# Cardiorenal syndrome: pathophysiology and potential targets for clinical management

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**Abstract** | Combined dysfunction of the heart and the kidneys, which can be associated with haemodynamic impairment, is classically referred to as cardiorenal syndrome (CRS). Cardiac pump failure with resulting volume retention by the kidneys, once thought to be the major pathophysiologic mechanism of CRS, is now considered to be only a part of a much more complicated phenomenon. Multiple body systems may contribute to the development of this pathologic constellation in an interconnected network of events. These events include heart failure (systolic or diastolic), atherosclerosis and endothelial cell dysfunction, uraemia and kidney failure, neurohormonal dysregulation, anaemia and iron disorders, mineral metabolic derangements including fibroblast growth factor 23, phosphorus and vitamin D disorders, and inflammatory pathways that may lead to malnutrition–inflammation–cachexia complex and protein–energy wasting. Hence, a pathophysiologically and clinically relevant classification of CRS based on the above components would be prudent. With the existing medical knowledge, it is almost impossible to identify where the process has started in any given patient. Rather, the events involved are closely interrelated, so that once the process starts at a particular point, other pathways of the network are potentially activated. Current therapies for CRS as well as ongoing studies are mostly focused on haemodynamic adjustments. The timely targeting of different components of this complex network, which may eventually lead to haemodynamic and vascular compromise and cause refractoriness to conventional treatments, seems necessary. Future studies should focus on interventions targeting these components.

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## Introduction

Heart failure and renal dysfunction frequently coexist. The term cardiorenal syndrome (CRS) is now frequently used to describe this scenario, but the definition of CRS has been a matter of debate and has evolved over time. In August 2004, a working group of investigators were gathered by the US National Heart, Lung, and Blood Institute to discuss various aspects of the interactions between the cardiovascular system and the kidneys. This group proposed the following definition for CRS: "At its extreme, cardio-renal dysregulation leads to what is termed cardio-renal syndrome in which therapy to relieve congestive symptoms of heart failure is limited by further decline in renal function."[1]

More recently, an increased emphasis on the bidirectional relationship between the heart and the kidneys has led some opinion leaders to suggest that CRS be defined in such a way that conveys the concept of this bidirectional relationship.[2] Therefore, CRS can be defined as the combined and often concurrent dysfunction of these two organs, which can be associated with haemodynamic impairments. The intersection of cardiac and renal dysfunction has important therapeutic and prognostic implications. The association between heart failure and renal insufficiency has been demonstrated in various studies[3–6] and it is known that proper functionality and meticulous interaction between the kidneys, the heart and other contributors such as the neurohormonal system is necessary for haemodynamic stability of the body.

This manuscript reviews the concept of CRS and its evolution and classification based on its complex pathophysiology. In addition, this article describes potential targets for the clinical management of patients with CRS.

## Epidemiologic concepts

Decreased glomerular filtration rate (GFR) is known as kidney failure. This condition can occur in acute or chronic settings with various aetiologies. According to the 2010 Centers for Disease Control and Prevention National Chronic Kidney Disease Fact Sheet, chronic kidney disease (CKD) is present in more than 10% of people aged 20 years or older in the USA (more than 20 million people).[7]

Heart failure is also a common disease that causes considerable health, social and economic burdens.

**Competing interests**
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**Key points**

- The so-called cardiorenal syndrome is a complex phenomenon involving multiple organ systems; traditional understanding of the mechanisms involved forms only a small part of the big picture
- Any overt or covert involvement of heart or kidney can affect the other organ and usually by the time of clinical manifestation, multiple components of the interconnected network of events are involved
- It is not usually practically possible to specify whether kidney or heart was the initiator of the events
- Besides haemodynamic interactions, many other components are involved in the pathophysiology of cardiorenal syndrome; these components can be potential targets for management
- Most studies, particularly major clinical trials, have targeted and are still focusing on the 'haemodynamic' mechanisms of cardiorenal syndrome; future studies need to concentrate further on the other elements of this complex pathophysiology

Nearly 6 million people in the USA have heart failure. The incidence of heart failure is close to 10% in individuals older than 65 years in the USA, and men and women aged 40 years have a 20% chance of developing heart failure at some point in their life. In 2007, one in nine death certificates in the USA mentioned heart failure.[8]

The association between kidney failure and cardiovascular diseases has been shown repeatedly, particularly in the past decade.[5,9–11] CKD was reported in 30% of patients admitted to hospital for heart failure in the Acute Decompensated Heart Failure National Registry (ADHERE), as compared with just over 10% in the general adult US population.[7,12] Numerous studies have demonstrated that kidney dysfunction is an independent risk factor for mortality and morbidity in patients with various cardiovascular diseases, including heart failure with impaired or preserved left ventricular systolic function.[3–6,11] In a study by Dries and colleagues, an estimated GFR (eGFR) of less than 60 ml/min was associated with increased all-cause mortality and pump-failure death.[3] Mann *et al.* demonstrated that patients with kidney insufficiency are at higher risk of cardiovascular death, myocardial infarction or hospitalization for heart failure than those with normal kidney function.[5] Rapid deterioration of kidney function in the elderly has been shown to be associated with an increased risk of heart failure and myocardial infarction.[11]

## Pathophysiology

### Traditional thoughts

For many years, CRS was generally known as impairment of kidney function due to hypoperfusion caused by failing cardiac pump function.[13,14] However, this idea and the one proposed by investigators at the US National Heart, Lung, and Blood Institute[1] described earlier is now considered an oversimplification of a much more complex pathophysiology. The bidirectional interplay between the heart and the kidneys and the impact of numerous other factors on this interaction have been shown to be fundamental in the pathogenesis of CRS.

### Direct haemodynamic mechanisms

The initial belief was that CRS started with left ventricular systolic dysfunction, which led to decreased renal blood flow. The latter resulted in activation of fluid retention mechanisms, which worsened cardiac pumping capacity that in turn created a vicious cycle that continued to deteriorate.[2] Even though this mechanism still makes sense as a contributing factor in CRS, its role as the main pathophysiologic component of CRS—or even as the essential haemodynamic factor underlying CRS—has been challenged by recent findings.

In fact, the association between kidney failure and heart failure, and the effect of this association on patient outcome, has been shown to exist even in heart failure patients with preserved left ventricular ejection fraction.[4,15] Furthermore, high central venous pressure is an important cause of renal dysfunction that is frequently overlooked. This negative effect of elevated renal venous pressure on kidney function has been known for several decades.[16,17] In 1988, Firth *et al.* evaluated the effect of increasing venous pressure on GFR using an isolated rat kidney preparation.[18] Normal perfusion pressure was maintained while venous pressure was increased in 6.25 mmHg steps. In this evaluation, increasing venous pressure above 19 cm of water produced significant reductions in GFR, sodium excretion, and fractional excretion of sodium, which resolved completely when venous pressure was restored to basal levels. In line with that finding, a 2008 study involving 196 patients with heart failure suggested an association between tricuspid valve regurgitation and reduced GFR.[19] More recently, in a 2009 study of 145 patients with acute decompensated heart failure (ADHF), Mullens *et al.* concluded that in fact venous congestion, not cardiac output, was the most important haemodynamic factor causing worsening of renal function.[20] Moreover, it is known that increased intra-abdominal pressure (IAP) is associated with impaired kidney function.[21] In a study of 40 patients admitted for ADHF, elevated IAP (IAP ≥8 mmHg) was seen in 24 (60%) of the patients and was associated with impaired kidney function.[22]

These findings have challenged the role of decreased cardiac output as the major contributor to the development of CRS. In other words, despite the traditional beliefs, even from a haemodynamic standpoint, there may be factors more important than cardiac output in the pathogenesis of CRS.

### Neurohormonal mechanisms

As discussed, simple haemodynamic variations are only a part of the complex pathophysiology of CRS. Several other mechanisms are involved and could potentially be used as a basis for the management of this condition. Vascular hypoperfusion, as occurs in heart failure, activates neurohormonal pathways. This mechanism is compensatory in physiological situations but at some point becomes detrimental by initiating and maintaining a vicious cycle.

#### *Autonomic nervous system*

Sympathetic hyperactivity is one of the harmful compensatory mechanisms that occurs in patients with heart failure and CRS. In a failing heart, there is persistent adrenergic hyperactivity, disproportional downregulation

of the myocardial β1-adrenergic receptors leading to a decreased ratio of β1-to-β2 receptors and defective receptor–signal transduction mechanisms.[23–26] The protective effects of β-adrenergic blocking agents against this effect is the reason that some physicians ironically call them inotropic agents in heart failure. Whether a potential direct effect of constant sympathetic overactivity on kidney function exists and whether or not its elimination can affect kidney function, is not well known. In a recent randomized controlled study of 106 patients with treatment-resistant systemic hypertension, renal sympathetic denervation was not associated with any significant change in renal function after 6 months based on serum creatinine level, eGFR and cystatin C level.[27] However, increased kidney sympathetic activation and catecholamine release in the setting of reduced catecholamine clearance owing to already impaired kidney function is a part of the self-deteriorating cycle that aggravates the kidney dysfunction and the heart failure.

### *Renin–angiotensin–aldosterone system*

Decreased renal perfusion stimulates renin secretion, which in turn activates the renin–angiotensin–aldosterone system (RAAS). The ensuing vasoconstriction, which results in increased afterload and consequently decreased cardiac output, is another vicious cycle in the pathogenesis of CRS. However, activation of the RAAS has additional important effects in the pathogenesis of CRS other than this direct haemodynamic effect.

Angiotensin II for instance, has been shown to have an important role in the synthesis of proinflammatory cytokines in the kidney, regulating cell proliferation, fibrosis and apoptosis as well as causing myocardial and vascular hypertrophy and endothelial dysfunction.[28,29]

Mineralocorticoid receptors that bind aldosterone are present in cardiomyocytes and cardiac fibroblasts and aldosterone has a role in cardiac hypertrophy, dilation and failure.[30,31] A recent animal study by Lother and colleagues showed that deletion of mineralocorticoid receptors in cardiomyocytes prevented dilation and failure of the left ventricle resulting from pressure overload. However, deletion of those receptors from the cardiac fibroblasts did not have such an effect.[31] Increased plasma aldosterone is associated with inflammation and fibrosis in the heart and blood vessels.[30] Aldosterone can also promote endothelial dysfunction.[28]

### *Arginine vasopressin*

Plasma levels of arginine vasopressin (AVP) increase in the setting of heart failure.[32] This increase in AVP levels not only causes vasoconstriction through vasopressin V1 receptors and a consequent increase in afterload, but can also produce water retention via vasopressin V2 receptors, which mediate the antidiuretic activity of AVP. This combination further invigorates the haemodynamic vicious cycle of CRS.

### *Adenosine*

The autacoid adenosine is known to have regulatory effects on kidney function through the adenosine A1 receptor. The effect is complex and varies in different parts of the kidney. The overall effect is a decrease in GFR, an increase in proximal tubular sodium reabsorption and diuretic resistance.[33,34] Increased plasma adenosine levels have been described in patients with heart failure.[35] In fact, adenosine generation increases during hypoxia,[34] which could occur in patients with heart failure, owing to circulatory compromise. Therefore, adenosine dysregulation can generate yet another self-deteriorating cycle contributing to the pathophysiology of CRS.

## Inflammatory mediators and oxidative injury

The contribution of inflammatory reactions and oxidative injury in the pathogenesis of heart failure, renal failure, and CRS has attracted some attention in the past few years. The association of inflammation with anaemia and cachexia is also well known. In fact, inflammation and oxidative stress are common pathways linking these pathological conditions, namely renal failure, heart failure, anaemia and cachexia.

In addition to its direct haemodynamic effects through sodium and water retention and through vasoconstriction, angiotensin II has been shown to be involved in a myriad of inflammatory and oxidative reactions. In an animal study performed by Ruiz-Ortega and colleagues, infusion of angiotensin II increased tumour necrosis factor (TNF) production in the kidney, increased renal synthesis of interleukin (IL)-6 and monocyte chemoattractant protein-1 (MCP-1) and elevated tissue levels of activated nuclear factor κB (NFκB).[29] Angiotensin II can also stimulate superoxide generation through activation of the enzymes nicotinamide adenine dinucleotide (NADH) oxidase and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase.[36] Superoxide is a reactive oxygen species (ROS) that can damage tissues. NADPH oxidase is present in myocardium and has shown increased activity in patients with heart failure.[37] The association of renal failure and its severity with the presence of ROS and increased NADPH oxidase expression has also been shown.[38,39]

Therefore, both heart failure and kidney failure can promote inflammatory and oxidative pathways and both are adversely affected by these pathways.

Inflammation can also contribute to anaemia by different mechanisms including the increase in the level of hepcidin that occurs in inflammation. Hepcidin decreases iron availability by diminishing intestinal iron absorption and inhibiting the release of iron from hepatocytes and macrophages.[40] Impaired elimination of hepcidin by the kidneys in the setting of kidney failure can exacerbate the situation and further complicate the interaction between cardiac failure, renal failure, anaemia and inflammation.

## Endothelial dysfunction

In addition to providing a physical barrier to the interior surface of the vessels, endothelial cells have other vital functions. These functions include the regulation of vascular tone, anti-inflammatory effects, anticoagulation and modulation of vascular permeability.[41,42]

Both heart failure and CKD are associated with endothelial dysfunction independently of each other.[43,44] Endothelial dysfunction is one of the major contributors to abnormal vasomotor activity in patients with heart failure.[45] Nitric oxide (NO), which is released by endothelial cells, is a major regulator of vascular tone through its potent vasodilatory effect.[41] Dysregulation of NO (also known as 'endothelium-derived relaxing factor' [EDRF]) is believed to be a major contributor to endothelial dysfunction in the setting of heart failure. More than two decades ago, Ontkean *et al.* demonstrated decreased EDRF activity in rats with chronic heart failure.[45]

Various mechanisms have been suggested for endothelial dysfunction in heart failure. Endothelial cells release NO in response to laminar shear stress.[46,47] Therefore, decreased shear stress secondary to pump failure is a potential mechanism for endothelial dysfunction in heart failure.[48] Furthermore, shear stress depends not only on blood flow, but also on blood viscosity. Decreased blood viscosity by reducing haemoglobin concentration can result in decreased shear stress and subsequent ischaemia-induced vasodilation.[49] Anaemia, which is common in CRS, can therefore be postulated as a contributor to decreased shear stress leading to worsening endothelial function and contributing to worsening cardiac and renal function.

Increased NADPH oxidase activity induced by angiotensin II, and in turn, inactivation of NO by superoxide and other ROS, have also been proposed as another potential mechanism for endothelial dysfunction.[2] In addition, TNF activity, which is increased in settings of both chronic heart failure[50,51] and CKD,[52] can cause downregulation of constitutive NO synthase and increase the rate of endothelial-cell apoptosis.[48]

### Atherosclerosis

Atherosclerotic vascular disorder is another common pathway between heart failure and kidney disease. Kidney disease is a known risk factor for the development of atherosclerotic cardiovascular disease,[9,53] and a lower level of kidney function, as indicated by lower GFR, is an independent risk factor for development of atherosclerotic disease.[9] Similarly, atherosclerotic disease can lead to kidney dysfunction and is the leading cause of ischaemic renal disease.[54] Therefore, atherosclerotic disease and renal disease can accelerate each other and take part in the pathogenesis of CRS.

### Proteinuria and cardiorenal syndrome

Proteinuria is associated with both kidney disease and cardiovascular disorders. In fact, an exponential association exists between the degree of albuminuria and cardiorenal risk.[55] In some populations, such as those with type 2 diabetes, reducing albuminuria using therapeutic measures such as angiotensin II antagonists is associated with a decreased risk of both renal and cardiovascular adverse outcomes, with a particular decrease in the risk of heart failure.[56] Nevertheless, it is not clear whether or not a causal relationship exists between albuminuria and cardiorenal disease. In other words, albuminuria might be solely a marker of the vascular endothelial damage[55] that can be seen with both renal disease and cardiovascular disease. Nevertheless, if severe enough, proteinuria can cause fluid retention and lead to further haemodynamic compromise in CRS.

### Anaemia and iron metabolism

The association of anaemia with CKD is well known, and treating anaemia has therefore been a central part of the management of patients with CKD. Anaemia is also prevalent in patients with heart failure and is associated with increased mortality and morbidity.[57,58] Anaemia in patients with heart failure is not only a result of the commonly associated CKD, but also secondary to the adverse effects of inflammatory markers on erythropoiesis and iron metabolism. Hepcidin, a peptide mainly produced by the liver, is a major regulator of iron metabolism. Hepcidin is eliminated by the kidneys and its production increases during inflammation. Through inhibition of enteric iron absorption and release of iron from its stores, hepcidin is thought to have a major role in the anaemia of CKD.[40] Activation of inflammatory pathways in heart failure and—in turn—increased hepcidin production, can contribute to the anaemia seen in heart failure. A recent study of 157 patients revealed that iron homeostasis was disordered and that circulating and functional iron levels were diminished in patients with heart failure, even in those with normal ferritin levels. Furthermore, disordered iron homeostasis in the patients with heart failure was associated with impaired exercise capacity and was more strongly associated with worse survival than was anaemia.[59]

In a 2011 study, Naito *et al.* reported impaired expression of duodenal iron transporters and hepatic expression of hepcidin in Dahl Salt-sensitive rats with heart failure.[60] Divakaran *et al.*'s study of hepcidin concentration in 97 patients with heart failure and 38 control subjects, however, concluded that hepcidin probably does not have a major role in pathogenesis of anaemia in patients with chronic heart failure.[61] Overall, it seems reasonable to consider hepcidin as a major regulator contributing to the anaemia of CRS.

On the other hand, anaemia can result in or exacerbate heart failure by various mechanisms including a direct effect of worsening haemodynamic compromise and endothelial dysfunction.[62,63] Therefore, anaemia and impaired iron metabolism have major roles in the pathogenesis of CRS.

### Muscle wasting and cachexia

Latent or overt cachexia including muscle and fat wasting is a common condition in both patients with CKD and patients with heart failure and is a strong risk factor for morbidity and mortality in these patient groups.[64,65] Both cardiac cachexia and renal cachexia are multifactorial. Decreased nutritional intake owing to anorexia and reduced nutrient absorption are factors that can cause muscle atrophy in many chronic diseases. However, neurohormonal and inflammatory pathways have major roles in the pathogenesis of cachexia. The RAAS, which is

known to be involved in the pathogenesis of heart failure and CKD, is also a major contributor to cachexia. In fact, activation of the RAAS in these circumstances leads to increased angiotensin II production, which is believed to cause muscle wasting and to increase NADPH oxidase activity, which in turn produces ROS. Angiotensin II also results in anorexia by its central effect, which leads to increased muscle atrophy.[66] Cachexia is an independent risk factor for poor outcomes in both heart failure and CKD, but the pathophysiologic mechanisms that relate cachexia to morbidity and mortality have not been clearly elucidated.[67] Comprehensive review articles pertaining to the role of cachexia in the outcomes of patients with heart failure or CKD can be found elsewhere.[68–70]

### Vitamin D deficiency

CKD is associated with vitamin D deficiency. Expression of vitamin D receptors in various cell types and consequently the role of vitamin D in an extensive variety of physiological and pathological conditions have been studied in the past decade. In addition, heart failure has been shown to be associated with vitamin D deficiency.[71,72] This association was thought to be at least in part due to the regulatory effects of vitamin D on blood pressure and parathyroid hormone.[73,74] However, evidence also exists that intravenous calcitriol may decrease angiotensin II levels and is associated with reversal of ventricular hypertrophy in patients on haemodialysis with secondary hyperparathyroidism.[75] In a 2011 study by Chen *et al.*, cardiomyocyte-specific deletion of the vitamin D receptor gene in mice was associated with increased myocyte size and left ventricular hypertrophy (LVH). The authors concluded that vitamin D has a direct cardiac antihypertrophic effect by means of vitamin D receptor signalling through the calcineurin pathway.[76]

These findings, along with the known contribution of vitamin D dysregulation in renal failure, suggest a possible prominent role for vitamin D deficiency in the pathogenesis of CRS and its potential position as a target in the management of CRS.

### Fibroblast growth factor 23

Fibroblast growth factor 23 (FGF23) is a major regulator of serum phosphorus levels, urinary excretion of phosphorus and calcitriol ($1,25(OH)_2D3$) modulation.[77] Patients with CKD have increased circulating levels of FGF23 which are associated with worsening of kidney function.[77] Elevated levels of FGF23 are also independently associated with LVH.[77,78] A recent study found that LVH can result from intramyocardial or intravenous injection of FGF23 into wild-type mice, while in an animal model of CKD, the presence of an FGF-receptor blocker could attenuate LVH.[78] Another recent study described serum FGF23 level as an independent predictor of mortality in a cohort of patients with systolic heart failure.[79] Therefore, FGF23 may have an important role in the pathogenesis of CRS and might be a future target for its management. Of note, however, is an animal study published in 2012 which reported that use of monoclonal FGF23 antibody in a rat model of CKD was associated with increased aortic calcification and increased mortality.[80] Further studies are necessary in this regard.

**Box 1** | Ronco *et al.*'s CRS classification*

**Type 1—acute cardiorenal syndrome**
Rapid worsening of cardiac function leading to acute kidney injury.

**Type 2—chronic cardiorenal syndrome**
Chronic abnormalities in cardiac function leading to progressive chronic kidney disease.

**Type 3—acute renocardiac syndrome**
Abrupt and primary worsening of kidney function causing acute cardiac dysfunction.

**Type 4—chronic renocardiac syndrome**
Primary chronic kidney disease causing decrease cardiac function, ventricular hypertrophy, diastolic dysfunction, and/or increased risk of adverse cardiovascular events.

**Type 5—secondary cardiorenal syndrome**
Presence of combined cardiac and renal dysfunction due to acute or chronic systemic disorders.

*Based on chronicity vs acuteness and based on primary vs secondary condition. Adapted from Ronco, C. *et al.* Cardiorenal syndrome. *J. Am. Coll. Cardiol.* **52**, 1527–1539 (2008).[14]

## Classification

An understanding of the bidirectional interaction between the heart and the kidneys and the mutual role of these organs in haemodynamic regulation, along with knowledge of other contributing factors capable of affecting this interaction, challenged the traditional thought that CRS was simply caused by cardiac pump failure followed by kidney hypoperfusion. In 2008, Ronco and colleagues suggested a classification system for the general term CRS on the basis of the presumed initial trigger of CRS pathogenesis.[14] This classification system categorizes CRS into five subgroups on the basis of whether acute or chronic heart or kidney disease is the primary initiator of the process or whether a third factor affects the heart and the kidneys simultaneously (Box 1). Although this classification system is conceptually sound, we believe that the practicality and clinical applicability of these types of classification systems are challenging. Further advancement in understanding of the pathophysiology of CRS, and more advanced diagnostic technology than is currently available, would be required to be able to specify, with a reasonable degree of certainty, the initiator of the complex network of events in CRS. In other words, in almost all cases, the heart, kidneys, neurohormonal systems and other relevant systems are already involved as contributing pathophysiologic factors by the time clinical manifestations are detectable. Therefore, it is currently almost impossible to define which factor was the initiator and which factor was its consequence.

Categorizing CRS based on the response to various treatment modalities would be practical and would help in the design of a treatment and management algorithm. In this regard, the degree of clinical significance of kidney failure versus heart failure or versus other contributing organ systems, at the time of clinical evaluation of the patient, could be of more practical value than knowledge of the organ that initiated the process.

**Table 1** | Proposed CRS classification based on putative pathophysiology and clinical applicability at time of patient evaluation

| CRS category | Definition | Comments |
|---|---|---|
| 1) Haemodynamic | Haemodynamic compromise is the major clinical manifestation | Can be subclassified as acute (1a) or chronic (1b) |
| 2) Uraemic | Uraemic manifestations are the most prominent clinical appearances | Can be subclassified as acute (2a) or chronic (2b) |
| 3) Vascular | Cardiovascular and/or renovascular manifestations are the most prominent clinical findings | Can be subclassified as acute (3a) or chronic (3b) and as atherosclerotic (as), thromboembolic (te) or endothelial dysfunction (ed) |
| 4) Neurohumoral | Electrolyte disorders, acid–base disorders or dysautonomia is the most prominent finding | Can be subcategorized into acute (4a) or chronic (4b) and into electrolyte (el), acid–base (ab) or autonomic dysregulation (ad) |
| 5) Anaemia and/or iron metabolism | Anaemia and/or iron metabolism dysregulation are the most prominent clinical manifestations | Can be subcategorized into acute (5a) or chronic (5b) |
| 6) Mineral metabolism | Dysregulation of calcium and phosphorus and their regulators including vitamin D and FGF23 are the most prominent clinical manifestations | This category is mostly chronic by nature |
| 7) Malnutrition–inflammation–cachexia | Malnutrition, cachexia and inflammatory state is the most prominent clinical manifestation | This category is mostly chronic by nature |

Each category shows the most prominent clinical manifestation of the patient that needs to be addressed first. The category of any given patient may vary with time and depends on the current clinical evaluation. The category at any point in time guides the clinician to the main focus of management. Abbreviations: CRS, cardiorenal syndrome; FGF23, fibroblast growth factor 23.

Here, we propose a pathophysiologically and clinically relevant classification system with seven distinct categories (Table 1). We believe that this classification system offers a systematic approach to improving understanding of CRS aetiologies and selection of the optimal therapeutic strategies.

## Diagnosis

Diagnosis of CRS can be made according to its definition, which includes kidney failure, heart failure and haemodynamic compromise. More advanced stages of CRS in both acute and chronic settings are not difficult to diagnose on the basis of clinical, laboratory and, if necessary, imaging techniques. Detection of earlier stages of CRS, however, can be challenging and requires clinical expertise as well as a high degree of suspicion.

Given the multiplicity of the factors and pathways involved in the pathogenesis of CRS and their interactions (Figure 1) it may be that earlier breakage of these vicious cycles is beneficial. By the time serum creatinine concentration rises and oliguria develops in a patient with acute CRS, the patient is often resistant to the available therapies.[81,82]

Biomarkers are gathering interest as a potential means of diagnosing acute kidney injury early. One of these markers, neutrophil gelatinase-associated lipocalin, has been studied in patients with CRS with some promising results.[81,83] However, further studies are needed to establish these biomarkers as a diagnostic tool in clinical practice.

Close haemodynamic monitoring of patients prone to developing volume overload is a helpful strategy for timely diagnosis of worsening CRS, which may need intervention. For this purpose, some implantable devices have been studied and marketed.[84] Furthermore, B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) are used as biochemical markers of decompensated heart failure and volume overload. However, with concomitant kidney dysfunction, these markers are less accurate. In a study of 831 patients with dyspnoea, BNP and NT-proBNP were equally accurate in predicting ADHF in patients with and without kidney dysfunction (defined as eGFR <60 ml/min/1.73 $m^2$). However, NT-proBNP was a better predictor of 1-year mortality in both groups.[85]

## Management

Conventional therapeutic strategies for CRS mainly focus on the correction of haemodynamic abnormalities. Often the implementation of such a strategy becomes complicated owing to treatment refractoriness and/or because of worsening dysregulation of one component (for example, kidney function) by targeting another component (for example, volume overload). Currently used and potential future target points for the management of CRS are presented (Table 2).

### Correcting volume overload

Unfavourable effects of volume overload and cardiopulmonary and venous congestion on various body organ systems have been described,[20,86] but correction of volume overload in the setting of ADHF is complicated. Diuretic resistance, particularly in advanced stages of CRS, is a challenge. Furthermore, worsening of kidney function, electrolyte abnormalities and neurohormonal stimulation following the use of loop diuretics represent additional complicating factors.[87]

It was hypothesized that selective vasopressin V2-receptor antagonists may be useful as aquaretics to correct volume overload in patients with ADHF without causing electrolyte abnormalities. However, The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial showed no effect of oral tolvaptan on long-term mortality or heart-failure-related morbidity.[88]

Administration of loop diuretics using continuous infusion was thought to be more effective than bolus intravenous doses for the treatment of volume overload, and to cause lower degrees of worsening kidney function. However, a 2011 prospective double-blind randomized trial of 308 patients with ADHF suggested otherwise.

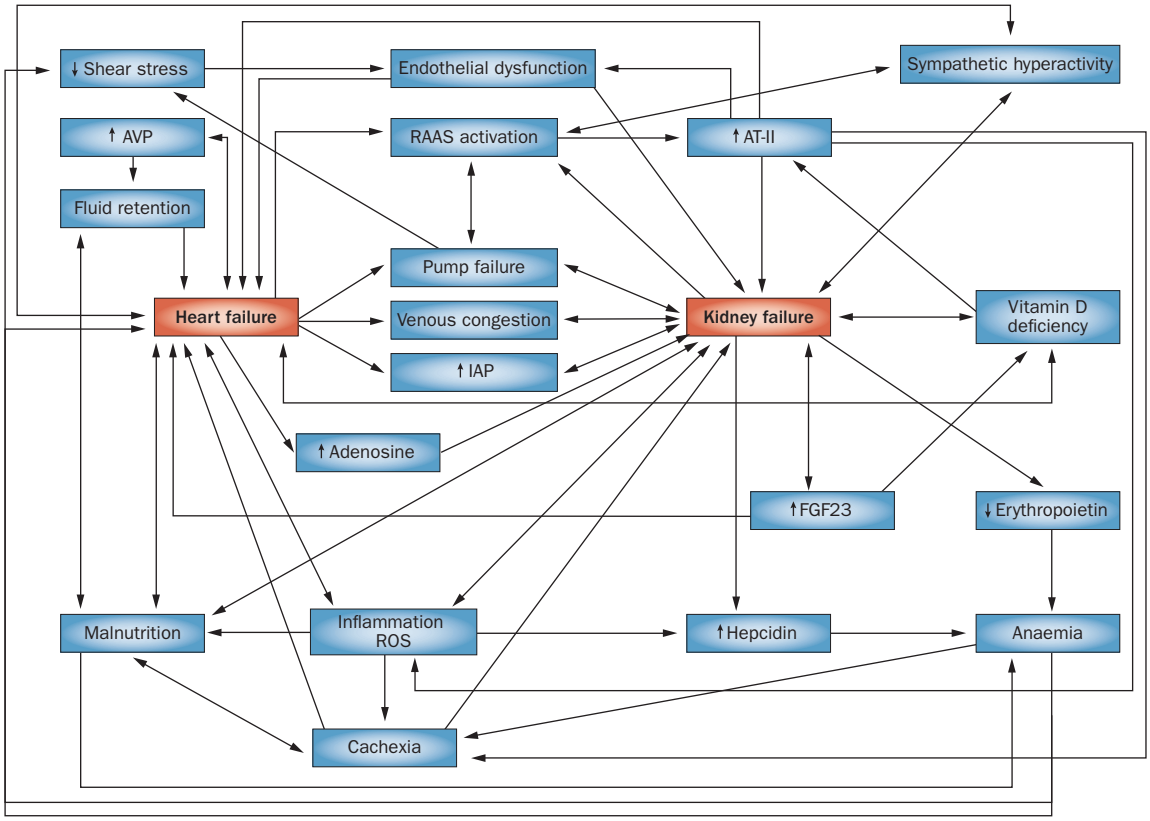


**Figure 1** | Putative pathophysiologic connections in cardiorenal syndrome. Abbreviations: AT-II, angiotensin II; AVP, arginine vasopressin; FGF23, fibroblast growth factor 23; IAP, intra-abdominal pressure; RAAS, renin–angiotensin–aldosterone system; ROS, reactive oxygen species.

In that study, no differences were observed in patients' global assessment of symptoms or change in the serum creatinine level from baseline to 72 h between those who received bolus intravenous furosemide and those who received a continuous infusion of furosemide.[89] However, methodological concerns about this study, including the use of inadequate doses of furosemide[90] and the selection of "global assessment of symptoms" as the study end point,[91] raised questions about the validity of the conclusions of this study.

Results of the Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure (UNLOAD) trial suggested that fluid removal by ultrafiltration was safer and more effective than fluid removal using intravenous diuretics in patients with ADHF.[86,92] At 90 days, the ultrafiltration group had fewer patients hospitalized for heart failure, fewer heart failure rehospitalizations and unscheduled visits and a shorter duration of hospitalization per patient. However, in 2012, results of Cardiorenal Rescue Study in Acute Decompensated Heart Fialure (CARRESS-HF) in 188 patients with ADHF demonstrated that use of a stepped pharmacologic-therapy algorithm including intravenous diuretics, vasodilators and inotropic agents was superior to use of ultrafiltration.[93,94] In this study, after 96 h of intervention, weight loss was similar in the pharmacologic therapy group and the ultrafiltration group, but patients who received pharmacologic therapy had more desirable changes in serum creatinine level (a mean decrease of 3.5 ± 46.9 μmol/l versus a mean increase of 20.3 ± 61.9 μmol/l) and a lower rate of reported adverse events.[93]

Further studies are still required to evaluate different aspects of these treatment modalities; the availability of these modalities and practical issues in various settings also need to be considered.

Limited studies have investigated the use of peritoneal dialysis to control volume status in patients with heart failure and CRS.[95–98] Considering the important effect of inflammatory pathways in the pathogenesis of CRS, it seems reasonable to take advantage of the biocompatibility of the peritoneal membrane and its superior ability to sieve inflammatory molecules compared with regular haemodialysis. Further studies are necessary in this regard.

In addition, super-high-flux dialysis membranes are capable of removing cytokines and inflammatory mediators[99] and may be able to improve cardiac function.[100] Further studies might be able to indicate applicability of this modality in the management of CRS.

### Other therapies targeting haemodynamics

Haemodynamic irregularities caused by the complex interplay between the cardiovascular system, kidneys and other contributors to CRS have been the major target of therapeutic interventions in CRS. To this end, vasodilators have been extensively used for heart failure patients with and without detectable renal impairment,

**Table 2** | Current and potential targets in the management of CRS

| Target | Current strategies | Potential strategies* |
|---|---|---|
| Haemodynamic impairment | Diuretics<br>Ultrafiltration<br>Vasodilators<br>Inotropic agents<br>Natriuretic peptides<br>ACE inhibitors<br>Digitalis<br>Dopamine<br>Mechanical circulatory assist devices<br>Heart and/or kidney transplantation | Vasopressin V2-receptor antagonists<br>ARBs<br>Peritoneal dialysis<br>Exercise training<br>Calcium sensitizers<br>Endothelin-receptor antagonists<br>Luso-inotropic agents (e.g. istaroxime)<br>Cardiac myosin activators |
| Uraemia | Conventional peritoneal dialysis and haemodialysis therapies | Toxin removal by super-high-flux haemofiltration and/or novel absorbents |
| Atherosclerosis, endothelial dysfunction and thromboembolism | Statins<br>Atherosclerosis risk factor modification<br>Antiplatelet agents<br>Anticoagulants | ACE inhibitors<br>ARBs<br>Endothelin-receptor antagonists<br>Aldosterone-receptor antagonists<br>Nitric oxide<br>Correction of pump failure and anaemia (by increasing shear stress and improving endothelial function)<br>Exercise training |
| Neurohormonal | ACE inhibitors<br>β-blockers<br>Aldosterone-receptor antagonists | ARBs<br>FGF23-receptor blockers<br>Adenosine A1-receptor antagonists<br>Direct renin inhibitors<br>Exercise training<br>Kidney sympathectomy |
| Anaemia and iron dysregulation | Iron<br>ESAs<br>Folic acid<br>Cyanocobalamin<br>Red blood cell transfusion (in certain circumstances) | Nutritional support<br>Vitamin C<br>Carnitine<br>Anti-hepcidin therapy |
| Mineral metabolism | Vitamin D agents<br>Phosphorus binders<br>Calcimimetics<br>Diet modification | FGF23-receptor blockers<br>FGF23 antibodies |
| Malnutrition–inflammation–cachexia | Nutritional support<br>Appetite stimulators<br>Exercise training | ACE inhibitors<br>ARBs<br>AIM<br>β-blockers<br>Ghrelin<br>Growth hormone<br>Anti-inflammatory and/or antioxidative agents<br>Volume overload correction (to improve gut wall oedema and nutrient absorption)<br>Muscle enhancers (e.g. anti-myostatin agents) |

*Strategies for which insufficient current clinical data exists to warrant routine clinical use in CRS or for which a questionable role exists for the particular mechanism. Abbreviations: ACE, angiotensin-converting enzyme; AIM, antioxidant inflammation modulator; ARB, angiotensin-receptor blocker; CRS, cardiorenal syndrome; ESA, erythropoiesis-stimulating agent; FGF23, fibroblast growth factor 23.

both in ADHF and in chronic situations. Vasodilators have potential adverse effects, such as hypotension, which cause variable tolerability to these agents in different clinical settings.[101,102] Newer pharmacologic agents, endothelin-receptor antagonists, have also been proposed and to some extent studied for the haemodynamic regulation of heart failure by vascular tone adjustment.[103] However, despite some promising results in earlier phase studies, larger randomized controlled trials failed to demonstrate the ability of these agents to improve symptoms, cardiac remodelling and clinical outcome in patients with heart failure.[104,105]

Inotropic agents increase cardiac contractility and hypothetically, therefore, should improve the impaired haemodynamic status in patients with heart failure and CRS. Nonetheless, extensive studies in acute and chronic situations have shown these agents to be associated with increased morbidity and mortality. Therefore, their use is limited to specific circumstances such as ADHF with shock or as a bridge to cardiac transplantation.[106] Calcium sensitizers such as levosimendan are used to increase contractility in heart failure. The acute and long-term beneficial effects of levosimendan have been described in clinical trials,[107] and levosimendan has been shown to have favourable effects on both myocardial contraction and relaxation,[108] despite earlier concerns that these agents may impair myocardial relaxation.[109] Pharmacologic agents such as istaroxime (which improves abnormal myocyte

calcium cycling), and cardiac myosin activators (which increase myofibril ATPase activity) have also been suggested and are also aimed at increasing cardiac contractility.[103] These agents need to be studied further before any potential use in clinical practice.

Some pharmacologic agents, such as nesiritide, have more than one haemodynamic effect. Nesiritide is a natriuretic peptide, which also has vasodilatory effects. Concerns of an increased risk of mortality in ADHF patients treated with nesiritide, shown in a pooled analysis of three studies,[110] were not confirmed in a meta-analysis of seven large randomized controlled trials.[111] Similarly, the effect of nesiritide on kidney function has been controversial, with many large trials not showing any significant effect of nesiritide on kidney function.[112,113] Furthermore, a meta-analysis of data from five randomized controlled trials of nesiritide use in patients with ADHF suggested that nesiritide attenuated the effect of increased serum creatinine level on mortality.[114]

Dopamine also has a number of haemodynamic effects and some of these effects vary with the administered dose. The natriuretic effect of dopamine has been known for decades,[115] and dopamine can also act as a vasodilator in the kidneys and increase renal blood flow and GFR.[115] In addition, dopamine has vasoconstrictive effects and can increase cardiac contractility. A recent study in patients with heart failure demonstrated that administration of dopamine was associated with dilatation of both large conductance and small resistance renal blood vessels, increased cardiac output and in turn increased renal blood flow.[116]

### Mechanical circulatory assist devices

In the past decade, the use of mechanical circulatory assist devices has increased for the management of advanced heart failure as a bridge to transplantation or as a destination therapy.

Poorer renal function before the implantation of ventricular assist devices (VADs) is associated with worse outcomes after implantation,[117–119] but multiple studies have shown recovery of kidney function after the implantation of VADs.[117,118,120–122] Furthermore, in those in whom a VAD is a bridge to heart transplantation, kidney function after heart transplantation correlates with the level of renal function obtained after the implantation of VAD.[123]

### Other potential therapeutic options

As mentioned, the initial understanding of CRS was limited to the haemodynamic interaction between the heart and the kidneys. Therapeutic modalities were, and still are, therefore focused mainly on haemodynamics. However, an improved understanding of the complex pathophysiology of the CRS should identify other potentially useful parts of this multifactorial pathological condition that need to be targeted or warrant further study.

#### *Correcting anaemia*

Correction of anaemia has been an integral part of the management of CKD for many years, but has only recently become a focus for patients with heart failure. How best to correct anaemia and what the target haemoglobin level should be, however, are subjects of debate.

According to a number of studies, complete correction of anaemia is not beneficial and in some cases is associated with adverse effects.[124–127] A 2008 study showed no significant clinical benefit of darbepoetin alfa in patients with symptomatic heart failure and anaemia.[128] Other studies are ongoing.[129] The Reduction of Events With Darbepoetin Alfa in Heart Failure (RED-HF) trial is expected to complete in 2013.[130]

Results of the published studies of anaemia correction are complicated by various factors including methodological concerns such as open-label designs instead of double-blind studies. Moreover, therapies such as iron or erythropoiesis-stimulating agents (ESAs), which are used to correct anaemia, have other desirable and/or adverse effects as well, which can affect the outcomes. Intravenous iron therapy, for instance, has been shown to improve exercise capacity and functional class of patients with heart failure even in the absence of anaemia.[131] However, iron therapy can also increase oxidative stress.[132] Similarly, through its receptors on various cell types, erythropoietin is believed to have cardioprotective effects by decreasing apoptosis, oxidative stress, inflammation and infarct size as well as increasing angiogenesis and preventing arrhythmias.[133] Renoprotective effects of erythropoietin and its analogues have also been shown,[134] but erythropoietin also has some adverse effects, such as hypertension, which might affect overall outcome.

Considering the complicated pathophysiology of the CRS and the nonerythropoietic effects of the medications, the optimal medical therapy of anaemia in CRS needs further study by large-scale multicentre prospective clinical trials.

#### *Inflammatory and neurohormonal targets*

Targeting neurohormonal pathways with medications such as β-blockers, angiotensin-converting-enzyme (ACE) inhibitors and aldosterone-receptor blockers (ARBs) is routine practice in the management of heart failure. Blockade of the RAAS, particularly in the setting of kidney function impairment, is associated with hyperkalaemia, which limits the application of this strategy in certain clinical situations. An orally administered, potassium-binding polymer (RLY5016) has been shown to be effective in preventing hyperkalaemia in patients with chronic heart failure.[135]

Although oxidative and inflammatory pathways are known major contributors to the pathophysiology of CRS, studies of therapies specifically aimed at these pathways in CRS are limited.

ACE inhibitors are commonly used in both heart failure and renal failure for their known inhibitory effects on the RAAS. Their subsequent haemodynamic effects have been studied more widely than their nonhaemodynamic effects. However, given the mentioned effects of angiotensin II on the oxidative and inflammatory pathways and its impact on endothelial function, ACE inhibitors and ARBs could hypothetically have additional

benefits in the management of heart failure, renal failure and CRS.

Studies regarding the potential effects of ACE inhibitors, ARBs and other therapies that target oxidative and inflammatory pathways, cachexia and endothelial function in CRS are scarce. Anker *et al.* studied 1,929 patients from the Effect of Enalapril on Survival in Patients with Reduced Left Ventricular Ejection Fractions and Congestive Heart Failure Trail (SOLVD) and 804 patients from the Vasodilators in Heart Failure Trial (V-Heft II), who had chronic heart failure, and concluded that ACE inhibition reduced the risk of weight loss in those patients.[136]

In a subanalysis of data from 5,888 participants in the Cardiovascular Health Study, the researchers concluded that ACE inhibitors might reduce cachexia and be associated with weight maintenance in older adults with treated hypertension or congestive heart failure.[137] In a study involving 27 patients with heart failure, after 6 months of oral β-blocker therapy, those with baseline cachexia gained more weight than those without baseline cachexia.[138] ACE inhibitors may also exert beneficial effects in heart failure through the improvement of endothelial function.[139]

Targeting the other sites of the inflammation–cachexia pathway (for example, ROS and NADPH oxidase/mitochondria crosstalk) has been suggested as potential future therapeutic approaches to cachexia.[66] The potential role that modulation of the oxidative and inflammatory pathways could have in the management of kidney failure is also beginning to attract attention. A phase II study investigated the effects of bardoxolone methyl, an antioxidant inflammation modulator, on kidney function in 227 patients with CKD and type 2 diabetes.[140] The phase III study that followed—the BEACON (Bardoxolone Methyl Evaluation in Patients With Chronic Kidney Disease and Type 2 Diabetes) study—was terminated in October 2012 on the recommendation of the independent data monitoring committee to stop the trial "for safety concerns due to excess serious adverse events and mortality in the bardoxolone methyl arm."[141] Whether or not other potential modulators of oxidative or inflammatory pathways may be beneficial requires further study.

Owing to presumed adverse effects of adenosine A1 receptor activation on kidney function in CRS, it was hypothesized that A1-receptor antagonists would be capable of increasing the diuretic effects of loop diuretics in patients with heart failure while maintaining kidney function. However, despite promising results of the prior studies on relatively small numbers of patients,[142,143] a recent study on 2,033 patients with ADHF and renal impairment failed to show the expected beneficial effects of rolofylline, an A1-receptor antagonist.[144]

### *Targeting vitamin D deficiency and calcium*

As a standard of care, vitamin D products are commonly used in the management of patients with renal failure. Given the findings demonstrating positive effects of vitamin D on myocardial cells and cardiovascular haemodynamics,[75,145] vitamin D seems to have the potential to become an essential part of the management of patients with CRS. However, in a multicentre, randomized, double-blind clinical trial including 227 patients with stages 3 or 4 CKD, mild to moderate LVH and preserved left ventricular ejection fraction, 48 weeks of therapy with paricalcitol, an active vitamin D compound, failed to change left ventricular mass index or improve studied measures of diastolic dysfunction, although improvements in left atrium metrics were observed.[146]

### *Exercise*

Exercise training has been shown in numerous studies to have beneficial effects in stable patients with heart failure. In fact, exercise is now a level 1 recommendation by the American College of Cardiology/American Heart Association guidelines for the diagnosis and management of adults with chronic heart failure.[147] Exercise exerts its beneficial effects through several mechanisms including regulatory effects on neurohormonal activity, oxidative and inflammatory mediators and pathways, endothelial function and metabolic function.[148] It can result in improved symptoms, exercise capacity and quality of life. Similarly, exercise training has been shown to have remarkable positive consequences on exercise capacity, haemodynamic and cardiovascular parameters, quality of life and some nutritional parameters in patients with CKD.[149]

Given the multiple common pathophysiologic pathways between heart failure and CKD, known beneficial regulatory effects of exercise on these pathways and the evidence that exercise is associated with desirable clinical outcomes in patients with heart failure and those with renal failure, exercise training could be hypothetically useful in suitable patients with chronic stable CRS. In an animal study, Lin and colleagues reported that renal dysfunction in rats with heart failure improved significantly following exercise training.[150] Further human studies will help to collect clinical evidence regarding the possible effects of exercise in CRS.

### *Kidney sympathetic denervation*

The Symplicity HTN-2 randomized controlled trial suggested efficacy and safety of catheter-based renal sympathetic denervation in controlling blood pressure in patients with treatment-resistant hypertension.[27] Given the fact that sympathetic overactivity is a contributor to the pathogenesis of CRS, renal sympathetic denervation has been proposed as a potential modality in CRS management.[2] However, the different effects of β1 and β2 adrenergic receptors on the pathways leading to CRS and the altered proportion of these two receptors in patients with heart failure[25] increase the complexity of the matter and make the value of renal sympathetic denervation questionable. This modality requires further investigation before it can possibly be considered in clinical practice.

## Conclusions

CRS is common in patients with heart failure and influences treatments and outcomes. CRS is a complex phenomenon and multiple body systems are involved in its pathophysiology. Traditional approaches to the treatment of CRS mainly target haemodynamic pathways,

but now neurohormonal pathways are also targeted to some extent. Further studies should also focus on areas involved in CRS that may be potential targets for treatment and have been studied less extensively; for example, inflammatory pathways, cachexia, vitamin D deficiency, anaemia and iron metabolism. We believe that the seven categories of CRS proposed here have relevant pathophysiologic, clinical and therapeutic implications. A compelling need exists for additional trials in this patient population in order to improve clinical outcomes.

**Review criteria**

The PubMed online database was searched for relevant full-text articles published in English in renowned journals between 2000 and 2012. The term "cardiorenal syndrome" along with the terms relevant to each subtitle of the current article were applied as search terms. Reference lists of identified papers were also reviewed for further leads. Other important articles relevant to specific subtitles were also considered as references regardless of the year of publication.


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**Author contributions**

P. Hatamizadeh and K. Kalantar-Zadeh researched data for the article, contributed to the discussion of content, wrote the article and reviewed/edited the manuscript before submission. G. C. Fonarow, M. J. Budoff, S. Darabian and C. P. Kovesdy were involved in the review/editing of manuscript before submission.