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EDITORIAL

Cardiorenal syndromes

Peter A McCullough, Aftab Ahmad

Peter A McCullough, Aftab Ahmad, Department of Medicine, Cardiology Section, St. John Providence Health System, Providence Park Hospital, Novi, MI 48374, United States
Author contributions: All authors contributed equally to this work.
Correspondence to: Peter A McCullough, MD, MPH, Department of Medicine, Cardiology Section, St. John Providence Health System, Providence Park Hospital, Institute, 47601 Grand River Avenue, Suite B-125, Novi, MI 48374, United States. peteramccullough@gmail.com
Telephone: +1-248-4655485 Fax: +1-248-4655486
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Abstract

Cardiorenal syndromes (CRS) have been subclassified as five defined entities which represent clinical circumstances in which both the heart and the kidney are involved in a bidirectional injury and dysfunction *via* a final common pathway of cell-to-cell death and accelerated apoptosis mediated by oxidative stress. Types 1 and 2 involve acute and chronic cardiovascular disease (CVD) scenarios leading to acute kidney injury or accelerated chronic kidney disease. Types 2 and 3 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. Both blood and urine biomarkers are reviewed in this paper and offer a considerable opportunity to enhance the understanding of the pathophysiology and known epidemiology of these recently defined syndromes.

Key words: Heart diseases; Kidney diseases; Cardiovascular diseases; Biological biomarkers; Creatinine

INTRODUCTION

Both cardiac and renal diseases commonly present in the same patient and have been associated with increased costs of care, complications, and mortality[1,2]. Cardiorenal syndromes (CRS), describing the dynamic inter-relationship between heart and kidney malfunction have been defined in a recent consensus process by the Acute Dialysis Quality Initiative (ADQI)[3]. This has generated five distinct syndromes upon which the epidemiology of CRS can be described. This paper will review this new classification and give concrete examples of each CRS, and discuss the available data on incidence and risk predictors. Finally, a succinct review of promising biomarkers will be presented that are very likely to change the described CRS epidemiological literature as we know it, based largely upon the measurement of a single blood biomarker-serum creatinine.

CLASSIFICATION OF CARDIORENAL SYNDROMES

The term cardiorenal syndromes suggests the presence of multiple syndromes with subtypes denoted by dysfunction of the principal organ (cardiac or renal or both) as well as the relative acuity of the condition. Both organs

must have or develop pathological abnormalities to fulfill the criteria for definition. The umbrella term "cardiorenal syndromes" was 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". Five subcategories of CRS are given below. Proposed pathophysiological mechanisms are described in Figure 1 for each syndrome.

POORLY LIGANDED, LABILE, CATALYTIC IRON AS THE BASIS OF OXIDATIVE STRESS REACTIONS

As shown in Figure 1, it has been recently determined that the process of oxidative stress resulting in cell dysfunction, accelerated apoptosis, and cell death is reliant on the cytosolic and extracellular presence of labile or catalytic iron. There are several steps in generation of reactive oxygen species (ROS). Oxygen may be reduced to form superoxide anion, which can then either dismutate or go through another reduction reaction by superoxide dismutase to form hydrogen peroxide which itself can then be reduced through several pathways. Overall, the net Fritz-Haber reaction is slow and in the presence of reduced transition metals such as ferric iron (Fe^{3+}), a Haber-Weiss reaction results in the formation of the highly damaging hydroxyl radical from the superoxide anion. Then in the presence of ferrous iron (Fe^{2+}), a Fenton-type reaction converts hydrogen peroxide to the highly damaging hydroxyl radical. Further reduction of the hydroxyl radical finally ends in the formation of water. It has been theorized that a common element to all forms of oxidative stress in the heart and kidneys involves the availability of unbound iron[4]. The body has an intricate management system for iron metabolism keeping it bound in transport proteins, heme, and cellular organelles for normal functioning[5,6]. If small amounts of iron are released from adjacent injured cells and not bound, this poorly liganded (labile or catalytic) iron in either the ferric or ferrous states, can facilitate the rapid generation of oxygen free radicals and the propagation of oxidative stress and injury across regions of vascular tissue[7]. Thus, it is possible that the fundamental pathophysiological basis for CRS is the loss of control over normal iron management after insults to either the heart or the kidneys in the form of hypoxia, chemotoxicity, or inflammation.

It has been interesting to note that intravenous infusions of iron in the form of iron dextran, iron sucrose, iron gluconate, and iron dextrin (polymaltose) have been proposed as a treatment for anemia in patients with heart failure. While in general the trials have demonstrated improvement in either anemia, symptoms, or both, there are as yet no published outcomes data[8]. Several studies have demonstrated that intravenous infusions of iron in normal volunteers and hemodialysis patients have resulted in a transient 3-4 fold rise in systemic levels of catalytic iron[9-11]. The clinical consequences of iron infusions and catalytic iron in heart failure (HF) patients, if any, are unknown at this time.

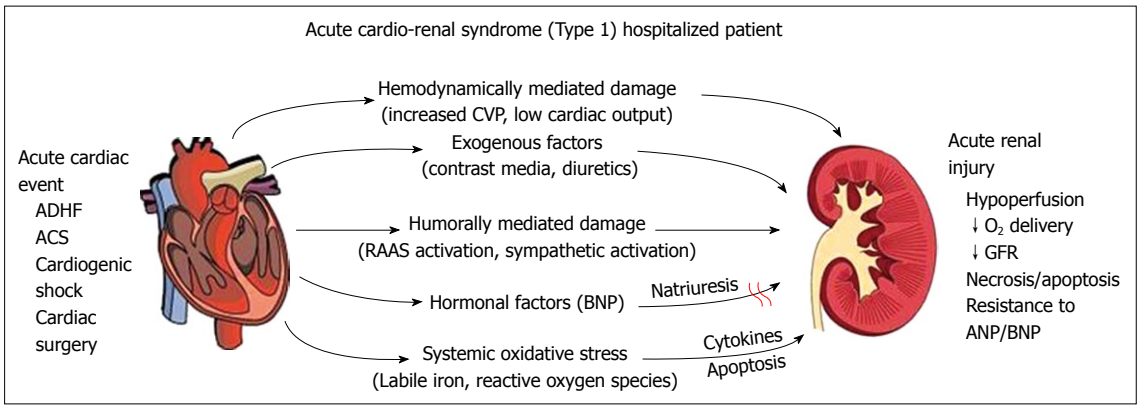
CATEGORIES OF SYNDROMES

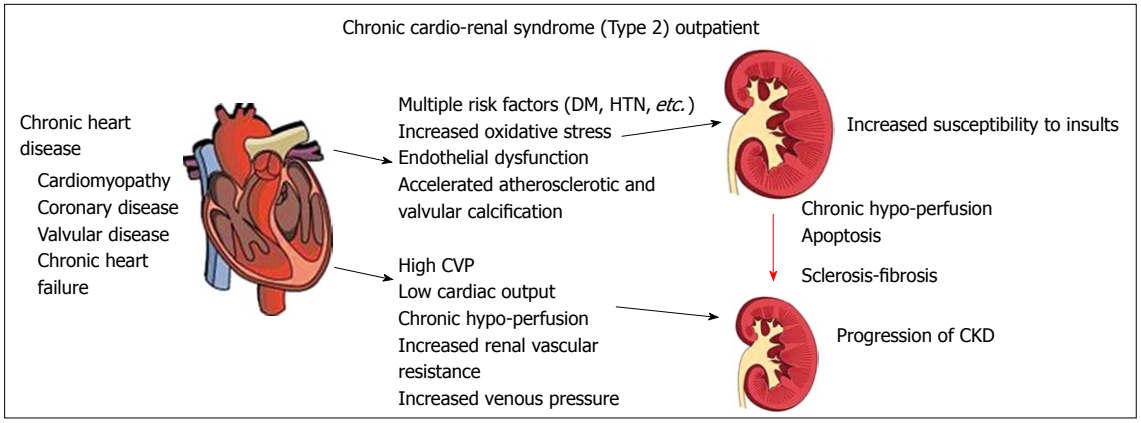
The broad and most important concepts of CRS include the following: (1) bidirectional organ injury or malfunction; (2) an inciting event for acute CRS; and (3) a precipitous decline in function for acute or chronic CRS.

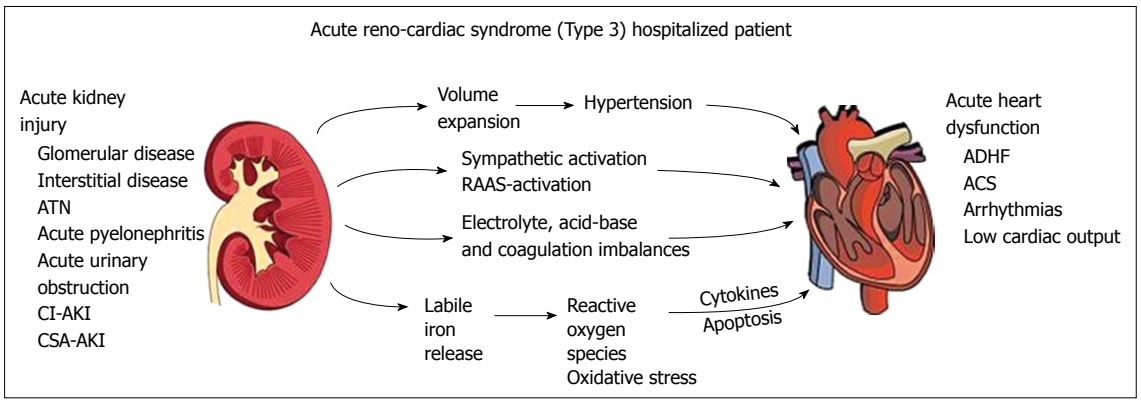
Acute cardiorenal syndrome

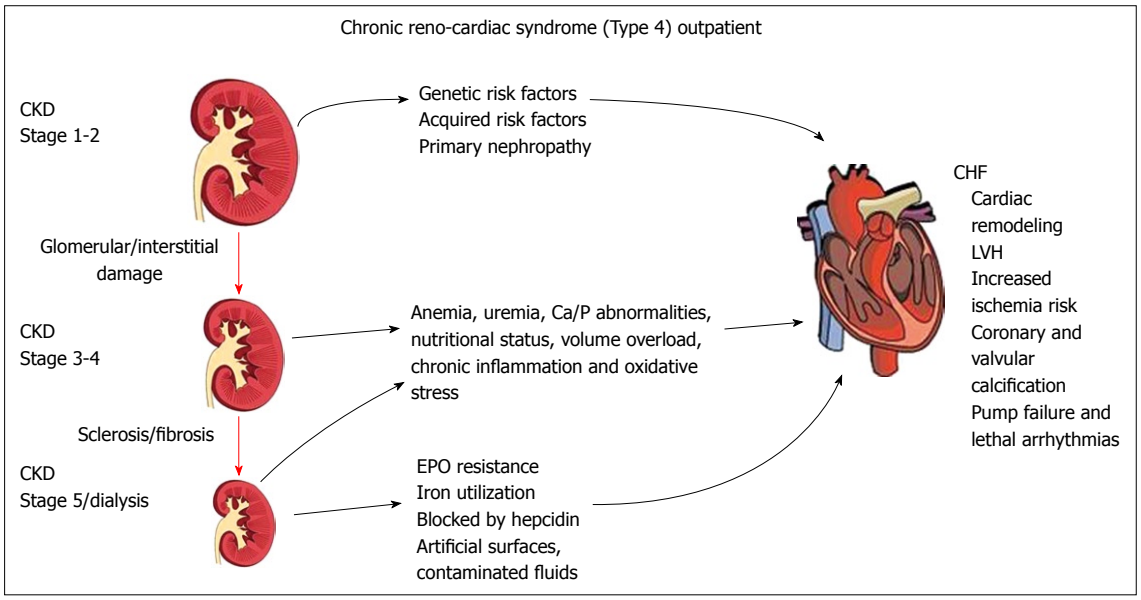
Acute cardiorenal syndrome (CRS Type 1): acute decompensation of cardiac function leading to acute renal failure. This is a syndrome of worsening renal function that frequently complicates acute decompensated heart failure (ADHF) and acute coronary syndrome (ACS). Seven observational studies have reported on the frequency and outcomes of CRS Type 1 in the setting of ADHF and five in ACS[4]. Depending on the population, 27%-40% of patients hospitalized for ADHF develop acute kidney injury (AKI) as defined by an increase in serum creatinine of $\geqslant$ 0.3 mg/dL[12,13]. Risk predictors for this complication include reduced baseline renal function, diabetes, and prior HF[13]. These patients experience more complicated hospital courses, longer inpatient stays, and higher mortality. In the Prospective Outcomes Study in Heart Failure (POSH) study, only in those with ADHF and a hospital course complicated by circulatory shock, hypotension, cardiac arrest, sepsis or ACS, a rise in serum creatinine did confer a higher 6-mo mortality[14]. Conversely, those with an increase in serum creatinine of $\geqslant$ 0.3 mg/dL but no other complications did not have higher mortality in the hospital, at 30 or 180 d. Thus, much of CRS Type 1 mortality is confounded by a complicated course and AKI. Importantly, it has been noted that CRS Type 1 in ADHF rarely occurs in the prehospital phase, and is observed after hospitalization, implying that some factor associated with hospitalization, namely diuresis, precipitates CRS. The use of loop diuretics, probably by further activation of the renin-angiotensin system and possibly worsening intra-renal hemodynamics, have been identified as one of the modifiable in-hospital determinants of CRS Type 1[15]. Testani *et al*[16] have recently shown in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial that the use of higher doses of loop diuretics, causing hemoconcentration, resulted in a 5-fold increased rate of worsening renal function. However, in this prospective trial of hemodynamic monitoring, aggressive diuresis was associated with a 69% reduction in mortality at 180 d. Several studies have now linked the presence of 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 drop in renal filtration that occurs during hospitalized treatment of ADHF[17].

The other major clinical scenario where CRS Type 1 develops is in the setting of urgent or elective coronary


Acute cardio-renal syndrome (Type 1) hospitalized patient
Acute cardiac event
ADHF
ACS
Cardiogenic shock
Cardiac surgery
Hemodynamically mediated damage
(increased CVP, low cardiac output)
Exogenous factors
(contrast media, diuretics)
Humorally mediated damage
(RAAS activation, sympathetic activation)
Hormonal factors (BNP)
Natriuresis
Systemic oxidative stress
(Labile iron, reactive oxygen species)
Cytokines
Apoptosis
Acute renal injury
Hypoperfusion
↓ O_2 delivery
↓ GFR
Necrosis/apoptosis
Resistance to ANP/BNP


Chronic cardio-renal syndrome (Type 2) outpatient
Chronic heart disease
Cardiomyopathy
Coronary disease
Valvular disease
Chronic heart failure
Multiple risk factors (DM, HTN, *etc.*)
Increased oxidative stress
Endothelial dysfunction
Accelerated atherosclerotic and valvular calcification
Increased susceptibility to insults
Chronic hypo-perfusion
Apoptosis
Sclerosis-fibrosis
High CVP
Low cardiac output
Chronic hypo-perfusion
Increased renal vascular resistance
Increased venous pressure
Progression of CKD


Acute reno-cardiac syndrome (Type 3) hospitalized patient
Acute kidney injury
Glomerular disease
Interstitial disease
ATN
Acute pyelonephritis
Acute urinary obstruction
CI-AKI
CSA-AKI
Volume expansion
Hypertension
Sympathetic activation
RAAS-activation
Electrolyte, acid-base and coagulation imbalances
Labile iron release
Reactive oxygen species
Oxidative stress
Cytokines
Apoptosis
Acute heart dysfunction
ADHF
ACS
Arrhythmias
Low cardiac output


Chronic reno-cardiac syndrome (Type 4) outpatient
CKD
Stage 1-2
Genetic risk factors
Acquired risk factors
Primary nephropathy
Glomerular/interstitial damage
CKD
Stage 3-4
Anemia, uremia, Ca/P abnormalities, nutritional status, volume overload, chronic inflammation and oxidative stress
Sclerosis/fibrosis
CKD
Stage 5/dialysis
EPO resistance
Iron utilization
Blocked by hepcidin
Artificial surfaces, contaminated fluids
CHF
Cardiac remodeling
LVH
Increased ischemia risk
Coronary and valvular calcification
Pump failure and lethal arrhythmias

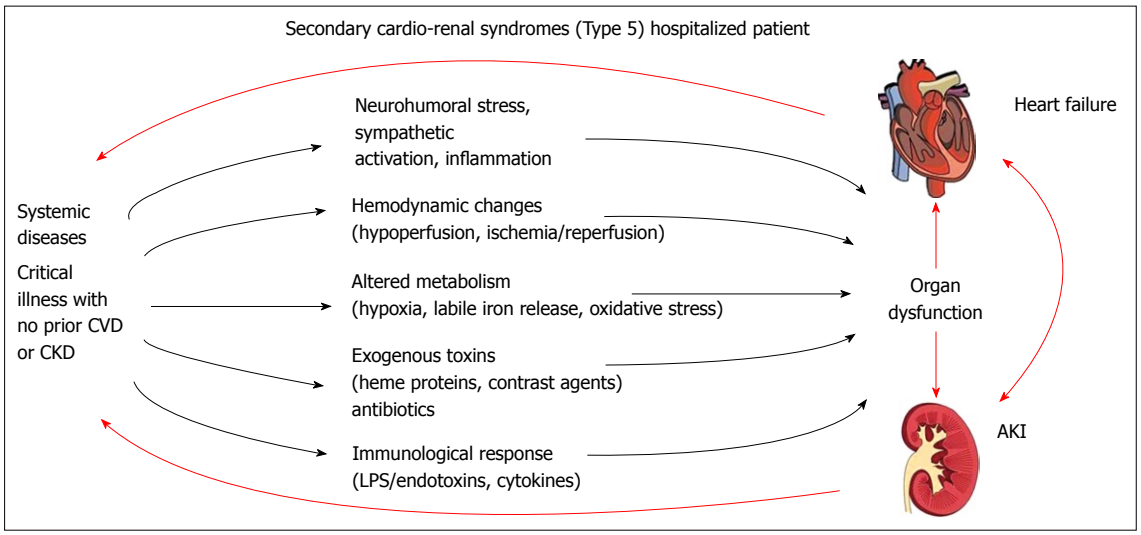


Figure 1 Pathophysiology and definitions of the five subtypes of cardiorenal syndromes. CVP: Central venous pressure; GFR: Glomerular filtration rate; BNP: Brain natriuretic peptide; ANP: Atrial natriuretic peptide; RAAS: Renin-angiotensin-aldosterone system ; ADHF: Acute decompensated heart failure; ACS: Acute coronary syndrome; CKD: Chronic kidney disease; CVD: Cardiovascular disease; ATN: Acute tubular necrosis; CI-AKI: Contrast-induced acute kidney injury; CSA-AKI: Cardiac surgery-associated AKI; CHF: Chronic heart failure; LVH: Left ventricular hypertrophy; EPO: Erythropoietin; LPS: Lipopolysaccharide.

revascularization for acute or chronic coronary disease. Acute contrast-induced and cardiopulmonary bypass surgery-associated AKI occur in 15% and 30% of patients, respectively[18,19]. Importantly, iodinated contrast which causes renal vasoconstriction and direct cellular toxicity to renal tubular cells is an important pre-existing factor in the few days before cardiac surgery. Cardiac surgery exposes the kidneys to hypothermic, pulseless reduced perfusion for 30-90 min, and thus represents a superimposed ischemic injury in the setting of a pro-inflammatory state[20]. It is possible that the extracorporeal circuit used in cardiopulmonary bypass surgery activates systemic factors that further induce AKI; however, attempts to limit this exposure have not resulted in significantly reduced rates of AKI[21]. Thus, these two scenarios are tightly linked, since almost every cardiac surgery patient operated upon in the urgent setting undergoes coronary angiography in the hours to days before surgery[22]. As with ADHF, CRS Type 1 in acute and chronic coronary disease has a confounded relationship with outcomes. In those with complications, CRS Type 1 appears to be independently associated with a 3 to 4-fold increase in mortality despite the availability of dialysis in the hospital[23,24]. In all forms of CRS Type 1, there is a risk of advancing to higher stages of CKD and ultimately the need for chronic renal replacement strategies[25]. The incremental and cumulative risk of these renal outcomes according to the clinical scenarios described above for an individual patient are unknown. Thus the important points concerning the epidemiology 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[26-28].

Chronic cardiorenal syndrome

Chronic cardiorenal syndrome (CRS Type 2): chronic abnormalities in myocardial function leading to worsened chronic kidney disease (CKD). This subtype implies that chronic CVD can contribute to the development of CKD. Six observation studies have reported on CRS Type 2, with a minority of reports reporting on CVD contributing to an excess risk of CKD[4]. It is recognized that the risk factors for atherosclerosis, namely diabetes, hypertension, and smoking are independently associated with the development of CKD[29]. 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[30]. Approximately 30% of those with chronic cardiovascular disease (CVD) meet a definition of CKD, and multiple studies have demonstrated the independent contribution of CVD to the worsening of CKD[31]. An important component of CRS Type 2 epidemiology is that CKD appears to accelerate the course of atherosclerosis and result in premature CVD events including myocardial infarction and stroke[32,33]. Importantly, 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[34]. Of these factors, phosphate retention appears to be the critical pathophysiological component stimulating the conversion of vascular smooth

muscle cells to osteoblastic-like cells which, *via* the Pit-1 receptor, are stimulated to produce extracellular calcium hydroxyapatite crystals in the vascular smooth muscle layer of arteries[35,36]. Thus, patients as a part of CRS type 2, more commonly have vascular calcification, less vascular compliance, and a higher degree of chronic organ injury related to blood pressure elevation and shear stress[37]. Despite these mechanisms specific to CRS, CRS Type 2 remains 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[38].

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 m^2[39]. Multiple studies have demonstrated that CKD is closely linked to more frequent hospitalizations and complications from pump failure and arrhythmias[40,41]. In addition, patients with CKD and end-stage renal disease have higher defibrillation thresholds and may not have the protective benefit of implantable cardio defibrillators as those with normal renal function[42]. Increased degrees of left ventricular hypertrophy and cardiac fibrosis are believed to be the biologic basis for these electrophysiological findings[43].

Acute renocardiac syndrome

Acute renocardiac syndrome (CRS Type 3): acute worsening of renal function leading to cardiac events. The most common scenario for CRS Type 3 is the development of 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. Volume overload alone has been shown to induce cardiac failure and reflect CRS Type 3 most clearly in the pediatric population[44]. However, in adults, when acute on chronic disease is a common occurrence, it is difficult to identify clear cases where AKI lead to cardiac decompensation. It is also possible that CRS Type 3 could precipitate in an acute coronary syndrome, stroke, or other acute cardiac event. Thus the epidemiology of this CRS subtype is not well defined for individual CVD events such as ACS, stroke, cardiac rehospitalization, arrhythmias, pump failure, and cardiac death[4].

Chronic renocardiac syndrome

Chronic renocardiac syndrome (CRS Type 4): chronic renal disease leading to the progression of cardiovascular disease. Over the past several decades there has been recognition of a graded and independent association between the severity of CKD and incidence as well as prevalence of CVD[2]. In a meta-analysis of 39 studies (1 371 990 participants), there was a clear relationship between the degree of renal dysfunction and the risk for all-cause mortality[45]. The unadjusted relative risk of mortality in participants with reduced kidney function was in excess of the reference group in 93% of cohorts. Fourteen of the 39 studies described the risk of mortality from reduced kidney function, after adjustment for other established risk factors. Although adjusted relative hazard ratios were on average 17% lower than unadjusted relative risks, they remained significantly greater than unity in 71% of cohorts. The overall mortality was influenced greatly by excess cardiovascular deaths, which constituted over 50% of cases. Thirteen studies have been identified as specifically reporting on CRS Type 4, most of which were in populations with end-stage renal disease[4]. It should also be recognized, that CKD contributes to CVD outcomes in CRS Type 4 by complicating pharmacological and interventional treatment[46,47]. For example, azotemia and hyperkalemia restrict the use of drugs that antagonize the renin-angiotensin system, thus fewer patients with CKD enjoy the cardiovascular benefits of angiotensin converting enzyme inhibitors, angiotensin Ⅱ receptor antagonists, and aldosterone receptor blockers[48,49]. It has been shown that CKD also worsens the presentation, severity, response to treatment, and cardiorenal outcomes in acute and chronic hypertension[50,51]. In addition, the perceived risks of AKI lead patients with CKD towards conservative management strategies which have been associated with poor outcomes in the setting of both acute and chronic coronary artery disease[52]. Finally, a recent study of silent brain injury (asymptomatic cerebral infarctions by magnetic resonance imaging) has been associated with a rapid decline in renal function in approximately 30% of patients[53]. This suggests the possibility that cerebrovascular disease could in some way contribute to more rapid progression of CKD.

Secondary cardiorenal syndrome

Secondary cardiorenal syndrome (CRS Type 5): 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. This is almost always in the setting of critical illness such as sepsis, multiple trauma, or burns. There are limited data on the incidence and determinants of CRS Type 5, in part because of confounders such as hypotension, respiratory failure, liver failure, and other organ injury beyond the cardiac and renal systems. This results in a difficult human model for investigation. Sepsis as a precipitator of CRS Type 5 is common and its incidence is increasing, with a mortality estimated at 20%-60%[54,55]. Approximately 11%-64% of septic patients develop AKI that is associated with a higher morbidity and mortality[56]. Abnormalities in cardiac function are also common in sepsis including wall motion abnormalities and transient reductions in left ventricular ejection fraction[57]. Observational data have found approximately 30%-80% of individuals with sepsis have measurable blood troponin I or T that are above the 99th detection limits[58]. These elevated cardiac biomarkers have been associated with reduced left ventricular function and higher mortality even in patients without known coronary

Table 1 Novel biomarkers of acute cardiac and renal injury

Biomarker	Mechanism of action	Advantages	Diagnostic approach	Potential therapeutic approaches
Catalytic (labile, poorly-liganded) iron	Leads to generation of the hydroxyl radical, the most destructive of ROS; released into the blood in patients with ACS[63]; thought to be involved in oxidative organ damage also in AKI[64]; local cellular and tissue availability of catalytic iron are likely to determine the degree and severity of organ injury in the setting of most hypoxic and other toxic insults[65]	In patients with ACS, the appearance of catalytic iron precedes the rise in serum troponin and detects acute myocardial infarction with an area under the ROC curve of > 90%[63]	Detection of non-transferrin-bound iron in blood by the bleomycin assay[63]	Use of iron chelators to diminish oxidative injury[66]
NGAL (lipocalin-2, siderocalin)	Natural siderophore produced by renal tubular cells that reduces the availability of catalytic iron, thus limiting oxidative damage and limiting bacterial growth	One of the earliest kidney markers of cardiac and renal injury in animals[65]; detected in humans shortly after AKI and predicts need for in-hospital dialysis[66]	Detection in blood and urine[67]	Overexpression reduces oxidative stress in ischemic injury[67]
Cystatin C	Cysteine protease inhibitor (housekeeping protein) produced by all nucleated cells that is freely filtered by the glomerulus and reabsorbed in the proximal tubule; no tubular secretion	Not dependent on muscle mass; better predictor of risk of adverse events in patients with CVD than creatinine or eGFR[68]	Detection in blood	-
KIM-1	Transmembrane glycoprotein not normally detected in urine[69]; detected in urine early after ischemic or nephrotoxic injury to cells of the proximal tubule[69]	Highly specific for AKI caused by systemic illnesses such as sepsis and not for pre-renal azotemia or drug-induced renal injury[68]; May be elevated before histologic evidence of proximal tubular cell death[69]	Detection in urine	-
NAG	Large lysosomal brush-border enzyme found in cells of the proximal tubule, not normally filtered by the glomerulus; elevated concentrations found in urine in the setting of AKI, CKD, diabetes mellitus, hypertension and heart failure[71]	Marker of the degree of tubular damage	Detection in urine	-
IL-18	Pro-inflammatory cytokine found in urine after acute ischemic damage to proximal tubules[72]; associated with AKI-related mortality, although not organ-specific[69]; might be involved in myocardial cell damage in the setting of ACS[73]	Sensitive and specific to detect ischemic AKI with an area under the ROC curve of 0.78[70]; levels rise 48 h before those of creatinine[68]	Detection in urine	Inhibitors expressed in stem cells are protective in models of myocyte injury[73]
L-FABP	Selectively binds free unsaturated fatty acids and products of lipid oxidation in cells in the setting of hypoxic tissue injury; detected in the urine in the setting of AKI[74]	Might predict dialysis-free survival in patients with AKI[75]	Detection in urine	-
Tubular enzymuria	Several enzymes, such as gamma glutamyl transpeptidase, alkaline phosphatase, lactate dehydrogenase, and α and π glutathione S-transferases are released from tubular cells[76-78]	A combination of measures of enzyme levels could potential indicate the presence and location of kidney injury[79]	Detection in urine	-

eGFR: Estimated glomerular filtration rate; KIM-1: Kidney injury molecule 1; IL-18: Interleukin-18; L-FABP: Liver-fatty acid binding protein; NAG: N-acetyl-β-(D)glucosaminidase; NGAL: Neutrophil gelatinase-associated lipocalin; ROC: Receiver operating characteristic; ROS: Reactive oxygen species.

disease[59-61]. Importantly, volume overload as a result of aggressive fluid resuscitation appears to be a significant determinant of CRS Type 5. Among 3147 patients enrolled in the Sepsis Occurrence in Acutely Ill Patients (SOAP), there was a 36% incidence of AKI, and volume overload was the strongest predictor of mortality[59]. Iatrogenic volume overload appears to play an important additional role, possibly along the lines described for CRS Type 1 and passive venous congestion of the kidney, in the pathogenesis of AKI. At the same time, volume overload increases left ventricular wall tension and likely contributes to cardiac decompensation in those predisposed to both systolic and diastolic HF[60]. In summary for CRS Type 5, both AKI and markers of cardiac injury followed by volume overload are common in sepsis, with each being associated with increased mortality. However, there is a current lack of integral information on the incidence of bidirectional organ failure and its pathophysiological correlates in a variety of acute care settings.

BIOMARKERS OF CARDIORENAL SYNDROMES

There is considerable interest in blood and urine biomarkers to detect CRS. For decades, the rise in serum creatinine has been the only detectable sign of a reduction in glomerular filtration. Creatinine has had the disadvantages of being linked to creatine and overall body muscle mass, hence varying according to body size in addition to the rate of renal elimination[61]. Furthermore, the kidney both filters and secretes creatinine. Finally, the assays used to measure creatinine have not be standardized across laboratories, therefore studies reporting values from multiple centers have inherent variation in values attributed to dif-

ferences in measurement technique[62]. Hence, there is a clear need for better laboratory markers of renal filtration. An ideal marker would be independent of muscle mass, reflect actual renal filtration at the time of measurement, and be sensitive to changes in actual GFR in order to alert clinicians to a meaningful change shortly after it occurs.

Unlike cardiac biomarkers indicating myocardial injury and overload (troponin, creatine kinase myocardial band, natriuretic peptides), the field of nephrology has been devoid of approved blood or urine markers of AKI. Thus the current paradigm is that when renal injury occurs, clinicians must wait to observe a reduction in GFR before AKI is inferred. The concept of measuring markers of the acute injury process is crucial to the early upstream identification of AKI before there is serious loss of organ function[63]. Table 1 is a summary of relatively novel renal markers and what is known about them in acute cardiac and renal injury. Their use in the years to come will undoubtedly influence the epidemiology of CRS.

IMPACT ON HOSPITAL MEDICINE

Cardiorenal syndromes as described in this paper are not spontaneous or primary conditions that arise in free-living populations. Acute CRS appears to occur once hospitalization and its associated care have occurred. Thus, there are determinants and clear precipitants to these syndromes that are potentially controllable by clinicians. Improved education and awareness concerning the risk factors and presence of CKD holds great promise for patients and clinicians to avoid contributors to CRS such as excess sodium intake, and use of intensive loop diuretics, nonsteroidal anti-inflammatory agents, thiazolidinediones, and iodinated contrast. The National Kidney Foundation Kidney Early Evaluation Program is a nationwide and now global community-based screening program that evaluates volunteers for CKD and its risk factors, with effective education for participants and their physicians[64]. This program, as it evolves and broadens, has a considerable opportunity to lessen the frequency of avoidable CRS in the future by spurring community awareness and clinical appreciation for CKD. Finally, the most important public health question concerning this field is wether or not a lessening of the frequency or severity of AKI will reduce hospital length of stay, cardiovascular, renal, and all-cause morbidity and mortality. Large scale clinical trials of preventive therapies that consign broad composite primary endpoints with biomarkers as secondary endpoints are needed to answer this pivotal question.

CONCLUSION

The ADQI consensus on CRS has yielded a framework for a better understanding of the epidemiology of the five subtypes of CRS[3]. A description of the epidemiology of the heart-kidney interaction is critical to our understanding of the overall disease burden associated with these specific CRS subtypes, and will guide future investigations into their pathophysiology, diagnosis, prognosis, and 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.

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