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# The cardiorenal problem

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## Summary

Cardiorenal syndrome (CRS) describes the reciprocally detrimental interaction between both acute and chronic cardiac and renal dysfunction. The syndrome is prevalent and carries a high mortality. CRS has five clinical subtypes, which share common pathogenetic mechanisms including neurohumoral and haemodynamic derangements. We describe several serum markers that offer improvements over traditional measurement of serum creatinine for the diagnosis of CRS. The mainstay of therapy of CRS is loop diuretics in the acute setting and ACE-inhibition in the chronic setting, the latter should in most cases continue despite therapy-associated increases in creatinine. Extracorporeal therapies remain second line treatment.

***Key words:*** *cardiorenal syndrome; renal dysfunction; cardiac failure*

## Introduction

Cardiorenal syndrome (CRS) refers to the increasingly recognised reciprocal association between cardiac and renal dysfunction, whereby injury to one organ directly promotes deterioration of the other.

The development of classification systems for acute (RIFLE, AKIN) and chronic (Kidney Disease Outcomes Quality Initiative (KDOQI) stages 1–5) renal dysfunction has simplified their diagnosis. Within Europe, the prevalence of both cardiac and renal dysfunction is increasing [1, 2]. Approximately 5% of acute medical admissions are related to heart failure [3] and among these patients 20% have renal impairment [4]. In chronic cardiac failure, chronic kidney disease (CKD) is the most common co-morbidity [5]. Conversely, cardiovascular causes account for approximately 40% of deaths in patients with CKD [6]. Combined cardiac and renal dysfunction in all settings is related to an extremely high morbidity and mortality [7, 8]. There may be reluctance among clinicians to fully treat either the cardiac or renal problem due to concerns of negatively affecting the other [9]. An awareness of the pathogenesis and effective treatment of CRS is therefore crucial for improving the prognosis of this large patient group.

Cardiorenal syndrome includes the four subtypes of acute heart failure behind the syndrome [7]:

1. Hypertensive pulmonary oedema with preserved left ventricular systolic function
2. Acutely decompensated chronic heart failure
3. Cardiogenic shock
4. Predominant right ventricular failure

Increasing research interest in CRS was consolidated in 2008 with development of a classification system based on clinical parameters [7] (table 2). In type 1 CRS, acute cardiac failure results in acute kidney injury (AKI), as defined using the Risk-Injury-Failure-Loss-End stage renal disease (RIFLE) criteria presented in table 1 or alternatively using the Acute Kidney Injury Network (AKIN) criteria. The initial cardiac insult may be ischaemic, due to acute coronary syndrome or cardiac surgery, or non-ischaemic, for example in the case of valvular pathology or pulmonary embolism. In type 2 CRS, chronic cardiac dysfunction causes progressive CKD. In type 3, AKI is responsible for a rapid deterioration in cardiac function. Type 4 refers to the contribution of CKD to chronic cardiac disease, including coronary artery disease, cardiac failure and arrhythmia. Finally, in type 5 CRS, a primary systemic problem, most frequently sepsis, is responsible for a secondary deterioration of cardiac and renal function. The syndrome is however characterised by common pathogenetic mechanisms across the five categories.

In this review, we mainly focus on type 1 CRS.

**Abbreviations**

| | |
|---|---|
| ACCF/AHA | American College of Cardiology Foundation/American Heart Association Heart Failure |
| ACE | angiotensin-converting enzyme |
| AKI | acute kidney injury |
| ANP | atrial natriuretic peptide |
| BNP | brain natriuretic peptide |
| CKD | chronic kidney disease |
| CRS | cardiorenal syndrome |
| FABP | liver-type fatty acid binding protein |
| GFR | Glomerular filtration rate |
| IL | interleukin |
| KIM-1 | kidney injury molecule 1 |
| NAG | N-acetyl-beta-D-glucosaminidase |
| NGAL | neutrophil gelatinase-associated lipocalin |
| NT-proANP | amino-terminal pro-atrial natriuretic peptide |
| NT-proBNP | amino-terminal pro-brain natriuretic peptide |
| RAAS | renin-angiotensin-aldosterone system |
| TNF-α | tumour necrosis factor alpha |
| UO | urine output |

## Pathophysiology

The cardiovascular risk factors of hypertension, diabetes, smoking and hypercholesterolaemia are relevant to both cardiac and renal disease. Affected patients are predisposed to developing dual organ dysfunction and are further disadvantaged by its corresponding increased mortality over single organ disease. Type 1 cardiorenal syndrome most often occurs as an acute-on-chronic phenomenon: the most frequent predisposing factors are a history of chronic renal or chronic cardiac failure.

### Neurohumoral and haemodynamic mechanisms

In type 1 cardiorenal syndrome, impaired left ventricular function leads to reduced stroke volume and cardiac output, arterial underfilling and venous congestion. These haemodynamic derangements result in activation of the renin-angiotensin-aldosterone system (RAAS) and in release of vasopressin and endothelin-1, which are responsible for salt and water retention and systemic vasoconstriction. The action of endogenous vasodilators including natriuretic peptides and nitric oxide are overwhelmed and oxygen delivery to the heart and brain is thus mainly preserved. However, the resulting decrease in cardiac output and renal vascular constriction lead to reduced renal perfusion and glomerular filtration rate (GFR) and the increased preload predisposes to further left ventricular impairment. Activation of the same pathways occurs during primary or during resulting secondary renal dysfunction. Thus the distinction between primary and secondary dysfunction is lost and a vicious circle develops. The maladaptive nature of the response becomes clear with appreciation of the positive impact on mortality of interruption of the RAAS using angiotensin converting enzyme (ACE) inhibitors.

Venous congestion with increased central venous pressure seems particularly important in the development of type 1 CRS. Animal experiments have previously demonstrated a direct transmission of increased central venous pressure to the renal veins and a resulting reversible decrease in GFR [11]. This is postulated to occur through increased renal venous pressure leading to a rise in glomerular vas efferens pressure, and a resulting reduced differential pressure between vas afferens and vas efferens, this differential pressure being the driving force for glomerular filtration. Alternatively, reduced renal perfusion pressure may cause direct hypoxic renal damage.

Less than 2% of acute cardiorenal syndrome can be accounted for by the subset of decompensated heart failure patients with cardiogenic shock [4]. The development of type 1 CRS has instead been correlated with acute hypertension at presentation [12]. In a study of 145 patients presenting with acute decompensated heart failure, no correlation between cardiac index and development of worsening renal function was found [13]. These results were mirrored in the ESCAPE study, in which right atrial pressure, an indicator of venous congestion, was significantly correlated with baseline GFR, whereas cardiac index was not [14]. The influence of renal venous pressure may explain the positive influence of diuretic therapy on GFR seen in some patients.

**Table 1:** RIFLE classification for acute kidney injury (from Cruz et al. [10]).

| | Creatinine/GFR criteria | Urine output (UO) criteria |
|---|---|---|
| **Risk** | Increased creatinine to 1.5 x *or*<br>GFR decrease >25% | UO <0.5 ml/kg/h for 6h |
| **Injury** | Increased creatinine to 2 x *or*<br>GFR decrease >50% | UO <0.5 ml/kg/h for 12h |
| **Failure** | Increased creatinine to 3 x *or*<br>GFR decrease >75% *or*<br>Creatinine >4 mg/dl (with acute increase ≥0.5 mg/dl) | UO <0.3 ml/kg/h for 24h *or*<br>Anuria for 12h |
| **Loss** | Complete loss of renal function for >4 weeks | |
| **ESRD** | End stage renal disease | |

**Table 2:** Classification of cardiorenal syndrome [7].

| | |
|---|---|
| Type 1 | Acute heart failure results in acute kidney injury |
| Type 2 | Chronic cardiac dysfunction causes chronic kidney disease |
| Type 3 | Acute deterioration in renal function causes acute cardiac dysfunction |
| Type 4 | Chronic kidney disease is responsible for cardiac dysfunction |
| Type 5 | A primary systemic disorder causes both cardiac and renal dysfunction |

### Contrast nephropathy

The administration of iodinated contrast agents, particularly in the setting of coronary angiography, is a frequent precipitant of type 1 CRS. Patients in whom baseline renal function is impaired are most susceptible to the toxic effects of contrast media, which typically result in a creatinine rise 24–48 h post-administration, potentially requiring renal replacement therapy, with resolution within one week. Contrast-related toxicity is attributed to a combination of direct cytotoxic damage to tubules, transient tubule obstruction by precipitated contrast material and hypoxia in the renal medulla due to disruption of the microcirculation.

### Chronic predisposing factors

In addition to the acute changes described above, underlying factors including inflammation, uraemia and anaemia predispose to the development of type 1 cardiorenal syndrome. Furthermore, in chronic cardiac or renal impairment, increased levels of angiotensin II result in a profibrotic, procoagulatory, atherogenic and arrhythmogenic state [15].

Chronic heart and chronic renal failure are associated with increased levels of the same pro-inflammatory cytokines including TNF-α, IL-6 and IL-1 [16, 17]. This chronic immune activation is postulated to contribute to myocyte dysfunction [18] and fluid overload [19] and increase oxidative stress resulting in further cardiac and renal damage.

Increased levels of uraemic toxins and uric acid have been recognised as a potential source of cardiovascular dysfunction [20]. Uraemic toxins may directly induce cardiac dysfunction by causing impaired myocyte contractility via interference with calcium entry into the cytosol, and increasing fibrosis and adverse cardiac remodelling following myocardial infarction [21].

Chronic cardiac and renal failure both commonly result in anaemia, which in turn worsens the prognosis among affected patients [22]. Anaemia is due to a combination of

factors including chronic immune activation leading to deranged iron metabolism, reduced erythropoiesis caused by renal dysfunction and dilutional anaemia caused by hypervolaemia.

## Diagnosis

The most common, traditional and economical test to estimate kidney function in the setting of heart failure is the measurement of serum creatinine level. Indeed, serum creatinine level together with urine output forms the basis of both the RIFLE and the AKIN consensus definitions of acute kidney injury. Both classification systems are suitable for diagnosis of AKI in cardiorenal syndrome and have been widely adopted [10]. The small molecule creatinine (molecular weight 113 Da) is endogenously produced by muscles and excreted by the kidneys. Thus deterioration in kidney function leads to increased serum creatinine level. The measurement of creatinine is straightforward and inexpensive. However, the limitations of serum creatinine as a marker are particularly relevant in the setting of cardiorenal syndrome. In particular, patients with cardiac failure tend to be of low muscle mass resulting in low creatinine levels, which can cause overestimation of kidney function. Kidney function estimation equations taking account of age, sex and race allow only partial correction for this problem and are not validated in acute renal dysfunction. Furthermore, creatinine is not only filtered in the glomerulus but is also secreted by the renal tubule. This secretion can maintain serum levels within the normal range during the early stages of reduced clearance by glomerular filtration. Consequently, creatinine is an insensitive marker of renal dysfunction, and changes in its serum concentration often lag behind when kidney function worsens acutely.

Cystatin C, a 13 kDa housekeeping protein produced by all nucleated cells, provides several advantages. It offers a serum marker of renal function which is less influenced by muscle-mass, age and sex, as well as liver disease and inflammation. In the physiological state, cystatin C is filtered at the glomerulus, reabsorbed and almost completely metabolised by renal tubular cells. Even minor changes in renal function result in a measurable difference in cystatin C serum concentration, and such a difference may be clinically useful as early as two hours following an acute insult [23].

Similarly, neutrophil gelatinase-associated lipocalin (NGAL), a 25 kDa polypeptide, is gaining increasing recognition as a marker for AKI. It is expressed by neutrophils and epithelial cells and involved in ischemic renal injury and repair processes [24]. It can be measured in blood and urine. Alvelos et al. recently showed that NGAL can be considered a potent biomarker in early prediction of CRS type 1 in patients with acute heart failure [25]. A multicentre prospective study evaluating 146 adult patients undergoing scheduled cardiac surgery demonstrated that increased preoperative plasma NGAL was an independent risk factor for post-cardiac surgery AKI. Moreover, plasma NGAL showed an earlier peak than serum creatinine, indicating that plasma NGAL can predict the recovery of AKI earlier [26].

Kidney injury molecule-1 (KIM-1) is a trans-membrane protein which belongs to the immunoglobulin gene superfamily. It is expressed on the proximal tubule apical membrane cilia of the injured kidney and can be measured in urine. In a recent study of chronic heart failure, urinary KIM-1 was increased in heart failure patients compared with healthy controls, increased significantly with decreasing left ventricular function and severity of New York Heart Association class and was also a predictor of all-cause mortality [27]. Furthermore, in 95 patients with acute kidney injury after cardiac surgery, KIM-1 was a good predictor for AKI progression.

Natriuretic peptides including brain natriuretic peptide (BNP) and atrial natriuretic peptide (ANP) are released during myocardial wall stress and represent a physiological attempt to counteract the neurohumoral derangements and hypervolemia seen in cardiorenal syndrome via their role to increase GFR, sodium and water excretion and vasodilatation. During the secretion of these hormones, their inactive terminal fragments, N-terminal proBNP (NT-proBNP) and N-Terminal ANP (NT-proANP), are cleaved in equimolar relation. The N-terminal parts of these hormones are more frequently measured due to their better pre-analytic stability.

The increased serum levels of natriuretic peptides observed in renal failure are partly due to reduced renal clearance, but are also likely to reflect increased production under the additional haemodynamic strain caused by renal dysfunction [28]. Natriuretic peptides may thus be thought of as a combined marker of cardiac and renal dysfunction. Natriuretic peptides are of prognostic as well as diagnostic value in CKD patients. In a cohort of 83 pre-dialysis CKD patients without clinical heart failure, NT-proBNP levels significantly correlated with the combined endpoint of cardiovascular event or mortality [29] and BNP levels have additionally been shown to be a mortality predictor in patients with heart failure [30]. In patients with community-acquired pneumonia and CRS type 5, natriuretic peptides were shown to accurately predict an early in-hospital AKI [31].

Further novel less established biomarkers of CRS are N-acetyl-beta-D-glucosaminidase (NAG), interleukin-18 (IL-18) and liver-type fatty acid binding protein (FABP).

## Treatment

Due to the broad spectrum of CRS, treatment must be tailored to the individual patient. There are no medical therapies that have been shown to directly improve renal function in patients with heart failure. Experience with patients receiving cardiac resynchronisation therapy or intra-aortic balloon pump has, however, demonstrated the reversible nature of types 1 and 2 CRS [32, 33]. Improvement of cardiac function is associated with improved kidney function, as shown in studies of cardiac resynchronisation therapy [34], underscoring the importance of cardiorenal interaction.

### Treatment in the acute setting

The established pharmacological management here includes diuretics and vasodilators.

Loop diuretics are the mainstay of therapy, although their effects on renal function in heart failure patients are vari-

able and range from decreased GFR, presumably as a consequence of reduced cardiac output, to a potential improvement in GFR which may be mediated by reduced renal venous pressure or by alleviating right-ventricular-dependent impairment of left ventricular filling. The American College of Cardiology Foundation/American Heart Association Heart Failure (ACCF/AHA) guidelines advise the use of diuretics to eliminate fluid retention even if this results in a mild to moderate deterioration in renal function [35]. This approach is based on evidence that intensive diuretic therapy improves survival even in the case of worsening renal function [36]. However, the optimal dosage and administration strategy remains unclear: in a prospective, double-blind, randomised trial involving 308 patients with acute decompensated heart failure, no difference in patient symptoms or change in renal function was found when diuretic therapy was administered as a bolus as opposed to a continuous infusion, or at a high as opposed to a low dose [37].

Serelaxin is a recombinant human relaxin 2 which acts as a vasodilator promoting increased arterial compliance, cardiac output and renal blood flow [38] and represents an emerging therapy for heart failure. In a randomised placebo-controlled trial of 1161 patients with acute heart failure and mild-to-moderate renal dysfunction, Serelaxin resulted in reduced dyspnoea and 180 day mortality [38]. A subsequent analysis where kidney function was assessed in more detail revealed a better renal outcome with serelaxin therapy than placebo: the serelaxin group had significantly lower serum creatinine and plasma cystatin C values in the first 5 days after enrolment and, in the case of cystatin C, serelaxin administration was also associated with a lower incidence of worsening renal function on day 2. Patients on serelaxin also had lower levels of blood urea nitrogen and of uric acid on each of days 1 to 5 after enrolment [39].

The situation for other pharmacological therapies is less clear. In the acute setting, positive inotropes dobutamin and dopamine raise cardiac index. A resulting improvement in renal function has however not been demonstrated. The situation is similar for calcium-sensitiser levosimendan [15] and for the phosphodiesterase-inhibitor milrenon [40]. In the ADHERE database, patients treated with vasodilators and diuretics had a significantly higher rate of worsening renal function than those treated with diuretics alone, but this effect could not be separated from patients requiring combination therapy having more severe heart failure [41].

The use of tolvaptan, a vasopressin 2 receptor antagonist, aims to inhibit the effects of neurohumoral activation in CRS. In the EVEREST outcome trial, tolvaptan did not influence primary endpoints of mortality or heart failure hospitalisation but did lead to an improvement in urine output. By contrast nesiritide, a recombinant human BNP, was found not to alter the risk of worsening renal function in patients with acute decompensated heart failure [42].

The effect of adenosine-antagonist rolofylline was investigated in the PROTECT trial, based on the observation that adenosine leads to preferential constriction of the afferent glomerular arteriole and consequent increased tubular sodium reabsorption. However, the groups showed no difference in cardiovascular outcomes or worsening of renal function, and rolofylline increased the risk of neurological events [43].

Unfortunately, the occurrence of diuretic resistance, which refers to persistent signs and symptoms of congestion despite adequate doses of intravenous diuretics, is particularly prevalent among patients with pre-existing renal impairment. In such patients, extracorporeal therapies may be indicated for fluid removal. Extracorporeal ultrafiltration uses a semi-permeable membrane to separate isotonic fluid from blood. Hereby, water is transported in response to a trans-membrane pressure gradient. Extracorporeal techniques can be performed intermittently (three times per week), daily and continuously. Continuous venovenous haemofiltration or intermittent venovenous haemodialysis use a synthetic extracorporal membrane and access to the circulation via a large-lumen catheter. Peritoneal dialysis uses the peritoneal membrane as the barrier between blood and ultrafiltrate, and access is achieved through an indwelling transcutaneous catheter inserted into the peritoneal cavity. In order to avoid haemodynamic instability and preserve residual kidney function by slowing fluid removal, continuous rather than intermittent renal replacement therapy is preferred for decompensated heart failure patients. Renal replacement therapy has several theoretical advantages over conventional diuretic therapy including controlled removal of isotonic fluid, acidosis correction and less neurohumoral activation [44]. However, depending on volume status, ultrafiltration may have positive or negative effects on neurohormone level and urine output, with patients with diuresis of less than 1l per day seeming to benefit [45]. The UNLOAD trial demonstrated better restoration of normovolaemia and reduced 90 day hospitalisation rates in 100 heart failure patients treated with ultrafiltration rather than conventional diuretics. This sustained beneficial effect of ultrafiltration is thought to be due to recovery of diuretic-responsiveness, which may be related to its correction of sodium dysbalance [45]. However, the benefits of renal replacement therapy are offset by its increased invasiveness and risk of AKI, which may then lead to dialysis-dependence, if excessive or too rapid ultrafiltration is performed [46]. In CARRESS-HF, a prospective randomised study comparing ultrafiltration or pharmacologic therapy for patients with heart failure and worsening renal function, there was increased creatinine and rate of adverse events in the ultrafiltration group. Current guidelines from the ACCF/AHA still recommend renal replacement therapy as a second-line treatment, particularly in patients with signs of fluid overload and diuresis of under 1l per 24 hours [47].

### Treatment in the chronic setting

The established pharmacological management here includes ACE-inhibitors, aldosterone-antagonists and beta-blockers.

ACE-inhibitors antagonise several of the pathways responsible for CRS: through reduced activation of the RAAS and production of angiotensin II, they lead to reduced adrenaline, noradrenaline and vasopressin levels as well as decreasing central venous pressure via venodilatory effects. However, they usually also lead to a small decrease in GFR mediated by preferential dilatation of the efferent

glomerular arteriole [48]. In the majority of patients, this occurs in the first three weeks after starting therapy and remains stable thereafter [49]. The IMPROVE-HF study examined the adherence to and effect of guideline-recommended therapies for heart failure in over 34,000 patients and showed that patients with reduced renal function received ACE-inhibitors, angiotensin-receptor blockers (ARBs) and aldosterone antagonists less frequently than those with normal renal function [9]. This may have been due to clinician concerns regarding the decrease in GFR normally observed after beginning ACE-inhibition. However, although patients with acute decompensated heart failure who suffer a decline in renal function have been observed to have a higher mortality [8], the cause of decline is important in determining outcome. Analysis of patients in the SOLVD study group showed that patients in whom an early decline in renal function occurred after starting enalapril did not have a higher mortality, whereas those with worsening renal function in the placebo group did [49]. Importantly, patients in the enalapril group had a preserved survival advantage despite reduced GFR. In the Minnesota Heart Survey, the one-year prognosis of patients with combined renal and heart failure was significantly improved by prescription of an ACE-inhibitor [50].

Careful consideration is required before initiating treatment with an ACE-inhibitor in the acute setting as it may induce acute cardiorenal syndrome in patients with acute salt and water losses, for example due to acute gastroenteritis. As ACE-inhibitors are predominantly renally excreted, the dosage should be adapted according to GFR. By contrast, ARBs undergo hepatic metabolism. The European Society of Cardiology advises monitoring with continuation of therapy when the creatinine level after beginning ACE-inhibition does not exceed 266 µmol/l and the serum potassium does not exceed 6 mmol/l. Should these limits be reached, the benefits of ACE-inhibition are such that stopping other nephrotoxic drugs and halving the dose of ACE-inhibitor is recommended before stopping the ACE-inhibitor outright [51].

Recent trials have supported traditional management of anaemia in patients with cardiorenal syndrome using iron substitution and blood transfusion over prescription of erythropoietin analogues due to the risk of thromboembolic adverse effects [52, 53].

Additionally, because of the key role of activation of renal sympathetic efferent nerves in neurohumoral mechanisms of CRS, several trials of selective renal denervation in CRS are ongoing.

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