within the myocardium and reduced adrenoceptor sensitivity in both renal and cardiac failure.[15] It also leads to increased myocyte apoptosis and increased release of neuropeptide Y, which induces vasoconstriction and disrupts immune functioning.[16]

AVP is normally suppressed by hypo-osmolality, but in heart failure it is secreted secondary to nonosmotic baroreceptor-mediated release and binds the V2 receptor; this causes increased water permeability in the collecting ducts and subsequent water reabsorption, increasing preload.[17] AVP also increases afterload through arterial vasoconstriction by stimulating V1a receptors.

In addition to the neurohumoral axis, the perfusion gradient across the renal capillary bed has also been implicated in CRS. Elevated central venous pressure is common in heart failure and elevated renal venous pressure causes reduced urine production. Damman and colleagues[18] reported that patients with baseline renal dysfunction or worsening renal function after hospital admission have significantly elevated central venous pressure compared with those with less or no renal dysfunction. Another study evaluated intra-abdominal pressure and found that it correlated with worsening renal function and that lowering intra-abdominal pressure improves renal function.[19]

The pathophysiology of CRS represents a complex interdependent system where substrates feed into one other and further exacerbate the diseased state of the heart and kidneys through vasoconstriction, fluid retention, and inflammation. However, despite the complexity, it offers many opportunities for therapeutic targets. Most previous

studies have focused on treatment of heart failure while excluding patients with concomitant renal insufficiency or the reverse, but few have evaluated the efficacy of treatment for CRS itself. To further complicate treatment, each patient with CRS has his or her own unique combination of comorbidities beyond cardiac and renal dysfunction. To date, management has focused on symptomatic relief and has frequently been related to removal of fluid in order to relieve congestion and dyspnea. Unfortunately, none of these therapies has been shown to improve survival or to slow the progression of the disease.

Diuretics are not without risks, especially in CRS, because they can also cause activation of the neurohormonal system and promote renal dysfunction, potentially increasing the risk of mortality.

Chronic neurohormonal axis stimulation and worsening kidney function lead to venous congestion and elevated central venous pressures. Loop diuretics relieve the symptoms of congestion even before diuresis occurs; they also reduce left ventricular filling pressures. The Heart Failure Society of America guidelines recommend loop diuretics as the mainstay of therapy in patients with congestive symptoms in the setting of acute heart failure. Diuretics are not without risks, especially in CRS, because they can also cause activation of the neurohormonal system and promote renal dysfunction, potentially increasing the risk of mortality.[20,21] There is evidence that furosemide decreases glomerular filtration rate and that high doses of diuretics are independently associated with sudden cardiac death or death from pump failure.[22] A Cochrane review examined eight trials comparing continuous infusion of loop diuretics with bolus injections in 254 patients with CHF and determined that urine output was significantly greater in patients who received a continuous infusion and that the duration of hospitalization was shortened by 3.1 days, as well as reducing mortality and improving safety profile.[23] Although there is substantial evidence that diuretics will decrease volume, there is increasing evidence that it is at significant cost to the patient. Another factor is diuretic resistance due to a combination of inadequate diuretic dose, excessive sodium or fluid intake, delayed intestinal absorption secondary to mucosal edema, decreased excretion of drug into the urine, and increased sodium reabsorption from the distal convoluted tubule, which is not blocked by loop diuretics.[24] To overcome diuretic resistance, patients should restrict their sodium and fluid intake and intravenous diuretics should be used to avoid the poor oral bioavailability. Addition of a thiazide diuretic or potassium-sparing diuretic can also be used if a patient still does not respond, the dose should be doubled, rather than increasing the frequency of dosing, in order to overcome the dose-response threshold.[25] It may also be beneficial to add a long-acting thiazide diuretic such as chlorthalidone to avoid more frequent shifts in fluid status. Some studies have suggested that adding salt-poor albumin to the diuretic regimen will aid in diuresis; salt-poor albumin is thought to aid in delivery of the diuretic to the kidney by keeping more volume in the vascular space in patients with low albumin levels.[26]

Because RAAS activation is at the heart of the pathophysiology of CRS, inhibitors of RAAS have been evaluated as therapeutic options. Angiotensin-converting enzyme (ACE) inhibitors have been shown not only to increase creatinine upon initiation, irrespective of baseline creatinine, but also to reduce mortality in heart failure. However, the majority of heart failure studies have excluded patients with renal insufficiency.[27] In the Cooperative North Scandinavian Enalapril Survival (CONSENSUS) study, the group with CHF who were treated with an ACE inhibitor had better outcomes, even though the mean serum creatinine increased.[27] Furthermore, the subgroup of patients with creatinine levels between 2 mg/dL and 3.4 mg/dL had improved outcomes.[27] Therefore, it appears that with baseline renal dysfunction, as delineated by creatinine levels, those who use ACE inhibitors have improved outcomes, and ACE inhibitor use should not be discontinued in these patients unless renal dysfunction continues to be impaired or if severe hyperkalemia develops.

When worsening renal function is primarily related to low cardiac index, such as that seen in cardiogenic shock, inotropes such as dobutamine, milrinone, and levosimendan (where available) have been used for a short term and with close monitoring. Inotropes increase the risk of mortality and arrhythmias in both acute and chronic heart failure despite their desirable hemodynamic effects.[28] There is some debate on the utility of dopamine and its ability to increase renal blood flow; however, there are no data to suggest a mortality benefit.[29] Dobutamine is a synthetic catecholamine that acts on β1 receptors and weakly on β2 receptors causing reduced afterload and improved myocardial contractility. Milrinone blocks phosphodiesterase inhibitor III and subsequently increases cyclic adenosine monophosphate, which has a similar effect to dobutamine but via a different mechanism.

Levosimendan stabilizes the conformational change of troponin to calcium and increases contraction. In the Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy (REVIVE) II study there was 33% symptomatic improvement in the treatment group. Despite this, the patients randomized to the levosimendan group had a trend toward increased mortality.[30] In a recent meta-analysis, treatment with levosimendan improved ejection fraction and cardiac index while decreasing pulmonary artery occlusion pressure when compared with either placebo or dobutamine. It also improved survival when compared with dobutamine alone.[31,32] Current heart failure guidelines state the evidence for dobutamine as class IIa, level B, dopamine as class IIa, level C, milrinone as class IIb, level B, and levosimendan as class IIa, level B.[33]

Vasodilators such as nitroglycerin or nesiritide, a synthetic B-type natriuretic peptide (BNP), are thought to have fewer deleterious effects on the kidneys while rapidly decreasing ventricular filling pressures and central venous pressures; at low doses they have minimal systemic hypotension. In theory, the decrease in venous pressure may decrease transrenal perfusion pressure and improve kidney function; however, no long-term benefits have been shown in studies.[34] BNP also causes vasodilation, induces sodium excretion, and suppresses RAAS in response to volume overload and myocardial wall stress. The decreased cardiac afterload increases cardiac output without having direct inotropic effects. Unfortunately, nesiritide does not seem to affect creatinine clearance, glomerular filtration rate (GFR), renal blood flow, urine output, or sodium excretion.[35] Nesiritide was compared with nitroglycerin in a study of 489 patients with heart failure and renal insufficiency; 83% of patients noted improvement in dyspnea after 24 hours. Therefore, nesiritide may have an effect on symptom improvement in patients with heart failure and renal insufficiency, but it does not have a direct effect on kidney function or appear to have a mortality benefit at 30 or 80 days.[36]

Another aspect of the neurohormonal axis is the secretion of AVP in response to diminished arterial volume in heart failure. Tolvaptan, a selective V2 receptor antagonist, hypothetically mobilizes free water clearance and increases serum sodium in hyponatremic patients.[37] The Efficacy of Vasopressin Antagonist in Heart Failure Outcome Study With Tolvaptan (EVEREST) demonstrated in 4133 patients hospitalized with acute heart failure that tolvaptan can decrease mean body weight, presumably through diuresis, and that it improves dyspnea. However, long-term outcomes were unchanged by tolvaptan.[38] This suggests that tolvaptan can decrease the water retention response in the kidney, but that it does not affect remodeling or fibrosis.

The efficacy of the adenosine A1 receptor blocker rolofylline is still equivocal. Adenosine is elevated in patients with heart failure and when it binds to receptors it can cause vasoconstriction of the afferent arteriole resulting in decreased renal blood flow. Therefore, antagonism of these effects should reduce renal dysfunction. The PROTECT study suggests that rolofylline causes increased weight loss and early dyspnea relief, as well as decreased short-term mortality.[39] However, the Study of KW-3902 for Subjects Hospitalized With Worsening Renal Function and Heart Failure Requiring IV Therapy (REACH UP) trial did not show that rolofylline had any benefit on clinical status or renal function in patients with acute decompensated heart failure and worsening renal function. The trial did show a trend toward fewer deaths and rehospitalizations at 60 days in the rolofylline-treated patients, but this was not statistically significant.[40]

Because congestion and elevated central venous pressure seem to be at the forefront of the pathophysiology of CRS, ultrafiltration has been used to decrease volume overload. The benefits of ultrafiltration lie in that there is no immediate neurohormonal stimulation like that seen with diuretic therapy. In the Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) trial, patients treated with ultrafiltration had decreased body weight, vasoactive drug requirement, and hospital readmission in 90 days, as well as restored diuretic responsiveness; however, these patients also trended toward higher serum creatinine levels during the first week of therapy and there was no evidence to suggest any mortality benefit.[41]

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Contrast-Induced Nephropathy After Invasive Cardiac Interventions

Radiocontrast media have been attributed to cause a form of acute renal failure, defined commonly as either a $>$ 25% increase in serum creatinine from baseline or an

absolute serum creatinine increase of 0.5 mg/dL. This condition may require dialysis transiently in high-risk patients, but is usually reversible and is known as contrast-induced nephropathy (CIN). However, the classification is becoming more obscure as the interdependent relationship of CRS continues to become better understood and with the increasing realization that AKI frequently occurs after cardiac procedures without exposure to radiocontrast material. Recently, Nuis and colleagues[42] found that 19% of patients who underwent transcatheter aortic valve implantation developed AKI and many had features that would suggest that they actually had acute or type 1 CRS as opposed to CIN. The patients who developed AKI had a greater prevalence of New York Heart Association class IV heart failure, prior myocardial infarction, or severe coronary artery disease, left ventricular dysfunction, low cardiac output, and diabetes. Even more suggestive is the fact that the baseline GFR and radiocontrast volumes were similar in both the patients who developed AKI and those who did not.[42] Because the prognosis and treatment implications are different for CRS than for CIN, it is imperative to appropriately classify patients who develop kidney injury after invasive procedures.

Treatment for CIN is focused mostly on prevention by using lower osmolar contrast, countering vasoconstriction with hydration, increasing flow through the nephron with diuretics, and protecting against inflammation and oxidative stress with statins, N-acetylcysteine (NAC) and sodium bicarbonate. Once severe CIN develops, hemodialysis may be employed until kidney function recovers. The pathophysiology has yet to be well elucidated, but it is believed that it is also multifactorial, and potentially similar to CRS. There is some evidence that oxidative stress through generation of ROS and inflammation, decreased renal blood flow, and contrast-induced direct renal tubule cellular damage may play a role.[43] Similar to CRS, after contrast exposure there is increased adenosine production, release of angiotensin II, arginine vasopressin, and decreased synthesis of NO.[43] Patients with certain comorbidities such as diabetes mellitus, CHF, chronic kidney disease, and those with advanced age, appear to have an increased risk for CIN.

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Statins are frequently used for their cholesterol-lowering properties; however, they have important cholesterol-independent effects that focus on decreasing oxidative stress and inflammation.[44] A recent meta-analysis that evaluated six cohort studies and six randomized controlled trials (RCTs) were unable to find statistically significant evidence that statin pretreatment effectively decreases the incidence of CIN after coronary angiography with or without percutaneous coronary intervention (PCI). However, it is possible that chronic use of statins, which is common in the cardiac patient population, may have a protective benefit against CIN.[45] When atorvastatin is specifically evaluated in statin-naïve patients with acute coronary syndrome undergoing PCI, it was found to prevent CIN and shorten hospital stay.[46] However, patients who developed CIN also received a statistically significant larger dose of radiocontrast media compared with those patients that did not develop CIN. Atorvastatin pretreatment did not protect against CIN in patients with chronic kidney disease in a previous study.[47] It is possible that prevention of CIN is statin specific (ie, not a class effect) and that atorvastatin may have some protective effect in a healthy kidney as long as there is a low contrast load, but evidence is needed before statin pretreatment can be recommended.

Statins are frequently used for their cholesterol-lowering properties; however, they have important cholesterol-independent effects that focus on decreasing oxidative stress and inflammation.

It is widely accepted that adequate periprocedural hydration has been shown to be effective for CIN prophylaxis.[48] Recently, the use of sodium bicarbonate has gained interest in renal protection for prevention of CIN and AKI after cardiac surgery. Urine alkalinization has been hypothesized to reduce the generation of free radicals and ROS, which may offer renal protection.[49] In an RCT of 265 patients with underlying chronic renal insufficiency, serum creatinine $\geq$ 1.5 mg/dL, who underwent coronary angiography, the combination of sodium bicarbonate and saline did not offer any protective benefit against CIN compared with saline hydration alone.[50] In a meta-analysis of 12 RCTs that evaluated patients with and without baseline renal dysfunction who underwent a procedure requiring radiocontrast material, hydration with sodium bicarbonate alone decreased the incidence of CIN in comparison with hydration with saline alone. However, when NAC was used along with hydration with either

sodium bicarbonate or saline, there was no difference between the sodium bicarbonate/NAC and saline/NAC regimens. Also, there was no difference between the two interventions when evaluating the need for renal replacement therapy or the incidence of in-hospital mortality.[51] This may suggest that the benefit of NAC in preventing CIN overrides any benefit derived from hydration with sodium bicarbonate. Unfortunately, the role of NAC in the prevention of CIN is inconclusive. Fifteen RCTs and their meta-analyses have demonstrated inconsistent results.[52]

Cardiac Surgery-Associated Acute Kidney Injury

The development of cardiac surgery-associated AKI (CSA-AKI)—especially surgery involving cardiopulmonary bypass—has been identified as the strongest single risk factor for death, with mortality rates as high as 40% to 80% if patients require renal replacement therapy. The risk of developing AKI after surgery is increased if the patient also has advanced age, CHF, or an ejection fraction $<$ 35%, pre-existing renal dysfunction, diabetes mellitus, or is having valvular surgery with or without coronary artery bypass grafting (CABG).[53] For the purposes of defining AKI, the RIFLE criteria (Risk, Injury, Failure, Loss, End-stage renal disease) and the AKIN (Acute Kidney Injury Network) staging system have been developed and use changes in serum creatinine level and urine output to standardize the definition. The AKIN staging system modified the RIFLE criteria to include a subset of patients who experienced a small change in renal function above physiological variation (increase in serum creatinine $\geq$ 0.3 mg/dL within 48 hours) who did not meet the risk category of the RIFLE criteria and to include patients with chronic kidney disease who were excluded by the RIFLE criteria until they had increased their serum creatinine level by 50%.[54] These criteria have recently been revised (McCullough PA; personal communication, 2012).

Similar to CIN, prevention (rather than rescue) probably has the best chance of minimizing the incapacity caused by postoperative AKI. One form of prevention is correcting any reversible pre-existing renal impairment prior to undergoing cardiac surgery. The risk of perioperative AKI is demonstrably greater if the patient has received more than 1.5 mL/kg of radiocontrast material within 5 days of undergoing surgery.[55] This lends support to the theory that the once distinct entities CIN, CRS, and CSA-AKI may have similar pathophysiological models of injury that can exacerbate each other and cause more kidney injury than they would alone. Additionally, the proposed mechanism of CSA-AKI involves inflammation, oxidative stress, and generation of ROS similar to the proposed underlying mechanisms of injury of both CIN and CRS.[56] The single best preventative measure would be careful preoperative risk stratification, delaying elective cardiac surgery where possible until comorbidities or risk factors for AKI have been eradicated or minimized, or perhaps modifying the procedure to avoid cardiopulmonary bypass if this is feasible given local expertise and practice patterns.

Statin pretreatment prior to cardiac surgery revealed a reduced incidence of renal failure and an absolute risk reduction in mortality, atrial fibrillation, and stroke in a meta-analysis of 16 observational studies that included 31,725 patients.[57] Another study confirmed that when statins are restarted early postoperatively the incidence of AKI is lower when compared with those patients who had their baseline statin either withdrawn or held until after postoperative day 1.[58] However, a different cohort study of 2103 patients demonstrated that simvastatin was not associated with a lower incidence of AKI after cardiac surgery.[59] Currently, there is a Cochrane review protocol in place to evaluate statin use to prevent postoperative AKI and it is hoped that analysis will provide more conclusive evidence.

The risk of perioperative AKI is demonstrably greater if the patient has received more than 1.5 mL/kg of radiocontrast material within 5 days of undergoing surgery.

Anemia during cardiac surgery has been implicated in increasing the risk of postoperative AKI. A retrospective analysis of 10,179 patients undergoing cardiac surgery found that when acute anemia exceeded a threshold of 50% reduction from baseline, it was associated with an increased incidence of adverse outcomes including requirement for renal replacement therapy, stroke, and in-hospital mortality.[60] Other evidence supports these data and reports that extreme hemodilution, defined as a hematocrit $<$ 21%, and/or blood transfusion have both been associated with increased adverse perioperative outcomes including dialysis and AKI.[61] In addition to large changes in both hemoglobin and hematocrit, large changes in mean arterial blood pressure (MAP) compared with baseline have an adverse effect on kidney function. High-risk patients, or those who possess at least one known AKI

risk factor, had 2.1-fold greater odds of developing AKI if the difference in their average intraoperative MAP varied more than 25 mm Hg from their preoperative MAP.[62] These data support the hypothesis that decreased renal perfusion and hemolysis, which may activate iron-mediated free radical pathways, may play significant roles in the mechanism of injury in postoperative AKI.

Pharmacological interventions have been studied extensively to try and protect renal function in the perioperative period. Inotropes, diuretics and natriuretic peptides, calcium channel blockers, ACE inhibitors, intravenous vasodilators, NAC, and sodium bicarbonate have all been evaluated based on the theory that postoperative renal injury occurs as a consequence of inflammation, generation of ROS, and decreased renal perfusion with subsequent reperfusion. A Cochrane review of RCTs that included patients who underwent all types of surgery reported that, when compared with controls, dopamine and fenoldopam did not have an effect on urine output, creatinine clearance, or renal blood flow.[63] However, a meta-analysis showed that fenoldopam may reduce AKI following cardiac surgery specifically, as well as having significant reductions in renal replacement therapy and mortality.[64,65] There is a significant risk of hypotension when using fenoldopam and the individual studies evaluated had small sample sizes. Further analysis shows that neither diuretics, natriuretic peptides, calcium channel blockers, ACE inhibitors, sodium nitroprusside, nor NAC had any appreciable effect compared with controls on postoperative AKI in a recent Cochrane review analysis.[63]

As discussed previously, sodium bicarbonate causes urine alkalinization and is thought to protect the kidneys from damage secondary to generation of toxic ROS that have enhanced activity at acidic pH.[66,67] In addition, aciduria can convert hemoglobin to methemoglobin that can precipitate and form casts inducing AKI. Sodium bicarbonate loading and infusion were associated with a lower incidence of acute renal dysfunction in cardiac surgery patients who underwent cardiopulmonary bypass, but the study was not powered for exploring potential differences in requirements for renal replacement therapy, duration of mechanical ventilation, or hospital mortality.[53]

Novel Biomarkers

AKI may not be reliably measured using serum creatinine and urine output; therefore, there is increasing research into novel molecular markers to better quantify the extent of AKI and to detect subclinical kidney injury. Some of the most promising biomarkers being evaluated are neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, interleukin (IL)-18, and kidney injury molecule-1 (KIM-1). Both the AKIN and RIFLE criteria rely on change in serum creatinine and urine output to stage AKI, but there are limitations to these studies. Serum creatinine is dependent on sex, muscle mass, and hydration status, and lags behind actual changes in renal function. Direct calculation of GFR gives a more accurate representation of renal function; however, it is cumbersome to calculate.[68] In addition, urine output is also unreliable because it can remain normal despite severe renal dysfunction or it can be decreased before any cellular damage actually occurs in the kidney.[68]

NGAL is produced by neutrophils and proximal tubular cells in the kidney and is highly expressed in response to kidney injury.[69] NGAL is elevated in urine within 2 hours of injury and it is ideal as a biomarker because it is small, resistant to degradation, and easily detected in blood and urine. It was initially recognized because it was one of the earliest and most rapidly induced genes in the kidney after ischemic or nephrotoxic injury in animal models.[70] Both serum and urinary NGAL have been found to be reliable predictors of AKI in cardiac surgical patients. Urinary NGAL measurements are probably more reflective of local renal injury, because it is noninvasive and relatively free of interfering proteins (also up-regulated in liver and lungs). In a small study, measurement of urinary NGAL at 24 hours after cardiac surgery predicted statistically significant prolonged intensive care unit length of stay. However, this same study did not find an increase in urinary NGAL immediately after cardiac surgery like many previous studies with larger sample sizes have found.[71]

Some of the most promising biomarkers being evaluated are neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, interleukin (IL)-18, and kidney injury molecule-1 (KIM-1).

Cystatin C is a cysteine protease inhibitor produced by all nucleated cells and filtered by glomeruli, but not secreted in the kidney tubules. It provides a better estimation of GFR than serum creatinine. It has predicted AKI as early as 2 days before an increase in serum creatinine.[72] In a study comparing patients after cardiac surgery, serum NGAL and cystatin C were superior markers of AKI compared with serum creatinine and urea. NGAL appears to detect subclinical AKI earlier than

cystatin C, which may be because cystatin C is a marker of clearance and GFR needs to be affected before increases in cystatin C are detected, whereas NGAL's early appearance in the urine and serum is independent of GFR.[73]

IL-18 is a pro-inflammatory cytokine that is activated in the proximal tubule cells and then excreted into the urine after ischemic AKI. It increases approximately 6 hours after injury has occurred and, when used in a ratio with serum creatinine, it may accurately predict AKI.[74] In a small study of patients after cardiac surgery, urine IL-18 and urine NGAL were increased in the group of patients who later developed AKI and peaked 2 to 4 hours after surgery.[75] However, urine NGAL was more sensitive and specific at early time points.

KIM-1 is also overexpressed in proximal tubule cells in response to injury and has been shown to predict AKIN stage 1 AKI 2 hours after CABG. Urinary measurement may differentiate ischemic AKI from prerenal AKI, and CKD and KIM-1 levels correlate well with the severity of injury when assessed histologically.[76] Elevated KIM-1 may be more specific to kidney injury than NGAL and is not affected by urinary tract infections or chronic kidney disease. KIM-1 may be useful to add specificity at later time points, with NGAL being the primary early biomarker to detect AKI.[70]

Urinary NGAL appears to be the most promising for early detection of AKI even though subclinical, and may play a role in predicting intensive care unit stays after cardiac surgery. However, both KIM-1 and IL-18 may have a role in increasing specificity and in later time points after the kidney injury has occurred. Cystatin C has a role in GFR estimation but the other molecular markers appear to be superior in early prediction of AKI.

Conclusions

The studies presented above all base their definition of renal dysfunction on changes in serum creatinine levels. In some of these studies the intervention was deemed a failure when it did not have an effect on serum creatinine; alternatively, a treatment may be reported as decreasing AKI based on its effect on serum creatinine even if it did not affect any clinical endpoints. Serum creatinine has been relied on as a biochemical indicator of renal function for decades; however, there is evidence that change in creatinine does not occur until hours or days after the onset of renal injury and this may prevent treatment in the earlier stages of AKI.[77] Other renal biomarkers such as NGAL, KIM-1, N-acetyl-b-glucosaminidase, IL-18, and cystatin C are being investigated and may offer a more sensitive and specific marker of renal injury as well as earlier detection. Using a different renal biomarker in some of the previous studies may detect statistically significant changes in the incidence of AKI as it relates to CRS, CIN, and cardiac surgery. Unfortunately, as of now, the data are mostly inconclusive as to the best prevention and management of these disease processes; however, with the use of new biomarkers, earlier detection may lead to earlier therapeutic treatments. New clinical studies should be designed to evaluate therapies once deemed to be ineffective when they were started after serum creatinine had increased and potentially irreversible kidney injury had occurred, as determined by a substantial decrease in glomerular filtration rate. Furthermore, proper interpretation of the new biomarkers, along with the cardiac biomarkers already used in clinical practice, can aid in proper diagnosis and therefore prognosis of the precise subtype of CRS, and—more importantly—can guide more specific therapy.

The dynamic and complicated relationship between the heart and the kidneys has been a topic of investigation for decades, but there is no strong evidence to support a specific treatment modality for CRS, CIN, or AKI after cardiac surgery. The strongest data lie in hydration as prevention for CIN; however, with hydration comes the risk of volume overload in patients with heart failure. Additionally, as more is learned about the complex pathophysiology of these once distinct entities, it becomes clear that there is pronounced overlap between both the mechanisms and treatment of these conditions. In the future, there needs to be further large, RCTs that include patients with different comorbidities because this permits more generalization to the patient a given clinician is currently treating. The current literature focuses almost primarily on one disease state and it is quickly becoming evident that the results reported thus far are not applicable to all patient populations. ■

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MAIN POINTS

- There is a complex association between cardiac disease and kidney dysfunction; many studies have examined the pathophysiology and treatment options for renal failure and heart failure as separate entities, but fewer studies have investigated them jointly.
- The pathophysiology of cardiorenal syndrome (CRS) is most likely related to volume overload and elevated cardiac filling pressures, rather than depressed cardiac output.
- Radiocontrast media have been attributed to cause a form of acute renal failure known as contrast-induced nephropathy. This condition may require dialysis transiently in high-risk patients, but is usually reversible.
- The development of cardiac surgery-associated acute kidney injury, especially surgery involving cardiopulmonary bypass, has been identified as the strongest single risk factor for death, with mortality rates as high as 80%.
- Proper interpretation of the new biomarkers, along with the cardiac biomarkers already used in clinical practice, can aid in proper diagnosis and therefore prognosis of the precise subtype of CRS, and (more importantly) can guide more specific therapy.

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