



# Pathophysiological Mechanisms and Advances in Diagnosis and Treatment of Cardiorenal Syndrome: A Comprehensive Review

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**Abstract:** Cardiorenal syndrome (CRS) is a syndrome in which acute and chronic functional abnormalities occur in one organ of the heart and kidney, leading to acute and chronic functional abnormalities in the other organ. The clinical diagnosis and treatment of CRS has its own specificity, and its pathophysiological mechanism is relatively complex. This paper provides an overview of the pathophysiological mechanism of CRS, the speciality of diagnosis and treatment of CRS, and progress in the target of injury markers in order to provide new ideas for clinical treatment. This paper summarizes the pathophysiology and pathogenesis of CRS, its diagnosis and treatment, and the progress of damage marker targets, in order to provide new ideas for clinical treatment.

**Keywords:** cardiorenal syndrome, heart failure, renal failure, mechanisms

## 1. Introduction

Cardiorenal syndrome (CRS) is a complex disease involving cardiac insufficiency and renal damage, with complex interactions between the two. According to the article, cardiorenal interactions are believed to be key to the development of CRS, in which the role of the neuroendocrine system is crucial, including the sympathetic nervous system, the renin-angiotensin-aldosterone system, and a variety of pathophysiological mechanisms such as oxidative stress, inflammatory responses, and hemodynamic disturbances.

Neurohormonal activation and hemodynamic disturbances play a crucial role in the mechanism of all cardiac-renal syndromes, regardless of the organ initially damaged and whether the disease is acute or chronic. The monitoring program of the neurohormonal system is a complex and well-established system involving the control of gene and protein expression, tissue responses such as inflammation and fibrosis, and cellular metabolism. In the early stages of cardiorenal syndrome, volume overload is the primary manifestation due to effective circulating arterial stasis and hemodynamic disturbances. To maintain sodium water balance, neurohormonal systems including the renin-angiotensin-aldosterone system, the sympathetic nervous system, the arginine pressor system, and the endothelial vasoconstrictor peptide system are activated. These systems lead to further water and sodium retention through water and sodium reabsorption, counteracting the role of the cardiac natriuretic system in promoting water and sodium excretion, ultimately creating a vicious cycle. The neurohormonal system can be activated by coexisting diseases such as diabetes mellitus, hypertension, and metabolic syndrome that are common to both cardiovascular disease and chronic kidney disease. These coexisting disorders and other factors that promote organ damage such as oxidative stress play a similar role in sensitizing sensitive target organs in patients with chronic kidney disease to damaging factors. These damaging factors may include hypertension, hyperglycemia, and hyperlipidemia, all of which can cause damage to target organs such as the kidney. The mechanisms of action of these damaging factors vary, but they are all associated with neurohormonal activation and hemodynamic disturbances. Therefore, the treatment of cardiorenal syndrome requires comprehensive consideration of multiple factors, including the regulation of the neurohormonal system, the correction of hemodynamic disturbances, and the co-treatment of cardiovascular disease and chronic kidney disease.

Endothelial dysfunction refers to the dysfunction of vascular endothelial cells, and this dysfunction can lead to a variety of vascular pathological states, including vasodilatory dysfunction. Endothelial dysfunction has been shown to be one of the important pathophysiologic mechanisms in diseases such as hypertension, coronary heart disease, chronic heart failure, diabetes mellitus, and chronic renal failure.

Endothelial dysfunction may lead to an important role in the pathogenesis of diseases such as atherosclerosis and proteinuria. In particular, the presence of micro-proteinuria suggests endothelial dysfunction of the capillaries, which indirectly reflects dysfunction of the endothelial system. Vasoconstriction-regulating factors released by endothelial cells include nitric oxide, endothelin-1, angiotensin II, inflammatory factors, and coagulation factors (e.g., plasminogen activator, plasminogen activator inhibitor 1), etc. Abnormal release of these factors may further damage the cardiovascular system and

the kidneys.

Because the kidney is a vascular-rich organ, disorders of the endothelial system can cause damage not only to the cardiovascular system but also to the kidneys. In diseases such as diabetes and chronic renal failure, endothelial dysfunction may lead to impaired renal microcirculation, which in turn leads to impaired renal function. Therefore, the treatment of these diseases needs to focus on improving endothelial function in addition to treatments targeting the cause of the disease.

## **2. Novel biomarkers and diagnostic specificities of CRS**

### **2.1 Uncertainty in monitoring volume changes with li-natriuretic peptide**

Among the novel biomarkers, Li-natriuretic peptide is widely used in the monitoring of volume loading status in patients with heart failure, however, for patients with CRS, especially those with renal insufficiency, Li-natriuretic peptide has a poor guiding effect and may interfere with the accurate judgment of the degree of deterioration. Therefore, the judgment of volume load changes in patients with CRS should be combined with central venous pressure (CVP), the degree of edema relief and other indicators, with a view to more accurately assessing the condition.

In terms of diagnosis and treatment specificity, combined diuretic therapy is considered an important strategy. Pharmacologic diuretics that reduce volume load play a key role in the treatment of CRS. Diuretics can significantly reduce the anterior and posterior cardiac load and alleviate the symptoms of heart failure, but high doses may cause diuretic resistance, leading to problems such as insufficient circulating blood volume and reduced renal blood flow. For this reason, adjusting the appropriate diuretic dose and optimizing the diuretic mode, as well as combined diuretic therapy may be more effective in reducing the volume load and reducing renal damage.:

### **2.2 Uncertainty of blood creatinine in monitoring deterioration of renal function**

Serum creatinine is widely used in assessing changes in renal function, but there is some uncertainty in its monitoring results. First, the limitation of serum creatinine is its inability to differentiate between prerenal hypoperfusion and renal kidney damage. In some cases, such as when bruising resolves in patients with CRS or when angiotensin-converting enzyme inhibitors (ACEIs) are applied, serum creatinine levels may show a small increase, which is mainly due to its effect on renal hemodynamics rather than damage to the kidney itself.

Second, elevated serum creatinine levels should not be used alone as a basis for assessing the degree of deterioration in renal function, but should be considered in the context of the entire clinical picture. Especially in patients with CRS, not all elevated serum creatinine levels adversely affect prognosis. For example, in the SOLVD trial of left ventricular dysfunction, analysis showed that deterioration of renal function early after ACEI initiation was not associated with an increased risk of death. The benefit of reduced risk of death persisted in patients who continued drug therapy at elevated creatinine levels.

Therefore, in patients with CRS, we need to pay more attention to other renal injury markers, such as NGAL and kidney injury molecule-1 (KIM-1), to more accurately assess and predict the deterioration of renal function, thus providing new ideas for clinical treatment.

### **2.3 New targets for CRS diagnosis**

New targets for the diagnosis of cardiorenal syndrome mainly include kidney injury molecule 1 (KIM-1), neutrophil gelatinase-associated lipoprotein (NGAL), and urinary endopeptidase-3 in urine. These novel markers of renal injury are able to predict renal injury earlier and more accurately when they are present, and are of great clinical value in the diagnosis of cardiorenal syndrome.

For example, NGAL is an early kidney injury-sensitive marker that is significantly elevated in the urine within a few hours after kidney damage, and is therefore important for the early diagnosis of cardiorenal syndrome. Meanwhile, KIM-1 is another molecule whose expression level is elevated after renal tubular epithelial cell injury, and its expression level in renal diseases is closely correlated with the degree of tubular injury, which can be used as an important diagnostic and prognostic indicator of cardiorenal syndrome.

In addition, traditional renal function indicators such as serum creatinine and urea nitrogen also play an important role in the diagnosis of cardiorenal syndrome. These indicators are not as sensitive and accurate as the newer renal injury markers, but they still have some reference value. For example, serum creatinine is an important indicator of renal function, and when its level is elevated, it usually indicates impaired renal function; while urea nitrogen can reflect whether the excretory function of the kidney is normal or not.

In summary, new targets for the diagnosis of cardiorenal syndrome mainly include KIM-1, NGAL, and urinary endopeptidase-3 in urine, etc. The emergence of these novel markers of renal injury provides an important basis for the

early diagnosis of cardiorenal syndrome. Meanwhile, traditional renal function indicators such as serum creatinine and urea nitrogen also have a certain reference value in the diagnosis of cardiorenal syndrome.

### 3. Conclusions

The principles of treatment of cardiorenal syndrome (CRS) focus primarily on improving cardiac and renal function while preventing complications. Treatments include pharmacologic and mechanical therapies, of which pharmacologic treatments cover positive inotropic agents, neurohormonal antagonists, diuretics, and vasoactive agents. Studies have shown that tolvaptan, a selective vasopressin V2 receptor antagonist, significantly reduces the symptoms of edema and dyspnea in heart failure and raises serum sodium levels without exacerbating the deterioration of cardiac and renal function. Adenosine antagonists have also shown potential therapeutic value for CRS as possible new therapies. Nevertheless, the treatment of CRS still faces many challenges. Treatment options for CRS should focus more on improving cardiac function, reducing volume overload, and optimizing fluid management. Only by correctly recognizing the disease characteristics of CRS, utilizing pathobiological understanding and efficient biomarkers, adapting appropriate therapeutic regimens, and performing early diagnosis and treatment, can we effectively improve the quality of life and long-term survival of patients.

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