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Cardiorenal syndrome-Pathophysiology

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Keywords

Cardiorenal; venous congestion; intraabdominal pressure; RAAS; oxidative stress; inflammatory mediators; uremic toxins

INTRODUCTION

The earliest mention of the term cardiorenal syndrome (CRS) came about from a 2004 National Heart, Lung, and Blood Institute Working Group conference evaluating the interaction between the heart and kidney.[1] The term is used to commonly refer to the collective dysfunction of heart and kidneys resulting in a cascade of feedback mechanisms causing damage to both the organs. Previously proposed definitions of CRS stressed the effects a diseased heart on causing dysfunction of the kidney with heart failure (HF) being the prototypical cardiovascular disease leading to kidney dysfunction from CRS. However, with further understanding of the pathophysiology of the disorder, it is now recognized that either the heart or the kidney can be the primary source of insult. Although the term CRS is often used globally to address the pathophysiologic interaction between the two organs, a recent classification of CRS proposed by the 7th Acute Dialysis Quality Initiate consensus conference has divided the syndromes into those that are “cardiorenal” (Figure 1) referring to when cardiac dysfunction leads to kidney dysfunction and those that are “renocardiac” (Figure 2) referring to when primary kidney dysfunction leads to cardiac dysfunction.[2,3] These syndromes are further classified based on their acuity and the presence of a systemic (non-cardiac, non-renal) illness that may play a role in the pathophysiology (Figure 3). However, often the causal relationship (cardiorenal vs. renocardiac) may not be ascertainable when risk factors like diabetes, hypertension and atherosclerosis affect the function of both organs in parallel leading to a common clinical picture. [4,5]

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Given the aging population, longer cumulative exposure to common risk factors including hypertension, obesity, diabetes and vascular disorders, and advances in medical therapy, procedures and devices to assist patients with HF live longer, the prevalence of CKD and HF are likely to continue to rise. [6,7] It is hence important to understand the various mechanisms involved in the propagation of this syndrome. In this manuscript, the authors will review the role of the heart and kidney in the development of different CRS, and the interplay between the complex pathophysiologic pathways resulting in vicious cycle and end organ damage.

EVALUATING A CHANGE IN KIDNEY FUNCTION

Acute kidney injury (AKI) refers to an abrupt reduction of kidney function, resulting in the retention of the urea and other nitrogenous toxins, dysregulation of the electrolytes and retention of extracellular volume. Several consensus definitions of AKI have been established using serum creatinine and urine output to accurately identify the patients with AKI in clinical settings as well as in epidemiologic and outcomes studies. The Kidney Disease: Improving Global Outcomes (KDIGO) [8] definition is currently the most commonly used and is defined as follows:

- Increase in serum creatinine by ≥0.3 mg/dl (≥26.5 micromol/l) in a 48 hours period, or
- Increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior seven days, or
- Urine volume <0.5 ml/kg/hour for six hours

KDIGO criteria further stage AKI in to three categories as shown in Table 1. [8]

However, there are concerns about the utility of serum creatinine as a biomarker to diagnose AKI in persons with HF. Volume overload in the setting of HF may lead to seemingly normal or even low creatinine values. Unmasking the effect of dilution is often mistaken for AKI leading to a decrease in dose or cessation of diuretics, which may be inappropriate.[9] In fact, patients with acute decompensated HF (ADHF) that are left with residual congestion have increased mortality and risk of readmission, [10,11]

The majority of patients with ADHF presents with signs and symptoms of fluid overload and is treated with diuretic therapy. [12] Up to 33% of patients may have an elevation in creatinine during treatment. [5] While this elevation can meet KDIGO criteria for AKI, the cardiology literature often refers to this as worsening renal function (WRF) because it is not clear there is evidence of kidney injury with every creatinine elevation and often the rise in creatinine is thought to be a hemodynamic effect. [7] Further confounding the issue is that a reduced muscle mass and protein intake and elevated levels of inflammation are common in advanced HF, and may be exacerbated by acute deteriorations in heart and kidney function and frequent hospitalizations. Alterations in these parameters may result in changes in serum creatinine leading to errors in estimated glomerular filtration rate (eGFR) thus negatively impacting care and outcomes for patients with HF and kidney disease.

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CKD is defined by KDIGO as an abnormality in kidney function or structure that is present for > 3 months. The most common functional abnormality is an eGFR < 60 mL/min/1.73 m2 with or without the presence of persistent kidney damage (albumin to creatinine ratio (ACR) of >30 mg/g, urine sediment abnormalities, tubular dysfunction, history of kidney transplant).[13] Recent KDIGO guidelines have classified CKD based on cause, GFR and degree of albuminuria (A1 < 30mg/g; A2 30–300mg/g; A3 > 300mg/g).

While albuminuria is often thought in the context of CKD, this is not always the case in patients with CRS. In the setting of HF and CRS, albuminuria may not be a product of CKD, but actually the effects of cardiac dysfunction.[14–16]

EPIDEMIOLOGY

Impairment in kidney function is common in HF patients and is associated with worse clinical outcomes than in persons without impaired kidney function. In the Acute Decompensated Heart Failure National Registry [ADHERE] which included > 105,000 patients admitted with ADHF, 91% of patients had some degree of renal dysfunction, with 64% having CKD stage 3 or higher. Patients with more severe renal dysfunction had worse in-hospital clinical outcomes (need for mechanical ventilation, admission to an intensive care unit, cardiopulmonary resuscitation, new-onset dialysis), greater length of hospital stay, and in-hospital mortality. Overall, eGFR was found to be an independent predictor of mortality. [17] In a meta-analysis of acute and chronic HF populations, the overall prevalence of CKD was 49% (with higher prevalence in acute HF [53%] vs. chronic HF [42%]). AKI was seen in 23–35% of patients. Both CKD and WRF were associated with significantly increased mortality risk. [18]

In addition to the lack of a consensus definition of AKI in the setting of HF, the clinical significance of these changes has recently been brought into question. Specifically, the context in which renal function changes needs to be considered when deciding on whether it is truly a deleterious state. Recent studies have demonstrated that AKI occurring in response to diuretic treatment associated with symptomatic improvement and signs of decongestion appears to be associated with improved outcomes whereas AKI without appropriate response to therapy is associated with worse outcomes. [19–21]

Contrary to this, and what one would think is a clinical improvement, other studies have shown improvement in renal function (IRF) in ADHF actually has worse outcomes. In a study of 900 patients admitted with ADHF, 31.4% of the population experienced IRF and had an increased mortality relative to the rest of the cohort.[22] Similar results were seen in the Diuretic Optimization Strategies Evaluation [DOSE], which was a multicenter, randomized, double blind, and placebo-controlled trial of diuretic strategies in ADHF patients. Analysis comparing the changes in renal function (stable, IRF, WRF) showed that patients with IRF compared with the rest of the cohort had a higher composite outcome of death, rehospitalization, and an emergency visits (HR 2.46, 95% CI 1.54–3.93, P <. 001).[23]

Serum creatinine has remained the most widely measured marker of kidney function but evaluates the function of the glomerulus and does not necessarily reflect tubular function or

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injury. This has led to a number of novel biomarkers being evaluated in the diagnosis of AKI, specifically from tubular damage. [24,25] A recent study looked at a panel of kidney tubular injury biomarkers including neutrophil gelatinase-associated lipocalin (NGAL), *N*-acetyl-[beta]-D-glucosaminidase (NAG), and kidney injury molecule 1 (KIM-1) in ADHF patients with and without WRF. [26] Kidney tubular injury biomarkers did not appear to have an association with WRF in the context of aggressive diuresis of patients with ADHF. This data suggests that the elevations in creatinine seen in the course of diuresis during ADHF, may not be AKI, thus bringing into the question the sensitivity of serum creatinine to diagnose 'true kidney injury'. Indeed, therapies such as ultrafiltration for HF have fallen out of favor, given the seeming lack of benefit and increased risk of AKI (using serum creatinine)[27], but whether this reflects true tubular damage needs to be confirmed using these novel biomarkers.

MECHANISM OF DISEASE PROCESS

Some of the difficulties in defining, researching, and treating CRS stem from the fact that multiple different pathophysiologic processes are involved (hemodynamic, hormonal, inflammatory). Thus, though it is more simplistic to consider individual pathophysiologic processes, these individual processes must be recognized as one portion of a larger multifaceted and complex pathophysiology (Table 2). Additionally, the significance and impact of each process varies depending on clinical status.

1. Role of central venous and intraabdominal pressure

Elevated intraabdominal pressure (IAP) can result in intraabdominal hypertension (IAH) and abdominal compartment syndrome (ACS) in severe cases. IAH is defined as unrelenting elevated IAP of ≥ 12 mmHg and IAP > 20 mmHg defines ACS. [28] IAP elevations are traditionally seen and discussed in the context of surgical complications but are now increasingly recognized as an important pathophysiologic contribution to the CRS.

ADHF results in volume overload and increased central venous pressure (CVP). To maintain blood flow through the vascular system an adequate pressure gradient is required across the capillary network. Elevated venous pressures attenuate the gradient for forward blood flow across the renal vasculature resulting in sluggish flow and causing congestion, glomerular dysfunction and a decrease in urine output. Various studies have demonstrated that elevated IAP results in reduced GFR and renal plasma flow[29,30] and that an elevated CVP is significantly associated with decreased kidney function.

In a study of 40 patients with ADHF, 60% of patient had elevated IAP. Patients with elevated IAP (≥8 mmHg) at baseline had higher serum creatinine levels compared with those with normal IAP (2.3 ± 1.0 mg/dl vs. 1.5 ± 0.8 mg/dl, p = 0.009, respectively). Interestingly, intensive medical therapy resulted in significant reduction in right-and left-sided filling pressures and an improvement in cardiac index (CI); these hemodynamic improvements did not correlate with improvements in renal function or IAP. However, changes in IAP did correlate with changes in renal function. This disconnect between hemodynamics and IAP likely explains why a subset of patients have deterioration in renal function despite improvement in hemodynamics since they have a persistent increase in IAP at follow up. [31]

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While elevated IAP and IAH have an important role in renal dysfunction, elevations in CVP have also been shown to closely correlate with renal function. A retrospective study conducted on patients who underwent right heart catheterization showed that an increased CVP (>6 mmHg) was associated with impaired renal function as well as a strong and independent predictor of all-cause mortality. [32] Similarly, another study of 145 patients with ADHF found that CVP were higher in persons who developed WRF compared to those who did not (18 ± 7 mm Hg vs. 12 ± 6 mm Hg, $p < 0.001$). [33] In addition, the mean baseline CI was actually higher in subjects who developed WRF suggesting that CVP may be more closely associated with eGFR than CI. Furthermore, a study of 196 patients with HF showed that tricuspid regurgitation was independently associated with lower GFR. [34] Significant tricuspid regurgitation can impair venous return and reflux blood into the renal-hepatic system.

2. Role of cardiac output and cardiac index

Initially, much of the progressive decline in renal function observed with HF was thought to be secondary to poor renal perfusion from a reduced cardiac output. The pathophysiologic theory is inadequate renal blood flow or perfusion pressure prompts renin release by the juxtaglomerular cells of the afferent arterioles because of a low flow state in the ascending limb of the loop of Henle and the pressure-sensing baroreceptors. This leads to:

- the retention of sodium,
- increased vascular congestion, and
- further worsening of renal function due to renal afferent arteriolar vasoconstriction.

In an animal study, an impaired response to an acute sodium load in rats with left ventricular dysfunction secondary to healed myocardial infarction demonstrated a model of circulatory impairment. [35] In theory, by augmenting contractility, heart rate, and CI, inotropes can lead to a short-term improvement in urine output, mental status, and other clinical indicators of organ perfusion. However, investigations suggest that this concept is very limited and management of patients with CRS based solely on the low-flow theory does not lead to improved outcomes. This is supported by findings from Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness [ESCAPE] study, a trial evaluating hemodynamically guided management of ADHF (using a pulmonary artery catheter) versus usual clinical care. [36] From the 433 individuals admitted with ADHF, the investigators found no correlation between baseline renal function and CI. Furthermore, improvement in CI did not result in improved renal function, prevention of death, or prevention of rehospitalization. An important caveat of the ESCAPE trial was patients were excluded if in cardiogenic shock or investigators felt invasive hemodynamic monitoring was clinically indicated.

Counter to these findings though, a more recent study of patients with acute cardiogenic shock did find an association between decreased CI and AKI. [37] This population was excluded from the ESCAPE trial, and these results suggest that in patients with an acute severe decline in cardiac output or a markedly depressed cardiac output, a low forward flow

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pathophysiologic state contributes to CRS. Despite this theory of low forward flow, treatment with inotropic agents in various groups of patients with HF and AKI did not change the clinical outcomes and further endorses the fact that CRS pathophysiology and management is far more complicated than previously thought. [38,39] Thus, in the acute setting, the influence of CI is variable and may contribute in the most severe forms of ADHF, but likely does not play a significant role in the majority of patients.

While these studies looked at ADHF, data is more limited in CHF. One study did evaluate a large cohort of patients undergoing right heart catheterization without a clear discrimination of acuity or stability of HF status. In this study, CI was found to correlate with renal function, but was not the sole contributing hemodynamic process. [32] As discussed above, central venous pressure is other dominant hemodynamic factor influencing renal function.

3. Role of neurohormonal dysregulation

The renin angiotensin aldosterone system (RAAS) plays an important role in the progression of kidney damage and worsening of HF. [40] In patients with HF, neurohormonal mechanisms are activated to restore tissue perfusion. Additionally in HF, over activity of the sympathetic nervous system (SNS) due to impaired baroreceptor reflexes results in increased renin release from the juxtamedullary cells of the kidneys. [41] Renin synthesis is also influenced by the hydrostatic pressure sensed at glomerular afferent arterioles, and the reduced quantity of chloride delivered to macula densa. [42]An elevation in renin leads to increased production of angiotensin II (Ang II) that has multiple maladaptive systemic effects on the heart, vasculature, and kidneys. In the kidneys, AngII causes renal efferent arteriolar vasoconstriction and an increased fraction of renal plasma flow filtered across the glomerulus. This result in an increased peritubular oncotic pressure and reduced hydrostatic pressure causing enhanced reabsorption of sodium in the proximal tubules. Ang II has a direct stimulating effect on proximal tubule sodium-bicarbonate co-transporters and apical sodium hydrogen exchangers, through which solute is proximally reabsorbed independent of the GFR. [43] Ang II also promotes the aldosterone mediated reabsorption of sodium in the distal tubules [42] and increases the expression of endothelin-1 (ET-1) in the kidney. [44] ET-1 is a potent vasoconstrictor, pro-inflammatory and pro-fibrotic peptide and leads to pathological changes resulting in kidney injury. [45]

Ang II type 1 receptors (AT_1) are also found in the heart. In animal models, stimulation of AT_1 receptors results in cardiac myocyte hypertrophy through paracrine release of transforming growth factor-β_1 and ET-1 from the cardiac fibroblast. [46] Ang II causes vascular smooth muscle contraction via the AT_1 receptors. Furthermore, Ang II mediates the oxidative stress via reactive oxygen species formation in the heart and kidney tissue leading to inflammation and hypertension. [47] In patients with HF, left ventricular dysfunction causes activation of SNS in an effort to maintain the perfusion through mechanisms such as increased contractility, lustitropy, and systemic vasoconstriction. [48]

Adenosine is released in response to increased sodium load in the distal tubule and via adenosine type 1 receptors in the proximal tubule and afferent arterioles; it mediates constriction of afferent arterioles and reduction of renal blood flow and GFR. Additionally, activation of adenosine type 2 receptors induces the release of renin and enhances sodium

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reabsorption at the proximal tubule and reduces diuresis. [49] Efficacy of adenosine type 1 receptor antagonist in CRS is controversial. The results of PROTECT (A placebo-controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for patients hospitalized with ADHF to assess treatment effect on congestion and renal function) trial showed that rolofylline group did not meet the primary (dyspnea improvement) or secondary (death, cardiovascular or renal rehospitalization, or persistent renal impairment) outcomes. Thus, further clinical studies are needed to determine the utility of adenosine A1 receptor antagonist in CRS population. [50]

Arginine vasopressin (AVP) is a nonapeptide synthesized in the hypothalamus, stimulated in response to serum osmolality. It has effects on glomerular hemodynamics, arterial blood pressure, and non-hemodynamic renal mechanisms. Patients with ADHF often have an activation of AVP release. AVP causes water retention via vasopressin V2 (V2) receptors in the collecting duct. Studies have shown that elevated AVP levels contribute to the progression of CKD. [51,52] The renal hemodynamic effects of AVP may be due to its effects on the RAAS. AVP could potentially stimulate renin secretion directly via activation of V2 receptors or indirectly through reduction in sodium concentration at the macula densa. [51] Plasma AVP has been found to be elevated in patients with left ventricular dysfunction without overt clinical HF and has been associated with poor outcomes. [53,54]

4. Role of oxidative stress

Oxidative stress is defined as an imbalance between oxidants and antioxidants resulting in excessive accumulation of former leading to cellular injury. [55] Reactive oxygen species (ROS) are generated as by-products of cellular metabolism, primarily in the mitochondria. [56] Oxidative stress ensues when formation of ROS surpasses the body’s antioxidative processing ability resulting in the accumulation of ROS leading to cellular damage, endothelial dysfunction and progression of atherosclerosis.

Oxidative stress in the setting of CRS can be triggered by ischemic injury, venous congestion (which causes circumferential wall stress in the endothelial cell membrane), and inflammation. [57,58] Most of the adenosine triphosphate (ATP) is produced from fatty acid oxidation in the heart, but in the setting of HF there is a shift from fatty acid oxidation to glycolysis in myocytes leading to myocardial ATP production decreasing by 30–40%. The energy deficiency is compensated by glycolysis but it is insufficient to meet the energy needs in HF leading to low threshold for hypoxemia, apoptosis, and cell death. Furthermore, due to reduced mitochondrial oxidative metabolism of fatty acid oxidation, there is accumulation of free fatty acids in myocytes, leading to lipotoxicity. [59] In a study, patients admitted with ADHF on admission who subsequently developed AKI were studied for markers of oxidative stress (IL-6, myeloperoxidase, nitric oxide, copper/zinc superoxide dismutase, and endogenous peroxidase). Results demonstrated significantly heightened presence of dual oxidative stress markers, in patients who developed CRS type 1.[60]

In addition to the deleterious effects of volume expansion and hemodynamics, RAAS and SNS activation also plays an important role in amplifying the oxidative stress in HF and CKD patients. Ang II has a deleterious effect by activating NADPH-oxidase promoting oxidative injury by producing ROS causing mitochondrial dysfunction. [61] The enhanced

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NADPH-oxidase activity has been demonstrated in endothelial cells, renal tubular cells and cardiac myocytes. [62–64]

Patients with advance CKD and end-stage renal disease (ESRD) have some factors such as, uremic toxins and dialysate solutions utilized in renal replacement therapy that could lead to increased synthesis and release of proinflammatory cytokines, oxidative stress, immune system dysregulation leading to carotid artery intima-media thickness (marker of early stage of atherosclerosis) and left ventricular hypertrophy. [65,66] ESRD patients have higher cardiovascular morbidity and mortality that could not be explained by classic cardiac risk factors; thus, perhaps oxidative stress, endothelial dysfunction, and hyperhomocysteinemia might be playing an additive role in these patients. [67]

5. Role of inflammatory mediators

Both CKD and HF are states of heightened chronic inflammation, resulting in the generation of pro-inflammatory biomarkers that play a crucial role in tissue damage to both organs leading to cell death and fibrosis. Important triggers that initiate and propagate the inflammatory cascade include the activation of SNS and RAAS, venous congestion, ischemia, and oxidative stress. Pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and TNF-α related weak inducer of apoptosis (TWEAK), members of interleukin-1 (IL-1) family, and interleukin-6 (IL-6) have been associated with HF as well as CKD. In kidneys, TNF-α and IL-6 promote accumulation of inflammatory cells in the interstitium by increasing monocyte chemoattractant proteins expressions. TNF-α also results in glomerular damage by mesangial cell apoptosis. [68] Some of these biomarkers are prognostic for all-cause mortality in HF patients, such as soluble ST2, which is a member of the IL-1 family. [69,70] Similarly, in CKD, IL-6 correlates well with progression of disease and also predicts the mortality. [71] It has also been shown that levels of these pro-inflammatory markers are higher in persons with CKD [72] and those on dialysis. [73]

C-Reactive protein (CRP), an acute phase reactant, has been shown to contribute in the pathogenesis of atherosclerosis through a variety of mechanisms. CRP activates the complement system and is widely distributed in early atherosclerotic lesions. [74,75] CRP is a potent stimulator of tissue factor production (a potent procoagulant) by monocytes and this effect is further augmented in the presence of inflammatory mediators. [76] A study of 4269 individuals hospitalized with ADHF, patients with CRP in the fourth quartile (≥ 9.6 mg/L) were independently associated with higher all-cause mortality (adjusted hazard ratio, 1.68) within 120 days after discharge. [77] In hemodialysis patients high CRP levels predict left ventricular dysfunction, cardiac hypertrophy, and mortality. [78,79] These inflammatory proteins are not simply inert markers of disease activity but rather play an active and complex role in the pathophysiology of CRS.

6. Role of renal failure associated disturbances

Protein-bound uremic toxins (PBUT) are currently an emerging area of interest due to their potential association with cardiovascular disease. [80,81] Indoxyl sulphate (IS) and p-crestyl sulphate (PCS) are the two most extensively studied PBUT that have demonstrated a role in the pathogenesis and progression of CRS. In normal kidneys, both are cleared through

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tubular secretion. Experimental studies have demonstrated detrimental effect of IS and PCS through alteration of oxidative stress, endothelial dysfunction and atherosclerosis. Both have been associated with nephrotoxicity, decreased endothelial proliferation, and impaired wound repair suggesting their role in progression of CKD. [82–85] A study using a nephrectomy CKD mouse model revealed effects of PCS on cardiac cells including increased apoptosis, increased interstitial and perivascular fibrosis, and a reduction in left ventricular diastolic function. Oxidative stress was implicated in PCS-induced changes in the heart muscle. [86] Furthermore, IS also augments oxidative stress in kidney and heart leading to cardiorenal fibrosis. [87–89] A study of 139 CKD patients demonstrated that IS was a powerful predictor of overall and cardiovascular mortality after adjusting for confounders. [90] Though there has been evidence suggesting a negative effect of PBUT on heart, kidney and vascular cells, further research is needed to better understand the role of PBUT in the pathophysiology of CRS.

Fibroblast growth factor-23 (FGF23), a hormone produced in the bone that controls phosphate and vitamin D metabolism by the kidney, is a strong predictor of adverse cardiovascular outcomes in patients with CKD and ESRD. Elevated FGF-23 has been associated with left ventricular hypertrophy (LVH) and mortality in advance CKD patients. [91] While it has been suggested that FGF23 may induce myocardial hypertrophy through a direct effect on cardiac myocytes, this remains debated due to the absence of alpha-klotho receptors (which mediate FGF23 action) in the heart. Other data also suggests that FGF23 may directly depress myocardial contractility and ventricular relaxation, cause hypertrophy and increase risk of arrhythmias, by altering calcium trafficking. [92,93]

7. Role of anemia

Anemia is common in patients with advance CKD and HF with the majority of these patients have anemia of chronic disease. The prevalence of anemia in CRS has been reported to vary from 5% to 55% with anemia reported to be an independent predictor of mortality. [94–96] In the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure) registry with over 48,000 patients, 51.2% had mild anemia (Hb<12.1 g/dl) and 25% were moderately to severely anemic (hemoglobin levels of 5 to 10.7 g/dl) [97]

In CKD patients, anemia is associated with:

- cognitive impairment,
- poor quality of life,
- progression of kidney disease,
- cardiovascular comorbidities, and
- higher mortality.[98]

In a multicenter survey of 5222 patients with CKD, 47.7% were found to be anemic (hemoglobin level ≤ 12 g/dl). [99]

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There are several ways anemia contributes to the pathophysiology of CRS. Lack of oxygen supply to a heart that is already under stress or kidney that is already damaged may cause ischemic insults that can results in progressive cell death in both the organs. Red blood cells contain many antioxidants, and therefore anemia may results in increased oxidative stress. [100] Anemia can cause tissue ischemia and peripheral vasodilation, which leads to activation of SNS, RAAS as well as release of ADH resulting in vasoconstriction, salt and water retention, and chronic renal venous congestion that leads to progressive nephron loss and interstitial fibrosis. Chronic anemic state also results in left ventricular hypertrophy and myocardial cell death from ischemia and necrosis. [101,102]

Although correction of anemia in CHF patients with erythropoiesis-stimulating agents (ESA) results in improved outcomes (reduced hospitalization, improved new york heart association class, 6-minute walk test, and quality of life) but normalization of the hemoglobin levels may not result in favorable outcomes. Trials targeting a higher level of hemoglobin levels (≥ 13 g/dL) surprisingly were associated with higher rate of adverse events. [103,104] The trial to reduce cardiovascular events with aranesp therapy [TREAT] was a randomized, double blind, placebo-controlled study with over 4000 patients. [105] The use of darbepoetin alfa in patients with diabetes, CKD, and moderate anemia who were not undergoing dialysis to achieve a hemoglobin level of approximately 13 g/dl did not reduce the risk of death or a cardiovascular event or a renal event. There was an increased risk of fatal or nonfatal stroke in patients assigned to darbepoetin alfa group. The RED-HF (The reduction of events by darbepoetin alfa in heart failure) was a randomized, double blind trial with 2278 patients with systolic heart failure and mild to moderate anemia (hemoglobin level, 9.0 to 12.0 g/dl). [106] Patients were randomized to either darbepoetin alfa (to achieve a hemoglobin target of 13 g/dl) or placebo. There was no difference in the primary outcome (death from any cause or hospitalization for worsening HF).

Anemia plays an important role in the pathophysiology of CRS and management of anemia is complex especially in patients with CKD and CHF. The main unanswered question is the range of hemoglobin levels to target in this population, targets based on CKD guidelines (10 to 12 g/dl) or higher (12 to 13 g/dl) but less than 13 g/dl (as trials with hemoglobin level of 13 or higher were associated with negative outcomes) is still unknown.

8. Pathogenesis of Type 5 CRS

Type 5 CRS (CRS-5) occurs when an overwhelming systemic disease process results in damage to heart and kidney simultaneously (Figure 4). Based on pathophysiology and severity of the disease process, CRS-5 has been distinguished into four stages: hyperacute, acute, subacute, and chronic. Systemic diseases that can result in CRS-5 are sepsis, connective tissue disorders such as lupus, sarcoidosis, amyloidosis, and cirrhosis. Injury to the kidney and heart is often mediated by pro-inflammatory cytokines, complement factors, and RAAS activation, which are often the common end pathway for other forms of CRS. For instance, in sepsis, increased renal vascular resistance and early rise in pro-inflammatory cytokines (IL-6) and oxidative stress can lead to organ damage. [107,108] Sepsis also results in autonomic nervous system dysfunction, and activation of RAAS. The plethora of effects of sepsis on the function of various organs, including heart and kidney, makes it very difficult

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to differentiate between the effects of sepsis itself and the effect of inter-organ cross-talk. Moreover, management of sepsis can contribute to the development of CRS-5. Fluid resuscitation can result in tissue edema and IAH, increase venous congestion and reduced renal perfusion. Iodinated contrast agents and certain drugs can results in myocardial depression and nephrotoxicity resulting in development and/or worsening of CRS-5. In chronic inflammatory and autoimmune disease processes, the concomitant damage to both the organs and ongoing cross-talk between the heart and kidney leads to a similar pathophysiologic mechanisms as discussed in other types of CRS. [109]

FUTURE DIRECTIONS

Despite an improved understanding of the different pathophysiological process involved in the development of CRS, therapies at improving outcomes in this population have only met with minimal success. One possibility for this may be the inability to accurately diagnose AKI using conventional biomarkers such as creatinine. Whether the incorporation of more novel filtration markers such as cystatin C, beta-2 microglobulin, beta trace protein will provide use with better estimates of kidney function needs to be evaluated further in the setting of HF. Further, based on emerging evidence, there is a need to incorporate more sensitive, and perhaps specific tubular markers of injury, inflammation and repair into the renal endpoints of HF clinical trials. [110]

CONCLUSION

Pathophysiology of the various types of CRS is complex and challenging. Given the rising burden of the disease, adverse clinical outcomes and high impact on mortality, early diagnosis of the syndrome is crucial. To improve the survival and morbidly associated with the disease, better understanding of various aspects of pathophysiology is needed to better mange these patients. CRS-5 is a complex and challenging condition to diagnose as the time and sequence of dysfunction of heart and kidney are dictated by the underlying cause and nature of condition.

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KEY POINTS

- Cardiorenal syndrome (CRS) is a term commonly refers to the collective dysfunction of heart and kidneys resulting in cascade of feedback mechanisms resulting in damage to both the organs.
- Multiple mechanisms (hemodynamic, neurohormonal, inflammatory, and oxidative stress) are involved in the pathophysiology of CRS.
- In CRS, renin angiotensin aldosterone system and sympathetic nervous system activation leads to salt avidity and volume overload.
- Venous congestion and elevated intraabdominal pressure plays an important role in the pathophysiology of CRS.
- The role of creatinine and novel biomarkers for diagnosing kidney disease in the setting of heart failure needs to be further evaluated.

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SYNOPSIS

Cardiorenal syndrome commonly refers to the collective dysfunction of heart and kidney resulting in a cascade of feedback mechanism causing damage to both the organs and is associated with adverse clinical outcomes. The pathophysiology of cardiorenal syndrome is complex, multifactorial, and dynamic. Improving the understanding of disease mechanisms will aid in developing targeted pharmacologic and non-pharmacologic therapies for the management of this syndrome. This review will discuss the various mechanisms involved in the pathophysiology of the cardiorenal syndrome.

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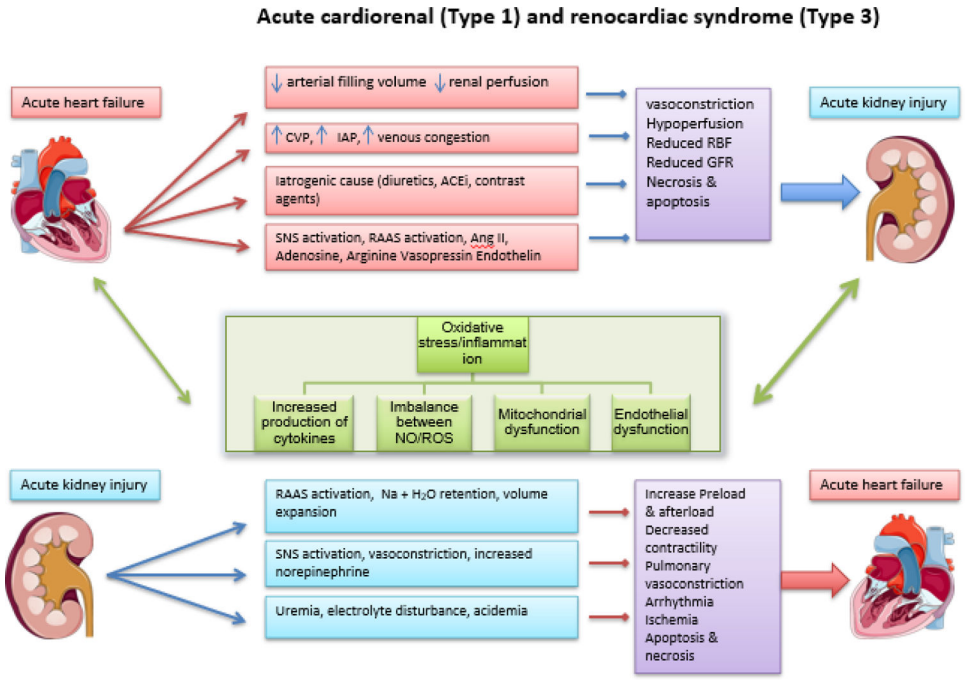

Figure. 1.

Pathophysiological interaction in acute cardiorenal syndrome (type 1) and acute renocardiac syndrome (Type 3).

CVP= central venous pressure; IAP= intraabdominal pressure; ACEi= Angiotensin converter enzyme inhibitor; RAAS= Renin angiotensin aldosterone system; SNS= Sympathetic nervous system; RBF= Renal blood flow; GFR= Glomerular filtration rate; NO= Nitrous oxide; ROS= Reactive oxygen species.

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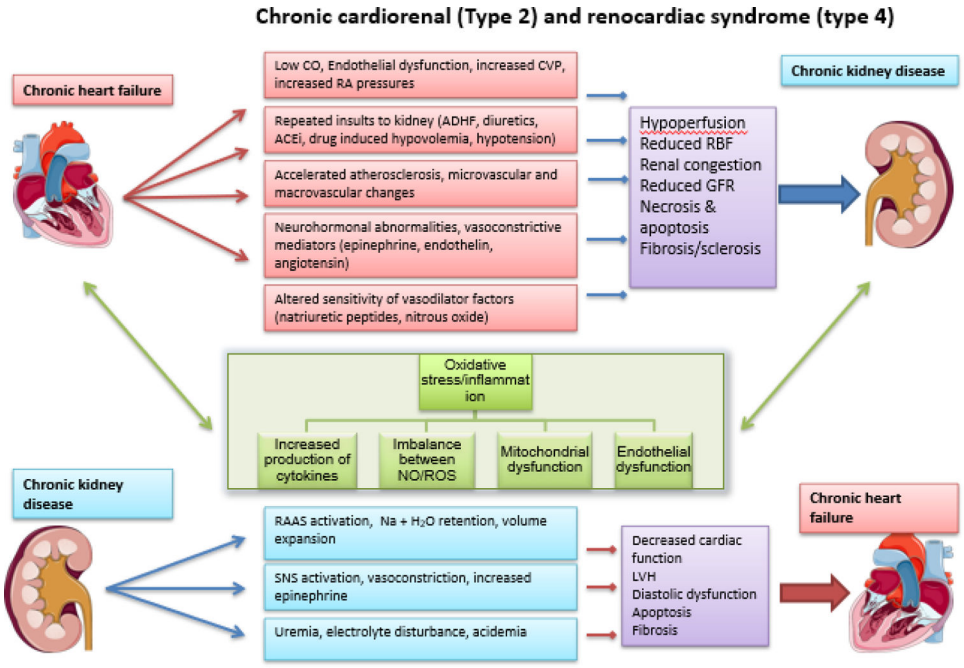

Figure. 2.

Pathophysiology of chronic cardiorenal syndrome (type 2) and chronic renocardiac syndrome (Type 4).

CVP= central venous pressure; IAP= intraabdominal pressure; ACEi= Angiotensin converter enzyme inhibitor; RAAS= Renin angiotensin aldosterone system; SNS= Sympathetic nervous system; RBF= Renal blood flow; GFR= Glomerular filtration rate; NO= Nitrous oxide; ROS= Reactive oxygen species.

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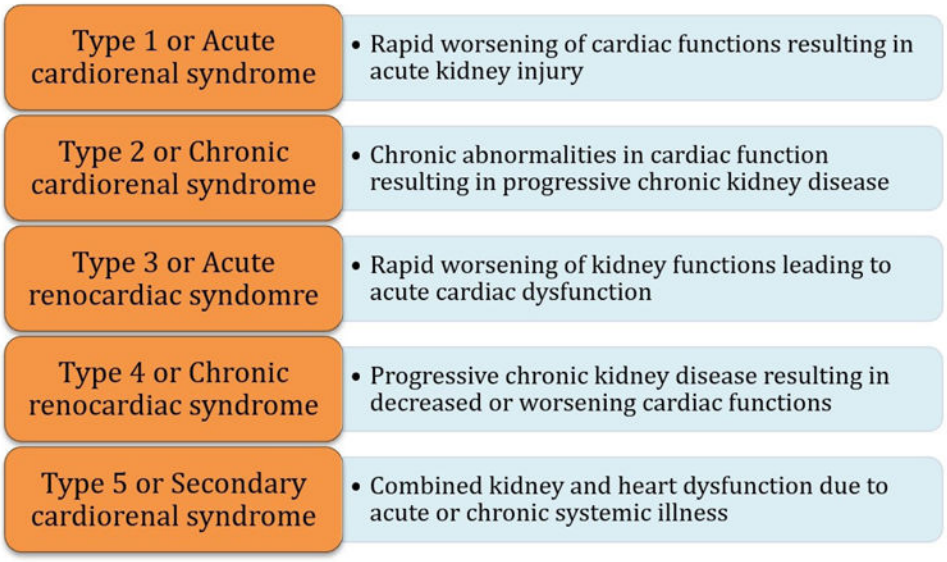

Figure 3.
Types of Cardiorenal syndrome.

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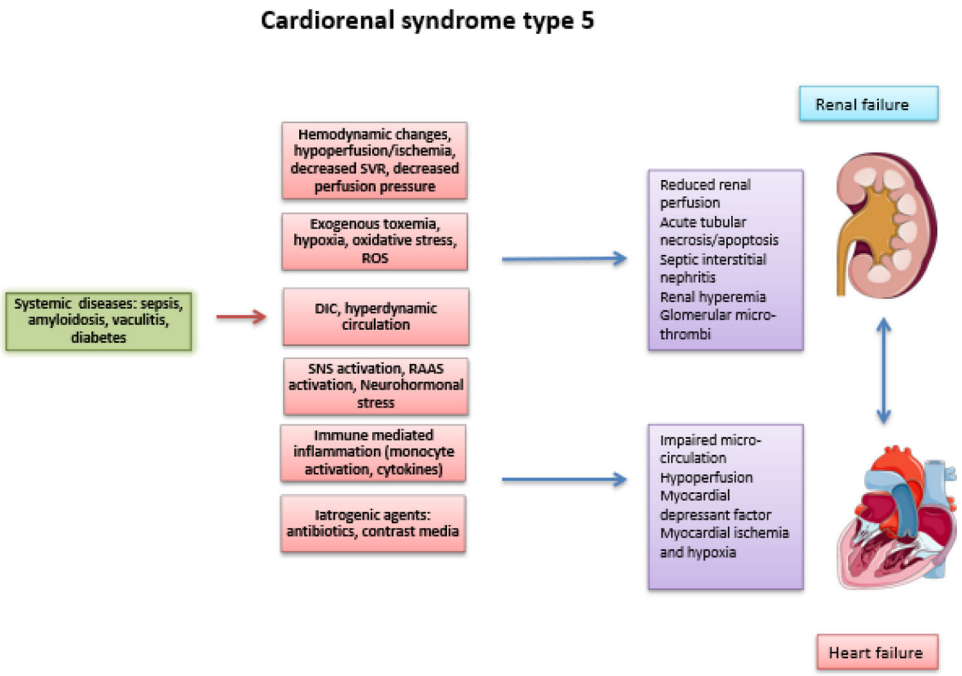

Figure. 4.

Pathophysiological interactions in cardiorenal syndrome (type 5).

SVR= Systemic vascular resistance; ROS= Reactive oxygen species; DIC= Disseminated intravascular coagulation; SNS= Sympathetic nervous system; RAAS= Renin angiotensin aldosterone system.

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Table 1.

KDIGO staging of Acute Kidney Injury

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline or ≥ 0.3 mg.dL increase	< 0.5 ml/kg.hr for 6–10 h
2	2.0–2.9 mg/dL times baseline	< 0.5 ml/kg.hr for ≥ h
3	3 times baseline or ≥ 4.0 mg/dL increase or initiation of RRT or in patients < 18 years a decrease in eGFR < 35 mL/min/1.73 m^2	< 0.3 ml/kg.hr for ≥ 24 h or anuria for ≥ 12 h

Abbreviations: eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy.

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Table 2

Summary of various mechanisms of cardiorenal syndrome

		End-organ Outcome	
Mechanism	**Mediator**	**Heart**	**Kidney**
• Increased central venous and intra-abdominal pressures	• Increased salt/water retention • Activation of RAAS/SNS	• Acute/chronic HF • Adverse remodeling of heart and lungs	• Renal venous congestion • Reduced GFR
• Reduced cardiac output and cardiac index	• Peripheral vasodilation/reduced vascular resistance • Reduced perfusion pressure	• Activation of RAAS/SNS detrimental to heart • Cardiac ischemia from reduced perfusion	• Reduced renal perfusion • Renal ischemia
• Neurohormonal dysregulation ○ RAAS activation ○ SNS activation ○ Adenosine/AVP	• Impaired baroreceptor reflexes • Increased renin secretion • Increased Ang II secretion • Increased aldosterone secretion • Increased ET-1 expression • Oxidative stress	• Myocyte hypertrophy, left ventricular dysfunction • Proinflammation, profibrotic effect • Hypertension	• Arteriolar vasoconstriction • Reduced GFR • Enhanced reabsorption of sodium/water • Proinflammation, profibrotic effect
• Oxidative stress	• Increased reactive oxygen species formation • Ang II–enhanced NADPH-oxidase activity • Uremic toxin–mediated cytokine release	• Left ventricular hypertrophy • Accelerated atherosclerosis • Endothelial dysfunction • Inflammation • Fibrosis	• Endothelial dysfunction • Accelerated atherosclerosis • Inflammation • Interstitial fibrosis
• Inflammatory mediators	• TNF-α • TWEAK • Members of IL-1 family • IL-6 • CRP	• Atherosclerosis • Inflammation • Left ventricular dysfunction • Cardiac hypertrophy • Myocardial cell death • Fibrosis	• Inflammation • Fibrosis • Atherosclerosis • Glomerular damage by mesangial cell apoptosis
• Renal failure–disturbances	• PBUTs (indoxyl sulfate, p-cresyl sulfate) • Chronic inflammatory cytokines • Oxidative stress • FGF-23 • Calcium/phosphate-mediated inflammation • Anemia	• Endothelial dysfunction • Atherosclerosis • Left ventricular dysfunction • Cardiac hypertrophy	• Atherosclerosis • Inflammation • Increased interstitial and perivascular fibrosis

Abbreviations: Ang II, angiotensin II; AVP, arginine vasopressin; CRP, C-reactive protein; ET-1, endothelin-1; FGF-23, fibroblast growth factor-23; GFR, glomerular filtration rate; IL, interleukin; PBUTs, protein-bound uremic toxins; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system; TNF-α, tumor necrosis factor alpha; TWEAK, tumor necrosis factor alpha–related weak inducer of apoptosis.