CMJ. 2024; 46(4): 234-239
DOI: 10.7197/cmj.1600386

Cumhuriyet Medical Journal

| cmj.cumhuriyet.edu.tr | Founded: 2004 Available online, ISSN:1305-0028 Publisher: Sivas Cumhuriyet Üniversitesi

# Overview of Cardiorenal Syndrome

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**Review**

*History*

*Received:* 12/12/2024
*Accepted:* 23/12/2024



**ABSTRACT**

Cardiorenal syndrome is a complex clinical condition affecting both the kidney and the heart. It is divided into 5 different subgroups according to various clinical features. However, in most clinical settings this is difficult to determine because the pathophysiology is complex, and the pathways are poorly understood. Given this complex clinical situation, many challenges arise in the management of both acute and chronic cardiorenal syndrome. In this review, the definition, classification, pathophysiology and treatment of cardiorenal syndrome were evaluated.

***Keywords:*** Cardiorenal syndrome, kidney damage, heart failure

# Kardiyorenal Sendroma Genel Bakış

**Derleme**

*Süreç*

*Geliş:* 12/12/2024
*Kabul:* 23/12/2024



**ÖZET**

Kardiyorenal sendrom hem böbrek hem kalbi etkileyen karmaşık bir klinik durumdur. Çeşitli klinik özelliklere göre 5 farklı alt gruba ayrılır. Ancak çoğu klinik ortamda patofizyolojinin iç içe geçmiş olması ve yolakların yeterince anlaşılmamış olması nedeniyle bunu belirlemek zordur. Bu karmaşık klinik durum göz önüne alındığında hem akut hem kronik kardiyorenal sendromun yönetiminde birçok zorluk ortaya çıkmaktadır. Bu derlemede, kardiyorenal sendromun tanımı, sınıflandırması, patofizyolojisi, tedavisi incelenmektedir.

***Anahtar Kelimeler:*** Kardiyorenal sendrom, böbrek hasarı, kalp yetmezliği

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*How to Cite:* Şahinbaş M. Overview of Cardiorenal Syndrome, Cumhuriyet Medical Journal, 2024; 46(4): 234-239.

## Introduction

The complex interdependent relationship between the kidney and the heart was described by Robert Bright in 1836. He identified distinct cardiac structural changes seen in those with severe kidney disease. Cardiovascular and kidney diseases have many common points of interaction. These are hemodynamic interactions between the heart and kidney in heart failure, the effects of atherosclerotic disease on both organ systems, neurohormonal activation, cytokines, biochemical perturbations along the anemia-inflammation-bone mineral axis in chronic kidney disease (CKD), and structural changes in the heart with progression of kidney disease. In addition, the term "cardiorenal syndrome" (CRS) encompasses a range of disorders involving the heart and kidneys in which acute or chronic dysfunction in one organ can lead to acute or chronic dysfunction in another organ.[1] This article focuses primarily on the definition, pathophysiology, and diagnostic and treatment strategies of CRS.

## Definitions and Phenotypes

The National Heart, Lung, and Blood Institute Working Group defined CRS in 2004 as a condition in which interactions between the kidneys and the circulatory system increase circulating volume, worsening symptoms of heart failure (HF), and causing disease progression. The working group emphasized that severe cardiorenal derangement leads to CRS and that treatment of congestive HF in this setting is limited by the decline in renal function.[2] This cardiology-centered perspective plays a fundamental role in understanding CRS, especially in acute heart failure. The Acute Dialysis Quality Initiative (ADQI) summarized the approach in 2008, dividing CRS into 2 main groups, cardiorenal and renocardial syndromes, taking into account the triggering factor of the disease process. Accordingly, the disease was further divided into 5 subtypes based on the sequential involvement of organs and their severity, and these are summarized in Table 1.[3] Although the ADQI CRS Classification has overcome some of the initial ambiguities in the definition of CRS, determining the initial injury and subsequent events and understanding the processes leading to decompensation of acute or chronic CRS/renocardiac syndrome can be challenging.[4]

## Pathophysiology

Part of the difficulty in identifying and treating CRS stems from the involvement of multiple complex pathophysiologic processes. The traditional explanation for the development of CRS focuses on the failure of the heart to produce adequate output, resulting in prerenal hypoperfusion.[1] The renin-angiotensin-aldosterone system (RAAS) plays an important role in the progression of renal damage and worsening of HF. Inadequate renal blood flow or perfusion pressure triggers renin release by the juxtaglomerular cells of the afferent arterioles via pressure-sensing baroreceptors in the ascending limb of the loop of Henle. Increased renin levels increase the production of angiotensin II (Ang II).[5] Ang II has various adverse effects on the heart, blood vessels, and kidneys. Ang II increases the filtration fraction by vasoconstricting the efferent arterioles in the kidney. It increases sodium reabsorption via aldosterone in the distal tubules. Ang II may lead to kidney damage by increasing the synthesis of endothelin 1, a potent vasoconstrictor and pro-inflammatory peptide.[6] Ang II causes transforming growth factor-β1 (TGF-β1) mediated hypertrophy in cardiac myocytes. It causes contraction of vascular smooth muscle on AT1 receptors. It also increases oxidative stress and inflammation. Left ventricular dysfunction in heart failure patients activates the sympathetic nervous system (SNS) to maintain perfusion. This results in increased contractility and systemic vasoconstriction. These mechanisms support perfusion in the short term but may exacerbate cardiac and renal dysfunction in the long term.[7] Elevated intra-abdominal pressure (IAP) can lead to intra-abdominal hypertension (IAH) and abdominal compartment syndrome in severe cases. IAP elevations are often seen as surgical complications.[8] In addition, it is increasingly common in the pathophysiology of CRS. IAP is high in 60% of patients with advanced chronic HF. While normal IAP values in healthy individuals are between 5-7 mmHg, IAP values between 8-12 mmHg in these patients are associated with kidney damage and this may lead to the development of Type 2 CRS.[9] HF causes volume overload and increased central venous pressure (CVP). Elevated venous pressures weaken the flow gradient in the renal circulation. This leads to congestion, glomerular dysfunction, and decreased urine output. Several studies have shown that elevated IAP results in decreased GFR and renal plasma flow, and an elevated CVP is significantly associated with decreased renal function.[10,11]

Pulmonary vascular resistance is in constant interplay with right ventricular function. In pulmonary hypertension, the stressed heart tries to balance pre-load and afterload to accommodate increased pulmonary vascular resistance. Resultant neurohormonal activation (endothelin, arginine vasopressin) leads to water and salt retention, worsening venous congestion, and further reduced cardiac output. This may cause a decrease in GFR.[1]

Anemia plays a major role in the pathophysiology of CRS. Failure to provide oxygen to an already stressed heart or a damaged kidney can cause ischemic damage that can result in progressive cell death in both organs. Red blood cells contain many antioxidants and therefore anemia can lead to increased oxidative stress.[12]

*Table 1.* CRS Classification

| Phenotype | Naming | Definition | Clinical Examples |
|---|---|---|---|
| **Type 1 CRS** | Acute CRS | Heart failure leading to acute kidney injury (AKI) | Cardiogenic shock and AKI after acute coronary syndrome (ACS), AKI after acute heart failure (AHF) |
| **Type 2 CRS** | Chronic CRS | Chronic heart failure (CHF) leading to CKD | Chronic heart failure |
| **Type 3 CRS** | Acute Renocardiac Syndrome | AKI leading to AHF | Heart failure during AKI resulting from volume overload, inflammatory attack and metabolic disorders in uremia |
| **Type 4 CRS** | Chronic Renocardiac Syndrome | CKD leading to CHF | Left ventricular hypertrophy (LVH) and heart failure resulting from cardiomyopathy associated with CKD |
| **Type 5 CRS** | Secondary CRS | A systemic process leading to both heart and kidney failure | Amyloidosis, sepsis, cirrhosis |

## Biomarkers and Diagnosis

### *Biomarkers*

Biomarkers contribute to the diagnosis of CRS. Cardiac biomarkers, B-type natriuretic peptide (BNP) and its inactive form, pro B-type natriuretic peptide (NT-proBNP), are helpful in the diagnosis and prognosis of both acute and chronic HF**.** BNP values are significantly higher in patients with acute HF without renal failure.[1] Studies have shown that better results are obtained in acute HF and NT-proBNP levels decrease in patients with decreased renal function after treatment. High NT-proBNP has been shown to contribute predictively to CRS risk stratification by BNP in patients with acute HF before the development of renal dysfunction.[13] High-sensitivity cardiac troponins I and T are established diagnostic and prognostic markers in acute myocardial infarction. Troponins increase with decreasing GFR, and a sustained elevation is associated with a higher risk of death.[14] In addition, suppressor of tumorigenicity 2 (ST2) measurements are valuable in predicting heart failure-related deaths and hospitalizations and are not affected by renal function.[15] Serum galectin-3 levels have also been shown to be independent predictors of cardiovascular mortality.[16]

Renal biomarkers, serum creatinine and changes in urine output are late signs of acute kidney injury, defining renal function. Cystatin C is a sensitive marker of GFR and has prognostic value as an indicator of hospitalization and mortality from acute heart failure.[17] Cystatin C, unlike creatinine, is less affected by age and non-renal factors.[18] Tubular damage markers include insulin-like growth factor binding protein 7 (IGFBP-7), tissue inhibitor of metalloproteinase-2 (TIMP-2), neutrophil gelatinase-associated lipocalin (NGAL), and kidney injury molecule-1 (KIM-1), but further studies are needed for these markers.[19,20]

### *Imaging Modalities*

Non-invasive imaging modalities play an important role in detecting markers of venous congestion and forward flow impairment in CRS and are easily accessible clinical tools at the bedside. Echocardiography can help diagnose congestive status with hemodynamic parameters such as CVP, systolic pulmonary artery pressure, pulmonary capillary wedge pressure/left atrial pressure, and cardiac output (CO).[21] In addition to CVP, there are other useful echocardiographic measurements such as lateral and septal wall longitudinal motion (E') in relationto mitral in flow velocity (E). The E/E' ratio is directly related to the pulmonary capillary wedge pressure; E/E' >15 means that the pulmonary capillary wedge pressure is ≥18 mmHg.[22,23] Decreased left ventricular ejection fraction, increased pulmonary artery pressure, and larger right ventricular diameter have been in dependently associated with an increased incidence of CRS.[24] Renal ultrasonography and intrarenal venous flow patterns are emerging tools for determining renal venous congestion and its clinical significance in CRS. Other renal hemodynamic parameters, such as renal arterial resistive index and renal perfusion index, are not used as predictors of clinical outcomes in CRS, despite the ircorrelation with CVP, mean arterial pressures, and effective renal plasma flow.[25] Renal ultrasonography provides information on the chronicity of the disease by assessing renal size, echogenicity, cortical thickness, and abnormal corticomedullary ratios. This is useful in determining whether AKI or CKD is the primary disorder in the clinical presentation of CRS.[26]

## Treatment

Due to the complex and heterogeneous pathophysiology of CRS, there are many difficulties in its treatment and method. The drugs used in the treatment of CRS have not been fully investigated in randomized controlled trials. Therefore, there is no consensus on the treatment strategies of CRS patients.[27] There are many drug groups and strategies used in the treatment of cardiorenal syndrome. Diuretics and ultrafiltration together with inotropic agents, beta-blockers (BB), angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs) or angiotensin receptor neprilysin inhibitors (ARNI), mineralocorticoid receptor antagonists (MRA) and sodium glucose transporter inhibitors (SGlT2i) are some of these drug groups.[28] Other treatment options include implantable defibrillator therapy (ICD) and cardiac resynchronization therapy (CRT).[29]

### Decongestive Therapy

Acute management of the patient with venous congestion often focuses on rapid correction of hypervolemia to aid symptomatic relief. There are effective treatments that result in decongestion, but none have been found to improve survival or reduce disease progression.[30] Similarly, although sodium restriction is recommended to prevent hypervolemia, its positive effect has not been demonstrated.[31] Loop diuretics (furosemide, bumetanide, torasemide and ethacrynic acid) are the preferred diuretics in acute or chronic HF.[32] The duration of action of loop diuretics is short, lasting 2 to 3 hours and up to 6 hours for intravenous bolus and oral administration, respectively. Intravenous furosemide has greater bioavailability than oral furosemide.[33] Torasemide has a longer half-life and therefore requires less frequent dosing. It has been shown that torasemide may be more effective in decongestive treatment of HF compared to furosemide.[34] Although diuretic synergy is effective in patients with acute HF, its effect in CRS is a matter of debate. It may also cause further deterioration of renal function.[35] Deterioration of renal function in type 1 CRS leads to higher hospitalization rates and mortality.[36] However, studies with high and standard doses of loop diuretics have not shown any significant difference in their effects on renal function. However, high-dose loop diuretics have been shown to provide better symptomatic relief. This suggests that loop diuretics may not contribute to kidney damage and that a decrease in eGFR may be an indicator of the severity of heart disease.[30,37,38]

The effectiveness of diuretics in decongestive therapy decreases with increasing severity of HF.[39] Impaired absorption, decreased renal blood flow, azotemia, and proteinuria cause decreased diuretic concentrations in the tubular lumen, leading to diuretic resistance. Diuretic resistance can be defined as continuing congestion despite increasing diuretic doses equivalent to 80 mg/day furosemide, less than 0.2% sodium excretion; and failure to excrete 90 mmol sodium in the next 72 hours despite taking 160 mg furosemide twice daily. Clinically, inadequate improvement in patients' symptoms, increased mortality after discharge, and rehospitalization are indicators of diuretic resistance. Although some pharmacological agents have been used in diuretic resistance, they have not been successful in the long term.[40] Thiazide-type diuretics do not show sufficient efficacy in CRS. In addition, another diuretic group, potassium-sparing diuretics such as spironolactone, has been tried but has not been shown to be beneficial.[41]

If fluid overload persists despite the appropriate maximal use of pharmacological treatment tools and/or renal replacement therapy (RRT) is required due to uremic indications and electrolyte disturbances, patients may receive invasive decongestive treatments such as ultrafiltration (UF) and RRT.[42] Intrafiltration is a mechanical process that removes isotonic fluid and low molecular weight molecules from the circulation and eliminates hypervolemia without neurohormonal activation. Different studies have addressed the effectiveness of ultrafiltration in patients with CRS. The RAPID-CHF study found better outcomes in CRS patients using ultrafiltration instead of pharmacological treatment.[43] In the UNLOAD study, patients with acute HF who underwent ultrafiltration were associated with a lower readmission rate 90 days after hospital discharge, despite no improvement in renal function.[44] In contrast, the CARRESS-HF study examined type 1 CRS patients with renal dysfunction in a randomized controlled manner. In this study, patients who underwent UF were found to have more side effects and less weight loss than those who used diuretics.[42] This difference was thought to be related to the worse renal function of patients in the CARRESS-HF study. A large-scale meta-analysis emphasized that UF was more effective and safe in the treatment of CRS without worsening renal function compared to diuretic therapy.[45]

### Inotropic and Vasodilator Therapy

In patients with type 1 CRS, the effects of inotropic agents and vasodilators to improve cardiac output and increase renal perfusion and provide diuresis may be beneficial. The most notable of these drugs are nitroglycerin and nesiritide. These two drugs have been shown to be more beneficial than inotropic agents such as dopamine and dobutamine.[28] Among inotropes, dopamine improves renal blood flow through its cardiac inotropic effect and its effects on β- and α-adrenergic receptors and renal dopaminergic receptors. Although some studies suggest a renal protective effect of low-dose dopamine in acute HF, a long-term benefit has not been demonstrated.[46] Few and sparse data are available on the use of other inotropes in CRS.[47]

### Beta Blocker Treatment

BB's have been included in the first-line treatment of chronic HF because of their ability to improve HF prognosis and mortality. However, a direct benefit has not been proven in patients with acute decompensated HF or CRS.[27]

### Renin Angiotensin Aldosterone Inhibitors Treatment

Inhibition of the renal angiotensin aldosterone system (RAAS) is the cornerstone of HF treatment. They are treatments that reduce mortality in HF. ACE inhibitors and ARBs have been shown to reduce mortality in HF and CRS, even in patients with severe renal impairment. However, close monitoring is recommended in these patients, especially for potassium levels.[28] Aliskiren, a direct renin inhibitor, has not been shown to be beneficial in improving hospitalization and mortality rates.[48]

In recent years, many studies have been conducted with sacubitril/valsartan, a combination of angiotensin receptor blocker and neprilysin inhibitor. ARNI caused less renal failure compared to other RAAS inhibitors. It also reduced mortality and hospitalization rates.[49,50]

### *Sodium Glucose Transporter-2 Therapy*

SGLT-2 reabsorbs glucose and sodium in the proximal tubule of the kidney. Blockade of SGLT2 improves overall survival, improves cardiovascular outcome, and has clinical benefits by reducing HF hospitalizations and renal failure.[29,51] The use of SGLT2i has been recommended as first-line therapy in guidelines for heart failure as well as for diabetic kidney disease and other subtypes of proteinuric glomerular disease.[52]

### *New Therapeutic Approaches*

There are different therapeutic approaches that are being tried and are being investigated in CRS. Studies with tolvaptan, a selective antagonist of the V2 arginine vasopressin receptor, have shown that this drug does not reduce the risk of cardiovascular events and HF-related hospitalizations.[53,54] However, it has been shown to provide cardiovascular benefits in patients with hyponatremia.[55] In recent years, activation of the erythropoietin receptor in the heart of patients with HF has attracted attention because activation of this receptor may play a protective role against apoptosis, fibrosis, and inflammation and may lead to improvement of cardiac structure and function.[56] Both improved cardiovascular mortality and modest improvement in renal function have been demonstrated in patients with gout treated with the uric acid-lowering agents allopurinol or probenecid. Probenecid has been shown to have inotropic properties and may be useful in HF as monotherapy or in combination with hydrochlorothiazide to increase diuresis.[56,57]

Implantable cardiac defibrillators (ICDs) are thought to be beneficial not only in HF but also in CRS.[29] However, it has been suggested that the effectiveness of these devices is reduced in patients with impaired renal function.[58] In addition to these approaches, there are many newly developed mechanical and non-pharmacological treatment methods. However, no clear benefits have been shown and further studies are needed for their development.[40]

## Conclusion

CRS is a group of diseases that can be chronic or acute, affecting the kidney and heart. Venous congestion, low arterial perfusion, and neurohumoral activation affect both organs, and if appropriate treatment is not given, a vicious cycle begins. Given the complex pathophysiology of CRS, many challenges arise in the management of both acute and chronic CRS. There are proven treatments, but there are also promising new approaches. Better knowledge of the pathophysiology and treatment options of CRS and a multidisciplinary approach will reduce mortality and morbidity in these patients.

***Financial Disclosure:*** The authors declared that this study has received no financial support.

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