CardioRenal Medicine

Cardiorenal Med
DOI: 10.1159/000500715
Published online: July 2, 2019


**Review Article**

# Neurohormonal, Endocrine, and Immune Dysregulation and Inflammation in Cardiorenal Syndrome

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**Keywords**
Cardiorenal syndrome · Neurohormonal mechanism · Inflammation · Immune dysregulation

**Abstract**
"Organ crosstalk" is the complex physiological communication between different body systems, and it is necessary for the optimal equilibrium and functioning of the organism. In particular, heart and kidney function is tightly connected, and interplay between these two organs occurs through a vast array of dynamic and bidirectional mechanisms. The term cardiorenal syndrome (CRS) indicates an interaction between the heart and kidneys in acute and chronic disease settings. In all types of CRS, multiple pathophysiological processes are implicated in the initiation and progression of organ injury. In addition to hemodynamic parameters, endothelial injury, immunological imbalance, cell death, inflammatory cascades, oxidative stress, neutrophil migration, leukocyte trafficking, caspase-mediated apoptosis, extracellular vesicles, small noncoding RNAs, and epigenetics play pivotal roles in the development of CRS. In this review, we will focus on neurohormonal, endocrine, and immune dysregulation and inflammation as mechanisms involved in the pathogenesis of CRS.



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## Background

"Organ crosstalk" is the complex physiological interaction between different body systems mediated through cellular, subcellular, molecular, neural, endocrine, and paracrine mechanisms which give rise to multiple forms of response. Physiological interaction between organs is necessary for the optimal equilibrium and functioning of the organism. On the other hand, in the disease setting, the toxic cell signaling induced by the primary injured organ can provoke structural and functional damage to distant organs [1]. Particularly, heart and kidney functions are closely interrelated through a variety of dynamic and bidirectional mechanisms [2].

The term cardiorenal syndrome (CRS) has recently been presented to underline the strong interaction between the cardiac and the renal system in acute or chronic disease [3]. According to the existing definition, five clinical syndromes have been classified according to their etymology (primary or secondary pathology) and time frame. In all types of CRS, multiple pathophysiological processes are involved in the induction and progression of organ damage. Furthermore, epidemiological studies on CRS have demonstrated that patients may change between different CRS types [4–6]. Recent works have shown that the multifactorial mechanisms leading to the clinical scenario include not only hemodynamic parameters (such as extracellular fluid volume, cardiac output, and arterial pressure), but also endothelial injury, immunological imbalance, cell death, inflammatory cascades, oxidative stress, neutrophil migration, leukocyte trafficking, caspase-mediated apoptosis, extracellular vesicles, small noncoding RNAs, and epigenetics [7–26].

In this review, we will investigate and focus on neurohormonal, endocrine, and immune dysregulation and inflammation as mechanisms involved in CRS development.

## Neurohormonal System Activation

Cardiac and renal functions are necessary for body hemodynamic stability through multiple neurohormonal mechanisms which involve the autonomic nervous system, renin-angiotensin-aldosterone system (RAAS), arginine vasopressin (AVP), and endothelin [27]. Neurohormonal activation plays an important role in the pathogenesis of CRS. Indeed, acute and chronic heart failure – a typical feature of CRS type 1 and type 2, respectively – is described by reduced cardiac output responsible for a reduction in renal perfusion pressure and leading to activation of the RAAS and baroreceptors [28].

The activated baroreceptors and RAAS induce AVP release, and consequently fluid retention, further heart decompensation, and tissue hypoxia [29]. In particular, AVP is responsible for aquaporin 2 water channel expression in the collecting duct and increased urine concentrations, as electrolyte-free water moves from the lumen into the interstitium and then into the circulation [30]. Moreover, direct effects of AVP on the renal vascular system, low cardiac output, and the activated RAAS result in progressive renal dysfunction because of afferent renal arteriolar vasoconstriction and reduced renal perfusion [31].

Activation of the RAAS and elevated levels of AVP are involved in the development of hyponatremia, the severity of which is related to the degree of the underlying neurohormonal activation [32] (Fig. 1). B-type natriuretic peptide (BNP) and its precursor NT-proBNP are released by the ventricles, and their levels usually increase in case of acute or chronic heart failure. Indeed, BNP release is induced by ventricular and atrial wall distension and neurohormonal activation [33]. However, increased levels of natriuretic peptides (NP) may be associated with renal dysfunction as well, thus serving as a valued diagnostic and prognostic test in different types of CRS [34].

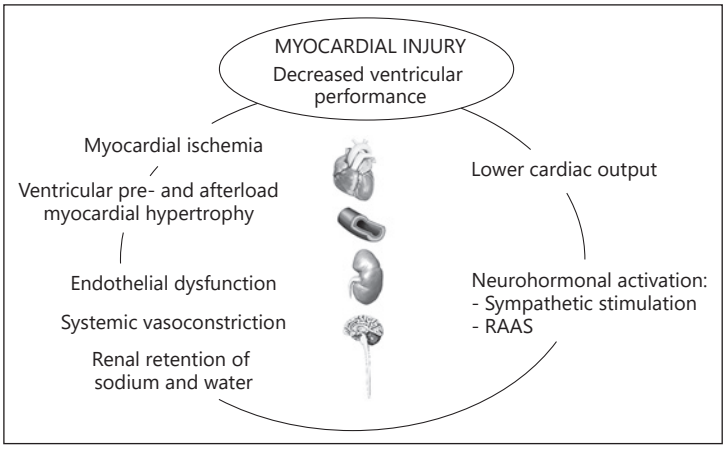


**Fig. 1.** Neurohormonal regulation in cardiorenal syndrome.

Even though the exact mechanism remains unclear, augmented myocardial wall stress, left ventricular hypertrophy, coronary disease, and cardiac remodeling may contribute to NP increases in the setting of CRS. Nevertheless, the relationship between BNP, heart failure severity, and kidney function remains to be better explained. Patients with chronic kidney disease have higher levels of BNP and NT-proBNP than gender- and age-matched subjects with normal renal function, even if there is no heart failure. Anyway, a cutoff value for distinguishing subjects with only renal disease from subjects with CRS has not been defined yet [33].

### Endocrine Dysregulation

Progressive loss of renal function in patients with CRS (particularly types 2 and 4) is associated with anemia, altered mineral homeostasis, salt and water retention, and inflammation, which can contribute to the development of cardiovascular complications [35]. Among the factors involved in renal injury and cardiac impairment, altered calcium and phosphate metabolism plays a pivotal role. In the setting of CRS type 4, progression of renal damage is responsible for reduced renal activation of vitamin D and diminished phosphorus excretion [36]. Consequently, hypocalcemia and hyperphosphatemia induce the secretion of parathyroid hormone (PTH), which increases bone absorption, renal absorption of calcium, and vitamin D synthesis [37]. Moreover, elevated phosphorus levels induce bone synthesis of fibroblast growth factor 23 (FGF23), which increases renal phosphorus excretion and decreases vitamin D production [38]. Progressive renal impairment and low production of vitamin D exacerbated by high concentrations of FGF23 reduce the kidneys' ability to regulate PTH secretion. Parathyroid glands may enlarge and become no longer responsive to regulatory signals such as vitamin D receptor activation and elevated serum calcium levels, thus requiring surgical removal [39].

Alterations in calcium metabolism increase cardiovascular events and mortality [40]. Indeed, mineral and bone disorder associated with chronic kidney disease is characterized by changes in bone characteristics (turnover, volume, and strength) and changes in mineral homeostasis (imbalances in calcium, phosphorus, vitamin D, and PTH), which may induce vascular calcifications and cardiac impairment. Furthermore, a decrease in vitamin D stimulates the RAAS, thus inducing water retention and vasoconstriction, which further increase arterial stiffening [41]. Moreover, a strong association between vitamin D deficiency and

cardiovascular disease was reported for the general population [42]. Among the cardiovascular effects of reduced vitamin D receptor activation, smooth muscle cell calcification, proliferation, and fibrosis lead to arterial stiffness, atherosclerosis, and left ventricular hypertrophy [43].

### Immune Imbalance

An immune-mediated dysregulation may be implicated in the pathogenesis of CRS, particularly in types 1 and 5 [13]. The significance of innate and adaptive immune responses to molecules released in case of either infection or tissue damage has recently been emphasized [44, 45]. The innate immune response is stimulated in a nonantigenic way in the setting of inflammatory states and infections. Myeloid cells with some "innate" neutrophils and lymphocyte subtypes, dendritic cells (DCs), monocytes/macrophages, natural killer cells, and natural killer T cells play fundamental roles. Macrophages and DCs release chemokines and cytokines and present antigens to lymphocytes [44, 46]. The adaptive response is a second approach the immune defense uses against specific antigens in humoral and cellular pathways.

Polarization of T cells secondary to the activation of DCs involves numerous signaling cascades. Toll-like receptor (TLR) pathways induce the activation of both immune response pathways. TLRs are recognition receptors binding to different molecules, particularly endogenous molecules deriving from injured tissue. TLR signaling produces a rapid response to tissue damage, and it is implicated in the induction of the immune response in the setting of heart and kidney disease [47]. Even though DCs are important immune regulators, their role in CRS has been only partially defined. Furthermore, intrarenal DCs are dominant resident leukocytes which play a pivotal role in kidney inflammation and immunity. In the normal mouse, CD11c-positive major histocompatibility complex class II-positive DCs are the most strongly represented leukocyte populations in the kidney [46]. These cells belong to the renal interstitial extracellular compartment, tactically located to interact with different molecules [48–50]. In this compartment, DCs are close to macrophages, fibroblasts, and epithelial cells, and they react to endogenous factors deriving from infiltrating and/or resident cells [12, 49, 50], displaying different functions. After stimulation, DCs may become a mature cell type with high levels of class II major histocompatibility complex and costimulatory molecules with low phagocytic capacity. Mature DCs are specialized in the activation of T cells.

Anyway, DCs are also implicated in the innate immune response because of the release of proinflammatory factors, such as IL-12, IL-6, TNF-α, MCP-1, and RANTES, interacting with natural killer T cells via CD40-CD40L [46, 51]. In recent studies, DCs have been found to prevent kidney injury according to the nature of the stimulus. For example, DC depletion prior to ischemia-reperfusion injury decreases consequent reperfusion injury and related renal dysfunction [52]. In contrast, DC depletion prior to cisplatin exposure worsens renal impairment and increases inflammation [53].

Recent studies have tried to better explain the pathophysiology of CRS types 1 and 5 using different in vitro experimental models. Monocytes treated with plasma from patients with CRS type 1 showed an upregulation of apoptosis as well as increased inflammation and oxidative stress levels when compared with those treated with plasma from patients with acute heart failure. Proinflammatory cytokines may induce apoptosis and necrosis through the activation of death signaling receptors and, indirectly, through an increase in reactive oxygen substrate production [14, 54].

### Inflammation

Immune dysregulation is associated with persistent inflammation. Continuous exposure to proinflammatory factors is responsible for tissue injury and organ dysfunction, also in the setting of acute and chronic CRS. Cytokines, eicosanoids, and chemokines regulate cellular responses through the interaction with genome-encoded receptors expressed in immune cells such as macrophages, monocytes, astrocytes, mast cells, and other cells of the innate immune system [55]. The upregulation of humoral factors released by injured cells leads to toll/IL-1 superfamily stimulation and nuclear factor-κB activation. Nuclear factor-κB translocates to the nucleus, thus inducing modifications in gene expression. TLR pathways result in both intra- and extracellular upregulation of inflammatory cytokine expression [56, 57].

In the recent literature, inflammation has been proposed as a potential stressor in acute and chronic cardiorenal impairment. Alterations in endothelial regulation, which can be associated with inflammation, have been demonstrated to affect afterload-preload mismatch in patients with heart failure, due to increased arterial stiffness and venous pressure or decreased venous capacitance. Higher central venous pressures (i.e., including higher renal venous pressures) induce kidney dysfunction and injury, as well as proinflammatory cytokine release. Moreover, an enhanced inflammatory status further worsens renal impairment. Moreover, kidney dysfunction directly affects acute and chronic cardiac clinical conditions and may be responsible for poor outcomes [58]. Different triggers (i.e., focal segmental glomerulosclerosis, mesangial proliferation, tubular necrosis, interstitial fibrosis, etc.) are usually related to pathologically distinct kidney lesions. Renal vessel damage induces intravascular clotting and increases the risk of extravascular hemorrhage; a close connection has been found between clotting and inflammation because of platelet activation (with attendant aggregation) responsible for cytokine and chemokine release, which promotes leukocyte recruitment. A coagulation-mediated release of mitogenic factors – in particular, epidermal growth factors, chemokines, and cytokines – causes cell barrier reepithelialization, thereby limiting fluid losses. In contrast, persistent deepithelialization increases the risk of chronic injury; however, uncoordinated epithelial hyperplasia is also detrimental (i.e., glomerular crescent formation) [58].

Ischemia, infection, and an uremic milieu have the potential to induce and activate diverse inflammatory components in both kidney and heart disease. In renal disease, cytokines released by other tissues may not be cleared, and their increase may contribute to systemic effects [12]. The induction of inflammatory mechanisms in the setting of CRS leads to the introduction of soluble mediators into the circulation, with detrimental effects on distant organs [59]. Monocyte migration with the consequent release of cytokines has been described in CRS types 1 and 5; oxidative stress and IL levels (IL-6 and IL-18) are also considerably augmented [14, 18, 54, 59, 60]. Recently, Virzì et al. [23] proposed an important crosstalk between inflammation, oxidative stress, anemia, and development of acute kidney injury in acute heart failure patients. In fact, lower hemoglobin levels were observed in CRS type 1 patients, and a negative correlation between hemoglobin and IL-6 levels was reported. These authors hypothesized that proinflammatory cytokine overexpression may be implicated in the pathogenesis of anemia in patients affected by heart failure and, in particular, in patients with CRS type 1. Inflammation may affect endothelial kidney function, with exposition to a proinflammatory and prothrombotic profile, vasoconstriction, and capillary obstruction leading to acute kidney injury. Furthermore, proinflammatory cytokines may depress bone marrow red cell production by destroying red cell precursors and by reducing erythropoietin receptor expression, leading to anemia. Reduction of renal oxygen delivery secondary to nephron hypoperfusion and low hemoglobin levels may alter aerobic cellular metabolism, leading to cellular death [23] (Fig. 2).

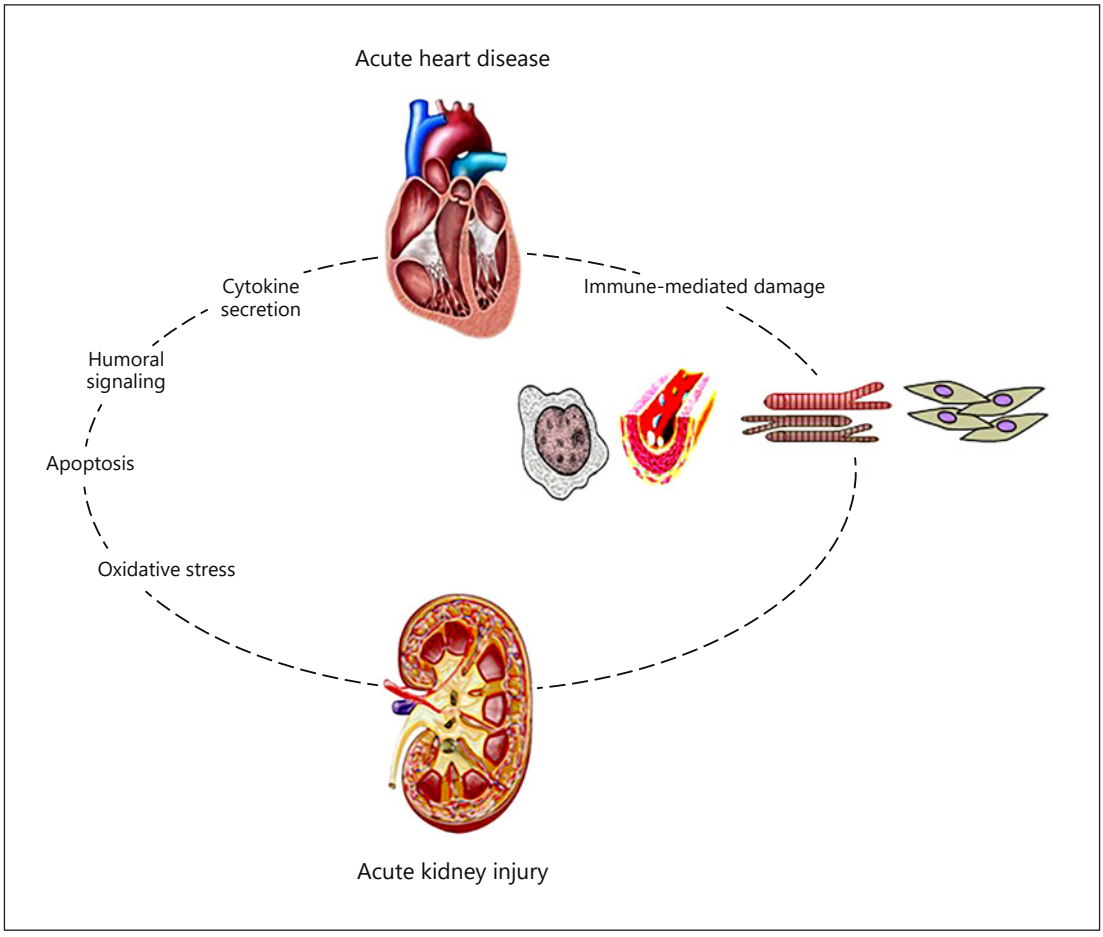


**Fig. 2.** Diagram illustrating and summarizing the pathophysiological mechanisms proposed for cardiorenal syndrome type 1.

## Conclusion

Cardiac and kidney functions are closely connected, and communication between these two systems occurs through different pathways. It has been proposed that the intersection between heart and renal dysfunction underlies common pathophysiological processes which may promote the development of CRS. Unfortunately, the puzzle of cardiorenal interaction is very complex and only partially solved; new information about many of the still missing parts is required. Further studies are urgently needed. In particular, controlled clinical studies with drugs investigating the new mechanisms involved in CRS remain at a preliminary stage. However, the results from ongoing studies will undoubtedly improve upcoming therapies in these clinical settings.

## Acknowledgements

We express our gratefulness to the Associazione Amici del Rene Vicenza (A.A.R.VI) ONLUS.

## Disclosure Statement

The authors declare no conflicts of interest or competing interests.

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