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Review

The Cardiorenal Syndrome: A Narrative Review

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Abstract

Cardiorenal syndrome is a multifaceted condition characterized by the interdependent dysfunction of the heart and kidneys, where pathology in one organ may precipitate or exacerbate dysfunction in the other, whether in acute or chronic forms. This syndrome underscores the complex bidirectional interactions between the cardiac and renal systems, including the hemodynamic interplay and the reciprocal physiological responses. It also involves alterations in neurohormonal and inflammatory biomarkers that are pertinent to its various clinical manifestations. This review offers a comprehensive analysis of CRS, focusing on its pathophysiological mechanisms, diagnostic approaches, and therapeutic strategies.

Keywords: Cardiorenal syndrome, heart failure, kidney disease, heart, kidney

DEFINITIONS and PHENOTYPES

Cardiorenal Syndrome (CRS) refers to the complex relationship between heart and kidney dysfunctions, where one organ's failure affects the other. In 2004, the Working Group of the National Heart, Lung, and Blood Institute initially defined CRS as a condition where interactions between the kidneys and circulatory systems increase circulating volume, worsening heart failure (HF) symptoms and advancing the disease. They noted that severe cardiorenal dysregulation results in CRS, where treatments for congestive HF symptoms are restricted by declining kidney function (1). This cardiocentric view remains key in understanding CRS, particularly in acute HF. Recognizing a broader clinical range, the Acute Dialysis Quality Initiative (ADQI) in 2008 classified CRS into two main categories: cardiorenal and renocardiac syndromes, depending on the primary disease process (2). The syndrome is divided into five subgroups based on the etiology, underlying pathology, time of onset, and the co-dysfunction of renal and cardiac systems due to systemic disease (**Table 1**) (3,4). This consensus definition aimed to enhance the accurate characterization of cardiorenal dysregulation for diagnostic and therapeutic purposes, streamline inclusion criteria for epidemiological studies, identify target treatment populations, and develop novel diagnostic tools for managing CRS. However, the ADQI classification presents some clinical limitations. When HFcoexists with acute or chronic renal injury, distinguishing between cardiorenal and renocardiac syndromes becomes challenging for physicians. Identifying which organ deteriorates first is complex, potentially leading to inaccurate staging in CRS phenotyping (5,6). Complex, interconnected pathways contribute to CRS, including diabetes mellitus, hypertension, HF, atherosclerosis, endothelial dysfunction, anemia and disorders of iron metabolism, and chronic inflammation (7). Many of these factors lack clearly defined temporal progression patterns. Hatamizadeh et al. proposed an alternative classification of CRS based on various clinical manifestations independent of the first organ affected (8). This classification includes uremic or vascular manifestations, anaemia or iron deficiency, neurohumoral disorders, haemodynamic instability, bone mineral metabolism problems and malnutrition-inflammation complex (8).

Assessing the significance of fluctuations in kidney function that meet the criteria for acute kidney injury (AKI) within the context of CRS is a major challenge

Table 1. Management Options in CRS

CRS Type	Nomenclature	Description	Clinical Examples
Type 1	Acute CRS	Acute HF leading to AKI.	ACS resulting in cardiogenic shock and AKI.
Type 2	Chronic CRS	Chronic HF leading to CKD.	Chronic HF resulting in progressive CKD.
Type 3	Acute renocardiac syndrome	AKI leading to acute HF.	HF in the setting of AKI due to volume overload and uremic toxins.
Type 4	Chronic renocardiac syndrome	CKD leading to chronic HF.	CKD-associated cardiomyopathy, LVH.
Type 5	Secondary CRS	Systemic disorders leading to simultaneous cardiac and renal dysfunction.	Sepsis, amyloidosis, and cirrhosis causing both HF and kidney failure.

CRS; cardiorenal syndrome, HF; heart failure, CKD; chronic kidney disease, ACS; acute coronary syndrome, AKI; acute kidney injury, LVH; left ventricular hypertrophy

in standardizing its definition and phenotypes. This is particularly true in acute HF, where decongestive treatments may complicate the evaluation of renal function biomarkers, such as serum creatinine and urine output. Historically, the literature on acute declines in kidney function in CRS has used inconsistent terms like kidney impairment and renal insufficiency, which has hindered accurate measurement and clinical interpretation of kidney injury. Efforts to standardize AKI definitions began with the RIFLE criteria (risk, injury, failure, loss of kidney function, and end-stage kidney disease introduced by the ADQI in 2002 and were later revised by the Acute Kidney Injury Network (9). The 2012 Kidney Disease: Improving Global Outcomes guidelines harmonized these criteria to facilitate early AKI detection, enable epidemiological comparisons, and standardize entry criteria and endpoints in clinical trials (10).

TYPES OF CARDIORENAL SYNDROME

Type 1 CRS (Acute Cardiorenal Syndrome)

Type 1 CRS, also known as Acute CRS, occurs when acute HF results in AKI. This type is commonly observed in situations such as acute coronary syndrome, where cardiogenic shock can severely impair renal function. The heart's inability to pump blood effectively leads to reduced kidney perfusion, triggering a cascade of neurohormonal responses that exacerbate renal injury. The management of Type 1 CRS often requires careful balancing of fluids, diuretics, and inotropic support to stabilize both cardiac and renal function (3,4).

Type 2 CRS (Chronic Cardiorenal Syndrome)

Type 2 CRS, or Chronic CRS, involves chronic HF progressively leading to chronic kidney disease (CKD). In this scenario, long-standing HF causes sustained renal hypoperfusion and activation of the renin-angiotensin-aldosterone system (RAAS), resulting in structural and functional kidney damage over time. Chronic HF and CKD feed into each other, creating a vicious cycle where the dysfunction of one organ exacerbates the failure of the other. Management strategies focus on slowing the progression of both HF and CKD through the use of RAAS inhibitors, beta-blockers, and careful fluid management (3,4).

Type 3 CRS (Acute Renocardiac Syndrome)

Type 3 CRS, or Acute Renocardiac Syndrome, describes a situation where AKI precipitates acute HF. This condition is often seen in patients with volume overload due to impaired renal function, leading to a rapid increase in cardiac workload. The accumulation of uremic toxins and electrolytic imbalances further contributes to myocardial dysfunction. Treatment involves addressing the underlying AKI, managing fluid balance, and providing supportive care to prevent worsening heart failure (3,4).

Type 4 CRS (Chronic Renocardiac Syndrome)

Type 4 CRS, also known as Chronic Renocardiac Syndrome, occurs when CKD leads to chronic HF. The long-term impact of CKD on the cardiovascular system includes left ventricular hypertrophy (LVH) and cardiomyopathy, which arise due to hypertension, fluid overload, and the toxic effects of uremic metabolites. These changes can eventually result in chronic HF. Management typically includes aggressive control of blood pressure, use of RAAS inhibitors, and interventions to manage fluid overload and metabolic derangements (3,4).

Type 5 CRS (Secondary Cardiorenal Syndrome) Type 5 CRS, or Secondary CRS, involves systemic conditions that simultaneously cause dysfunction in both the heart and kidneys. Examples include sepsis, amyloidosis, and cirrhosis, where the underlying systemic disease leads to multi-organ failure. The management of Type 5 CRS is complex, requiring a multidisciplinary approach to treat the systemic disorder while supporting both cardiac and renal function (3,4).

PATHOPHYSIOLOGY

Prerenal hypoperfusion, resulting from the heart's inability to maintain adequate forward flow, contributes to the development of CRS. This activates the

sympathetic nervous system (SNS), vasopressin release, and RAAS, leading to fluid retention and worsening HF (11). In HF, the overactivity of the SNS, resulting from impaired baroreceptor reflexes, leads to increased renin release from the juxtaglomerular cells in the kidneys (12). Elevated renin levels lead to increased production of angiotensin II (Ang II), which has several maladaptive effects on the heart, vasculature, and kidneys. In the kidneys, Ang II causes vasoconstriction of the renal efferent arterioles, enhancing the filtration fraction and increasing peritubular oncotic pressure while reducing hydrostatic pressure (13). This process promotes sodium reabsorption in the proximal tubules. Ang II directly stimulates proximal tubule sodium-bicarbonate co-transporters and apical sodium hydrogen exchangers, facilitating solute reabsorption independently of glomerular filtration rate (GFR) (14). It also enhances aldosterone-mediated sodium reabsorption in the distal tubules and increases endothelin-1 expression, a potent vasoconstrictor and pro-inflammatory peptide, leading to kidney injury (15).

Ang II type 1 receptors in the heart can cause cardiac myocyte hypertrophy through paracrine signaling involving transforming growth factor-β1 and ET-1 from cardiac fibroblasts. Ang II induces vascular smooth muscle contraction via AT1 receptors and mediates oxidative stress through reactive oxygen species, contributing to inflammation and hypertension. In HF patients, left ventricular dysfunction triggers SNS activation to maintain perfusion through increased contractility, lusitropy, and systemic vasoconstriction (16). However, this lack of localized flow is not the sole mechanism affecting the pathophysiology of CRS. To ensure the kidneys receive enough oxygen, the difference between arterial driving pressure and venous outflow must be sufficient for proper renal blood flow and glomerular filtration. In HF, elevated central venous pressure (CVP) reduces the perfusion gradient across the glomerular capillaries, diminishing renal function. Right ventricular enlargement and dysfunction can raise venous pressure, hindering left ventricular filling and lowering cardiac output. Elevated blood pressure and central venous congestion directly affect renal function in acute HF patients. A retrospective study on patients undergoing right heart catheterization found that a CVP greater than 6 mmHg was associated with reduced renal function and was a strong, independent predictor of all-cause mortality (17).

Increased intra-abdominal pressure (IAP), intra-abdominal hypertension (IAH), and CVP are closely linked to renal function. A study of patients undergoing right heart catheterization found that CVP over 6 mmHg significantly raises all-cause mortality risk and is associated with decreased renal function (18). In advanced chronic HF, 60% of patients have elevated IAP, with normal values in healthy adults between 5 and 7 mmHg. An IAP of 8–12 mmHg in these patients correlates with renal damage, leading to CRS type 2 (17). Decongestive therapy can improve serum creatinine by reducing abdominal congestion.

CLINICAL ASSESMENT and DIAGNOSIS

The patient's history and physical examination, combined with an evaluation of both acute and chronic cardiac and renal damage, as well as the current status of HF compensation, are essential for identifying the initial organ damage that leads to CRS. AKI may follow acute coronary syndrome, or rapid cardiac dysfunction might be observed in patients with AKI due to dehydration. A thorough patient history is essential for identifying the condition causing CRS. Information about drug use and previous laboratory and imaging results, such as baseline creatinine levels and past echocardiographic findings, can provide additional insights (4).

On physical examination, signs of fluid overload should be assessed, including elevated jugular venous pressure, ascites, edema, rales on lung auscultation, hypotension, decreased peripheral pulses, and abnormal heart rates (either tachycardia or bradycardia), along with decreased cardiac output. If the primary cause of CRS is renal in origin, symptoms such as anemia, nocturia, oliguria, or anuria may be evident. Potential predisposing risk factors for the development of CRS should be investigated. Male gender, advanced age, arterial hypertension, diabetes mellitus (DM), obesity, anemia, nutritional deficiencies, history of previous surgery and atrial fibrillation (AF) are independent risk factors for the development of AKI (19,20).

In patients with chronic HF, particularly those with normal or partially normal renal function, The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation refines kidney function categorization and risk stratification, though its accuracy is influenced by factors such as age, race, diet, sex, and body mass (21). Cardiac cachexia and muscle loss can lower serum creatinine levels, potentially leading to overestimation of GFR in advanced HF (22). Thus, relying solely on eGFR may not detect early renal dysfunction accurately. Kidney biomarkers should not only provide insights into kidney function deterioration but also identify pathophysiological conditions predisposing to acute or worsening renal function.

Cystatin C, a cysteine protease inhibitor, offers a more accurate assessment of kidney function than serum creatinine, as it is less affected by factors like age, nutritional status, and body weight (23). It is particularly useful in advanced HF and in patients with left ventricular assist devices, though its use is limited by cost and applicability in cases where creatinine levels are misleading (24). Additionally,

residual renal function (RFR) helps maintain normal GFR values until a significant portion of nephrons are lost, offering a sensitive measure of kidney function decline and recovery potential (25). However, current RFR evaluation methods are not easily applicable in clinical practice and often require protein loading and reassessment of creatinine levels.

In chronic HF, microalbuminuria, characterized by a urinary albumin-to-creatinine ratio of 30 to 300 mg/g, serves as a marker of renal hemodynamic disturbances and indicates progression of CKD (26). This biomarker is associated with an increased risk of CRS and adverse clinical outcomes, independent of estimated GFR and serum creatinine levels. Tubular biomarkers, including N-acetyl beta glucosaminidase and kidney injury molecule-1 (KIM-1), are released during tubular damage and provide prognostic information regarding renal dysfunction and mortality, independent of eGFR (27). Additional biomarkers such as uromodulin, beta-2 microglobulin (B2M), and alpha-1 microglobulin (A1M) are also elevated in tubular injury (28).

Galectin-3 (Gal-3) is a significant biomarker for renal dysfunction and cardiovascular disease progression. It promotes fibrosis, fibroblast proliferation, and collagen deposition, contributing to cardiac and renal fibrosis. Elevated levels of Gal-3 correlate with reduced GFR and increased risk of CKD, highlighting its potential as both a diagnostic marker and therapeutic target for CRS (29). Neutrophil gelatinase-associated lipocalin (NGAL), a lipocalin protein expressed by neutrophils and epithelial cells, is filtered by the glomerulus and reabsorbed by proximal tubules (30). Increased urinary NGAL levels indicate tubular damage and can precede serum creatinine rises, although its clinical applicability is constrained by sampling variability and interference from conditions such as sepsis and inflammation (31). Fatty acid-binding proteins (FABPs), including liver-specific FABP (FABP-1) and heart-specific FABP (FABP-3), are associated with AKI and ischemic tubular damage, with elevated FABP-3 levels correlating with adverse cardiovascular outcomes in chronic HF (32,33).

Tissue inhibitor of metalloproteinase 2 and insulin-like growth factor binding protein 7 are emerging biomarkers that reflect cellular stress and injury, playing crucial roles in cell-cycle arrest during early phases of injury to prevent cell division until damage is repaired. These biomarkers offer superior accuracy in predicting AKI compared to Cystatin C, KIM-1, L-FABP, NGAL, and IL-18 (34). Patients with CKD typically exhibit elevated baseline levels of brain natriuretic peptide (BNP) compared to individuals with normal renal function. This elevation is primarily attributed to impaired renal clearance, particularly affecting NT-proBNP, as well as chronic pressure and volume overload, and CKD-associated cardiomyopathy (35). Furthermore, BNP levels are significantly higher in patients demonstrating CRS relative to those with acute AHF without renal impairment (36). Further research is needed to elucidate the implications of variations in natriuretic peptide levels, particularly in the context of renin and neprilysin inhibitor therapies, especially in patients with CRS.

TREATMENT and MANAGEMENT

Management of CRS focuses on addressing both the underlying causes and the syndrome's complications, primarily involving volume overload (Table 2). The main treatment approach involves fluid removal using diuretics or ultrafiltration (37). Loop diuretics are considered highly effective and can be used alone or with other diuretics. Two debated strategies for administration are continuous infusion and intravenous boluses, with creatinine clearance guiding dosing (38). Adding a thiazide diuretic can help overcome resistance, while ultrafiltration is useful in resistant cases (39).

RAAS activation due to fluid retention impacts cardiac preload and afterload, worsening cardiac and renal function. Inhibiting RAAS with angiotensin coverting enzyme (ACE) inhibitors and angiotensin receptor blockers can break this cycle and prevent further damage. Using ACE inhibitors in chronic HF doesn't negatively affect prognosis despite worsening renal parameters (40).

Table 2. Management Options in CRS

Treatment Option	Mechanism of Action	Clinical Considerations
Diuretics	Promote natriuresis and fluid excretion.	Monitor for diuretic resistance and electrolyte imbalances.
Tolvaptan	Vasopressin receptor antagonist promoting free water excretion.	Used for hyponatremia; monitor sodium levels.
RAAS Inhibitors	Reduce RAAS activation, decreasing blood pressure and fluid overload.	Monitor renal function and potassium levels.
Beta-Blockers	Reduce heart rate and myocardial oxygen demand.	Titrate carefully to avoid bradycardia or hypotension.
Non-Pharmacological	Dietary modifications, lifestyle changes, and regular monitoring.	Essential for overall management of CRS.

RAAS; renin angiotensin aldosterone system, CRS;cardirenal syndrome

The potential benefits of sodium-glucose co-tranporter-2 (SGLT2) inhibitors are attributed to reductions in systemic and renal arterial stiffness, hyperglycemia, hyperlipidemia, and decreased inflammatory molecule expression (41). Effects such as lowered blood pressure and reduced intravascular volume are likely due to osmotic diuresis, occurring from inhibition of sodium reabsorption alongside glucose (42). SGLT2 inhibitors also increase adenosine release by enhancing sodium delivery to the macula densa, which then triggers tubuloglomerular feedback to constrict afferent arterioles, reducing intraglomerular pressure (43).

Spironolactone and eplerenone manage neurohormonal fluctuations, protecting cardiac and renal function (44). Careful monitoring for hyperkalemia is necessary when used with ACE inhibitors, especially in those with renal impairment, as they may address loop diuretic resistance in hypervolemia (45).

Sacubitril/valsartan, an angiotensin receptor-neprilysin inhibitor, reduces mortality and hospitalization in HF with reduced ejection fraction compared to enalapril, without significantly affecting eGFR decline or end-stage renal disease progression (46). Furthermore, it may increase the urinary albumin-to-creatinine ratio in HF with preserved ejection fraction (47).

Overactivation of the mineralocorticoid receptor (MR) is crucial in the progression of both renal and cardiovascular diseases (48). It promotes inflammation and fibrosis, exacerbating kidney damage and cardiovascular complications (48,49). Finerenone is highlighted as a new treatment option that addresses the limitations of traditional MR antagonists like spironolactone and eplerenone. It is more selective and has shown greater effectiveness in reducing albuminuria, slowing CKD progression, and lowering the risk of cardiovascular events (48-50). Clinical trials such as FIDELIO-DKD and FIGARO-DKD demonstrated finerenone's efficacy in reducing CKD progression and cardiovascular risk in patients with T2D and CKD (51,52). The FIDELIO-DKD trial showed that finerenone reduced CKD progression by 18% and decreased cardiovascular events by 14%. The FIGARO-DKD trial confirmed these findings, showing a reduction in HF hospitalizations by 29% and a significant decrease in cardiovascular mortality.

Finerenone should be integrated into the treatment regimen for patients with T2D and CKD, particularly those already on ACE inhibitors or ARBs and SGLT2 inhibitors. The combined use of these therapies addresses hemodynamic, metabolic, and fibrotic pathways in CKD, offering a comprehensive approach to managing both renal and cardiovascular risks (51,52).

Tolvaptan is a vasopressin V2 receptor antagonist used to manage hyponatremia in HF patients, including those with CRS (53). By blocking the effects of vasopressin, tolvaptan promotes free water excretion without significant sodium loss, helping to correct hyponatremia. In CRS, tolvaptan can be particularly useful in patients with fluid overload and hyponatremia who do not respond adequately to conventional diuretics. Its use requires careful monitoring of serum sodium levels to avoid overly rapid correction of hyponatremia.

In the treatment of CRS, both peritoneal dialysis (PD) and hemodialysis (HD) play crucial roles, especially in managing fluid overload and removing uremic toxins. The roles of PD and HD differ based on the type and severity of CRS, as well as the patient's specific clinical condition.

Peritoneal dialysis is often used in CRS due to its gentle and continuous nature of fluid removal, making it suitable for patients with significant cardiac dysfunction. PD avoids the large fluid shifts that can occur with hemodialysis, which can lead to hemodynamic instability, particularly in patients with HF. The use of PD in CRS can help manage fluid overload and improve symptoms of HF by removing excess fluid more gradually and continuously, reducing the risk of hypotension and further cardiac stress.

PD is particularly advantageous in patients with chronic HF (Type 2 CRS) and those with coexisting CKD (Type 4 CRS), as it allows for better control of fluid balance without causing significant fluctuations in blood pressure. Additionally, PD has been shown to reduce hospitalizations and improve the quality of life in these patients by maintaining more stable hemodynamics.

Hemodialysis is commonly used in the management of AKI in CRS (Type 1 CRS) and in end-stage renal disease associated with CRS. HD is effective in rapidly removing uremic toxins and excess fluid, which is critical in acute settings where rapid correction of metabolic disturbances is necessary. However, the rapid fluid removal associated with HD can lead to hypotension and myocardial stunning, especially in patients with compromised cardiac function.

In CRS, the choice to use HD must be carefully considered, balancing the need for rapid fluid removal with the potential risks to cardiac function. HD is typically reserved for patients who require aggressive management of fluid overload and electrolyte imbalances that cannot be managed with diuretics or PD. In some cases, HD may be combined with ultrafiltration techniques to achieve more controlled fluid removal.

In addition to pharmacological treatments, non-pharmacological strategies are essential in the conservative management of CRS. These include dietary modifications, such as sodium and fluid restriction, as well as lifestyle interventions like weight management,

exercise, and smoking cessation. Regular monitoring of renal function, electrolytes, and fluid status is also crucial in managing CRS.

Limitations

The review integrates information from a broad range of studies and clinical trials, many of which may differ in terms of patient populations, methodologies, and endpoints. This variability can complicate the synthesis of findings and may affect the generalizability of the conclusions drawn. Despite efforts to classify and define CRS, inconsistencies in terminology and diagnostic criteria across studies pose challenges in comparing results and may lead to variability in clinical application. The lack of a universally accepted definition of CRS phenotypes limits the precision of diagnosis and treatment strategies. Much of the data referenced in this review is derived from cross-sectional or short-term studies. The long-term outcomes of various treatment strategies for CRS, particularly concerning emerging therapies, remain underexplored, limiting the ability to draw definitive conclusions about their efficacy over time. While the review discusses several emerging biomarkers for CRS, the clinical applicability of these biomarkers is still under investigation. The evidence supporting their use in routine clinical practice is not yet robust, and there may be limitations in their accessibility and cost-effectiveness in different healthcare settings. The review emphasizes pharmacological approaches to managing CRS, potentially overlooking the importance of non-pharmacological interventions, lifestyle modifications, and patient-centered care strategies. This focus may not fully capture the multidisciplinary approach required for optimal CRS management. The studies included in this review may have a geographic bias, predominantly representing data from Western populations. This could limit the applicability of the findings to populations in other regions, where genetic, environmental, and healthcare system differences may affect CRS presentation and management. The field of cardiorenal medicine is rapidly evolving, with new research and clinical trials continuously emerging. As a result, the review may not fully encompass the most recent advancements or reflect the latest clinical practices.

CONCLUSION

CRS represents a significant clinical challenge due to its complex pathophysiology, varied phenotypes, and the interdependence of heart and kidney functions. The classification of CRS into five distinct types underscores the need for tailored diagnostic and therapeutic approaches that address the specific underlying mechanisms and clinical presentations of each type. Advancements in the understanding of CRS have led to the development of novel biomarkers and therapeutic strategies, which show promise in improving patient outcomes. However, the heterogeneity of the condition, coupled with the ongoing challenges in standardizing definitions and treatment protocols, highlights the necessity for continued research.

The emergence of new pharmacological agents, such as SGLT2 inhibitors and selective mineralocorticoid receptor antagonists like finerenone, offers hope for more effective management of CRS by targeting both cardiac and renal pathologies. Despite these advancements, the management of CRS remains complex, requiring a multidisciplinary approach that integrates pharmacological treatments with lifestyle modifications and close monitoring of renal and cardiac functions.

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