

Review Article

Cardiorenal Syndrome - A Review Article

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Abstract:

Cardiorenal syndromes (CRS) describe the dynamic inter-relationship between heart and kidney malfunction. Recent studies have clearly defined its various types and pathophysiology. Improved survival, cardiovascular risk factors (diabetes, hypertension, dyslipidemia), diagnostic and therapeutic intervention are some contributors in its causation. Types 1 and 2 CRS involve acute and chronic cardiovascular disease (CVD) scenarios leading to acute kidney injury or accelerated chronic kidney disease. Types 3 and 4 CRS describe acute and chronic kidney disease leading primarily to heart failure, although it is possible that acute coronary syndromes, stroke, and arrhythmias could be CVD outcomes in these forms of CRS. Finally, CRS type 5 describes a simultaneous insult to both heart and kidneys, such as sepsis, where both organs are injured simultaneously. This article focuses on different types, pathophysiology, novel biomarkers, preventive and treatment aspects of cardiorenal syndromes.

Key words: Cardiorenal syndromes; Heart failure; Kidney failure; Biomarkers.

Introduction:

Cardiorenal syndrome is defined as “disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other”.¹ The coexistence of cardiac and renal disease significantly increases mortality, morbidity, complexity and cost of care² and carries an extremely bad prognosis. Two main mechanisms involve poor left ventricular systolic performance resulting in decreased renal blood flow and venous congestion including increased intraabdominal pressure contributing to renal insufficiency.^{2,3} Proper use of the term CRS should correct a common misunderstanding that kidney dysfunction in heart failure (HF) is a direct consequence of impaired renal blood flow in the setting of depressed left ventricular systolic function. Recent investigations do not support this as the sole derangement in CRS. Increasing evidence supports the roles of central venous congestion, neurohormonal elaboration, anemia, oxidative stress, and renal sympathetic activity as other potential contributors to this complex syndrome.⁴

The following *classification* of CRS has been proposed by Ronco.²

Type 1 (acute)- Acute heart failure results in acute kidney injury (AKI)

Type 2- Chronic cardiac dysfunction causes progressive kidney disease (CKD)

Type 3- Abrupt and primary worsening of kidney function cause acute cardiac dysfunction.

Type 4- Primary CKD contributes to cardiac dysfunction, which manifested by coronary artery disease, HF or arrhythmia.

Type 5 (secondary)- Acute or chronic system disorder (eg. Sepsis or diabetes mellitus) causing both cardiac and renal dysfunction.

Epidemiology:

Heart failure is a common chronic condition affecting 2% of the adult population and resulting in over 1 million annual admissions⁵ making it the leading cause of hospitalization in both developing and developed world adults over the age of 65 years. Patients with chronic kidney disease (CKD) have a greater risk of cardiovascular disease (CVD) mortality ranging from 15 to 30 times that of healthy individuals, with an associated disproportionate use of healthcare resources.⁶

Acute cardiorenal syndrome (CRS Type 1):

Acute cardiorenal syndrome is acute decompensation of cardiac function leading to acute renal failure. This is a syndrome of worsening renal function that frequently complicates acute decompensated heart failure (ADHF) and acute coronary syndrome (ACS). Risk predictors for this complication include reduced baseline renal function, diabetes and prior HF.⁷ Hospitalized patients for ADHF develop acute kidney injury (AKI) as defined by an increase in serum creatinine of ≥ 0.3 mg/dL.^{7,8} Type 1 CRS is rare in pre-hospitalized patients. In hospital, the use of loop diuretics leads to activation of the renin-angiotensin system and worsening of intra-renal hemodynamics.⁹ Testani et al¹⁰

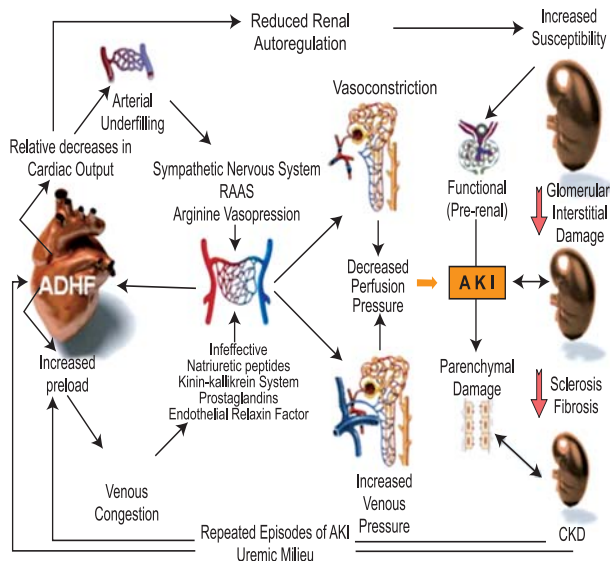
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showed that the use of higher doses of loop diuretics, causing hemoconcentration, resulted in a 5-fold increased rate of worsening renal function. It also showed that aggressive diuresis was associated with a 69% reduction in mortality at 180 d. Several studies have shown an elevated central venous pressure and renal venous congestion to the development of CRS Type 1. Thus, the relative balance of venous and arterial tone and congestion of the kidney appear to be important in the fall of renal filtration that occurs during hospitalized treatment of ADHF. Acute contrast-induced and cardiopulmonary bypass surgery-associated AKI occur in 15% and 30% of patients, respectively.^{11,12}

Thus the important points of CRS Type 1 are: (1) the mortality risk appears to be confounded by other non-renal complications occurring during the hospitalization; (2) intravascular iodinated contrast alone and in cases where cardiac surgery follows coronary angiography, direct cellular toxicity from the contrast itself, results in an observed rise in serum creatinine predominately in those with baseline reductions in renal filtration with additional risk factors, including diabetes, heart failure, older age and larger contrast volumes; and (3) in the setting of ADHF, superimposed use of iodinated contrast or other cardiac procedures is associated with longer lengths of stay and higher mortality which is possibly in part, attributable to CRS Type 1.¹³⁻¹⁵

Pathogenesis of Type 1 CRS

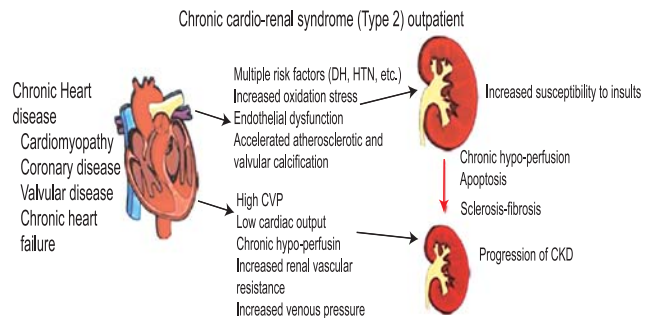


Acute decompensated heart failure (ADHF) via arterial underfilling and venous congestion sets off a series of changes in neurohormonal and hemodynamic factors that culminate in acute kidney injury (AKI). CKD = chronic kidney disease; CRS = cardiorenal syndrome; RAAS = renin-angiotensin-aldosterone system.

Adapted from: Cardiorenal Syndrome Type 1: Pathophysiological Crosstalk Leading to Combined Heart and Kidney Dysfunction in the Setting of Acutely Decompensated Heart Failure. *J Am Coll Cardiol.* 2012;60(12):1031-1042.

Chronic cardiorenal syndrome (CRS Type 2):

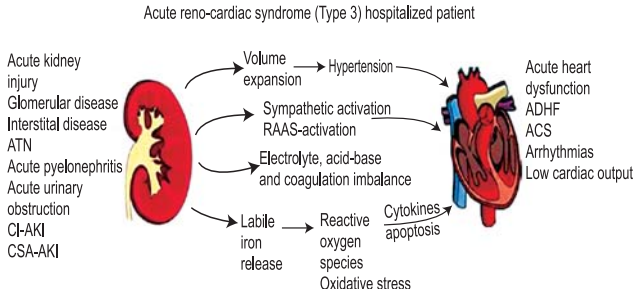
Chronic cardiorenal syndrome (CRS Type 2) is characterized by chronic abnormalities in myocardial function leading to worsened chronic kidney disease (CKD). Studies have shown that 45.0%-63.6% of patients with chronic HF have evidence of CKD defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min per 1.73 per square metre.¹⁶ It is recognized that the risk factors for atherosclerosis namely diabetes, hypertension and smoking are independently associated with the development of CKD.¹⁷ In addition, chronic abnormalities in systolic and diastolic myocardial performance can lead to alterations in neurohormonal activation, renal hemodynamics and a variety of adverse cellular processes leading to apoptosis and renal fibrosis.¹⁸ CKD accelerates the course of atherosclerosis and results in premature CVD events including myocardial infarction and stroke.^{19,20} CKD and its metabolic milieu work to cause advanced calcific atherosclerosis through CKD mineral and bone disorder characterized by phosphate retention, relative vitamin D and calcium availability and secondary hyperparathyroidism.²¹ Patients with CRS type 2 commonly have vascular calcification, less vascular compliance and a higher degree of chronic organ injury related to blood pressure elevation and shear stress.²² CRS Type 2 is heavily confounded by the “common soil” of atherosclerosis and CKD. The cardiometabolic syndrome and neurohormonal activation affect both organ systems; thus, it is difficult to tease out the temporal sequence of pathophysiological events for most individuals which are occurring over the period of decades.²³



Adapted from: McCullough PA. Cardiorenal syndromes. *World J Cardiol.* 2011; 3(1):1 -9.

Acute renocardiac syndrome (CRS Type 3):

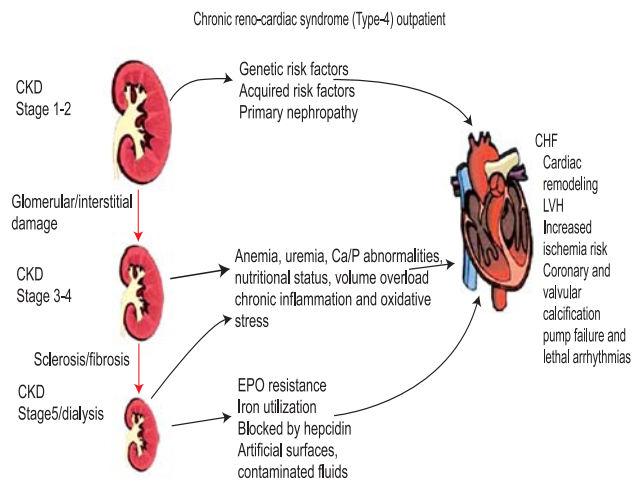
Acute renocardiac syndrome (CRS Type 3) is characterized by acute worsening of renal function leading to cardiac events. The most common scenario for CRS Type 3 is the development of acute kidney injury (AKI) that results in volume overload, sodium retention, neurohormonal activation, and the development of clinical HF with the cardinal features of pulmonary congestion and peripheral edema.²⁴



Adapted from: McCullough PA. Cardiorenal syndromes. World J Cardiol. 2011; 3(1):1-9.

Chronic renocardiac syndrome (CRS Type 4)

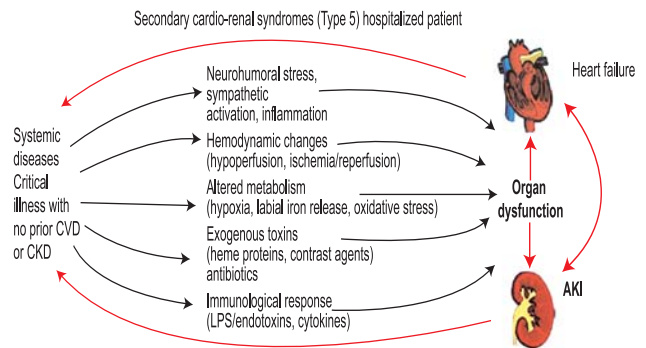
Chronic renocardiac syndrome (CRS Type 4) is characterized by chronic renal disease leading to the progression of cardiovascular disease. There has been recognition of a graded and independent association between the severity of CKD and incidence as well as prevalence of CVD.²⁵ Several studies showed that there was a clear relationship between the degree of renal dysfunction and the risk for all-cause mortality.²⁶ CKD contributes to CVD outcomes in CRS Type 4 by complicating pharmacological and interventional treatment.^{27,28} For example, azotemia and hyperkalemia restrict the use of drugs that antagonize the renin-angiotensin system.^{29,30} CKD also worsens the presentation, severity, response to treatment and cardiorenal outcomes in acute and chronic hypertension.^{31,32}



Adapted from: McCullough PA. Cardiorenal syndromes. World J Cardiol. 2011; 3(1):1-9.

Secondary cardiorenal syndrome (CRS Type 5)

Secondary cardiorenal syndrome (CRS Type 5) is systemic illness leading to simultaneous heart and renal failure. It is recognized that a systemic insult, particularly in a younger patient with no prior heart or kidney disease, can lead to simultaneous organ dysfunction. Sepsis as a precipitator of CRS Type 5 is common and its incidence is increasing, with a mortality estimated at 20%-60%.^{33,34} Approximately 11%-64% of septic patients develop AKI that is associated with a higher morbidity and mortality.³⁵ Abnormalities in cardiac function are also common in sepsis including wall motion abnormalities and transient reductions in left ventricular ejection fraction.³⁶



Adapted from: McCullough PA. Cardiorenal syndromes. World J Cardiol. 2011; 3(1):1-9.

Biomarkers:

Serum creatinine (SCr) is a degradation product of muscle cells and represents a surrogate for the efficiency of glomerular filtration. It has poor predictive accuracy for renal injury, particularly, in the early stages of AKI.³⁷

Neutrophil gelatinase-associated lipocalin (NGAL), also known as lipocalin-2 (LCN-2), plays an important role in the innate immune response to bacterial infection.³⁸ NGAL was first reported as an early biomarker for ischemic renal injury after cardiac surgery in children.³⁹ Cutoff value of 170 ng/mL, NGAL was associated with development of type 1 CRS within 48 to 72 hours with a sensitivity of 100% and a specificity of 86.7%.⁴⁰

Kidney injury molecule-1 (KIM-1) is a transmembrane glycoprotein with an immunoglobulin and mucin domain. A number of studies have demonstrated KIM-1 to be a marker of AKI occurring after CPB surgery and cardiac catheterization.⁴¹⁻⁴³

Plasma level of cystatin C (CysC) was a strong and independent marker of CRS and mortality in acute heart failure patients.⁴⁴ In patients with chronic systolic heart failure, plasma CysC levels were directly correlated with ventricular dysfunction and were suggested as a prognostic factor.⁴⁵

Urinary N-acetyl- β -D-glucosaminidase (NAG) is increased in postoperative AKI patients with cardiac surgery but not in stable renal function.⁴² Similar to KIM-1, NAG was also associated with increased risk of death or hospitalization in chronic heart Failure.⁴⁶

IL-18 has shown inconsistent results in prediction of postoperative AKI in cardiac surgery patients.^{42,47} It was reported that using combined biomarkers (KIM-1, NAG, and NGAL) for early detection of postoperative AKI enhanced the sensitivity compared to using single biomarkers.⁴¹ Other biomarkers that have proved useful include neutrophil gelatinase-associated lipocalin (NGAL) and fatty acid-binding protein (FABP).

Three different *natriuretic peptides* (NPs) have been identified: atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and N-terminal fragment proBNP (NT-proBNP). Carr SJ et al. demonstrated that the plasma BNP level predicted the overall mortality and cardiovascular events in patients with predialysis CKD without clinical signs of heart failure.⁴⁸ A recent study also indicated that NT-proBNP was a more powerful predictor for mortality and cardiovascular death in asymptomatic dialysis patients compared with cardiac troponin T (cTnT).⁴⁹

Management

Acute Cardiorenal Syndrome: Type I

Preventive Approaches

The basic principles include avoidance of volume depletion, removal of superimposed renal toxic agents, minimization of the toxic exposure (iodinated contrast, time on cardiopulmonary bypass) and the use of antioxidant agents such as N-acetylcysteine and BNP in the perioperative period after cardiac surgery.^{50,51} Use of continuous renal replacement therapy (CRRT) provides three important protective mechanisms that cannot be achieved pharmacologically as follows: (1) it ensures euvolemia and avoids hypo- or hypervolemia; (2) it provides sodium and solute (nitrogenous waste products) removal and (3) by both mechanisms above, it may work to avoid both passive renal congestion and a toxic environment for the kidneys.⁵²

Management

Type I CRS appears in the setting of ADHF or cardiogenic shock for a number of reasons, with hemodynamic derangements ranging from acute pulmonary edema with hypertension through severe peripheral fluid overload to cardiogenic shock and hypotension. The goal of diuretic use should be to deplete the extracellular fluid volume at a rate that allows adequate time for intravascular refilling from the interstitium. To achieve adequate diuresis, infusions of

loop diuretics have been demonstrated to have greater efficacy than intermittent dosing.⁵³

If kidney function continues to worsen, blockade of the RAAS may be a contributing factor, necessitating withholding or delaying the introduction of angiotensin-converting-enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) in order to maintain the GFR.

Type I CRS patients with preserved or elevated blood pressure, vasodilators such as nitroglycerin and nitroprusside are often used to relieve symptoms and improve hemodynamics. When patients have low blood pressure and poor renal perfusion, positive inotropes such as dobutamine or phosphodiesterase inhibitors may be required.⁵⁴

Chronic Cardiorenal Syndrome: Type II

Preventive Approaches

Pharmacologic therapies that have been beneficial for chronic CVD have been either neutral or favorable to the kidneys including use of RAAS antagonists, beta-adrenergic blocking agents and statins. Furthermore, other strategies include glycemic control in diabetes and blood pressure control in those with hypertension.⁵⁵

Management

Interruption of the RAAS is the primary aim in the management of Type II CRS. However, RAAS blockade can lead to significant decrease in kidney function and/or elevated potassium. However, creatinine tended to stabilize, and in many instances, improved over the course of the study. In terms of aldosterone blockade, drugs such as spironolactone and eplerenone are important adjuncts to therapy in patients with severe heart failure. Both CHF and CKD are associated with anemia, which is commonly treated with erythropoiesis-stimulating agents. Furthermore, the action of erythropoietin in the heart may reduce apoptosis, fibrosis and inflammation. Hence, there has been intense interest in using erythropoiesis-stimulating agents in heart failure patients.⁵⁶

Acute renocardiac Syndrome: Type III

Preventive Approaches

The major management principle concerning this syndrome is intra and extravascular volume control with either use of diuretics and forms of extracorporeal volume and solute removal (CRRT, ultrafiltration, hemodialysis). In the setting of AKI, prevention of left ventricular volume overload is critical to maintain adequate cardiac output and systemic perfusion and avoid the viscous downward spiral in both cardiac and renal function.⁵⁷

Management

In Type III CRS, AKI occurs as a primary event (e.g. acute glomerulonephritis) or secondary event (e.g. radiocontrast, exogenous or endogenous nephrotoxins, postsurgical etc.) and cardiac dysfunction is a common and often times fatal sequelae. A common example of Type III CRS occurring in the hospital setting is contrast nephropathy, particularly in patients undergoing coronary and other angiographic procedures who have risk factors such as pre-existing CKD, diabetes, older age or volume contraction. In these susceptible populations, prevention may provide the best opportunity to “treat” or avoid Type III CRS. Many potential preventive strategies have been studied, including parenteral hydration (hypotonic or isotonic saline or bicarbonate), diuretics, mannitol, natriuretic peptides, dopamine, fenoldopam, theophylline and N-acetylcysteine.⁵⁸

Chronic Renocardiac Syndrome: Type IV

Preventive Approaches

Optimal treatment of CKD with blood pressure and glycemic control, RAAS blockers and disease-specific therapies, when indicated, are the best means of preventing this syndrome. Morbidities of CKD, including bone and mineral disorder and anemia, should be managed according to CKD guidelines.^{59,60}

Management

The management of Type IV CRS is a multifaceted approach focusing on the decline of cardiovascular risk factors and complications common to CKD patients. These include anemia, hypertension, altered bone and mineral metabolism, dyslipidemia, smoking, albuminuria and malnutrition.⁶¹ Several therapies targeting such uremic complications as anemia, homocysteine, calcium-phosphate product and hyperparathyroidism are supported by studies demonstrating the association between adverse cardiovascular events and these conditions.

Secondary Cardiorenal Syndromes: Type V

Preventive Approaches

There are no proven methods to prevent or ameliorate this form of CRSs at this time. Supportive care with a judicious intravenous fluid approach and the use of pressor agents as needed to avoid hypotension are reasonable but cannot be expected to avoid AKI or cardiac damage.⁶²

Management

Type V CRS includes a heterogeneous group of disorders such as sepsis, SLE, amyloidosis and diabetes mellitus. Sepsis is one of the more common acute disorders that involves multiple organs, and often causes co-dysfunction

of kidneys and heart. Recognition of Type V CRS as an entity in sepsis and other systemic disorders will allow further research into the signaling and mechanisms of injury and allow for the development of rational and efficient therapies.

Conclusion:

Cardiorenal syndrome is an interdependent involvement of both the heart and the kidney in a spiral fashion. Decrease in GFR or creatinine clearance in patients with decompensated heart failure involves longer hospital stays, higher hospital costs, higher in-hospital mortality rates and more readmissions but still the prognosis is grave. Earlier use of slow high-dose intravenous diuretics, dialysis with ultrafiltration for treatment of congestion, inotropes and left ventricular assisted device to stabilize the hemodynamics and maintenance of the renal perfusion is the vital component for a short period of time, which is a clinical challenge of initial management. Recent studies have identified and characterized several novel biomarkers for HF and AKI. These advances will herald better understanding, diagnosis, and treatment of CRS. It is anticipated that these biomarkers will help make an earlier diagnosis of CRS possible, as well as identify the specific type of CRS. It is hoped that some of these new biomarkers will either provide sufficient risk prediction or early diagnosis of all patients for novel preventive and treatment strategies to ameliorate the course of CRS, and subsequently, the long-term outcome.

Conflict of Interest : None

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