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# Biomarkers and physiopathology in the cardiorenal syndrome

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ABSTRACT

Acute cardiorenal syndrome (CRS) corresponds to an association of acute heart failure and a worsening of renal function. The detection of acute kidney injury (AKI) unfortunately occurs at a late stage of CRS, leading to an increased mortality of the patients. In this review, we described the pathophysiology of CRS and discussed the potential interest of biochemical biomarkers (namely creatinine, cystatin C, NGAL, KIM-1, fatty acid binding protein, Nacetyl-β-D-glucosaminidase and IL-18) that could potentially help to detect AKI earlier and thus reduce the morbi-mortality of the patients suffering from CRS.



## 1. Introduction

Patients with acute heart failure (HF) often develop acute worsening renal function (WRF) in the course of the disease. Their condition is then called acute cardiorenal syndrome (CRS) [1]. In this review, we have limited the discussion to the cardiorenal syndrome of type 1. Managing patients with HF is already challenging, but the presence of associated WRF can greatly increase mortality and morbidity [2]. Early diagnosis and treatment are the keys to decrease mortality, to prevent re-hospitalizations and to reduce healthcare costs. In this context, new biomarkers have shown remarkable specificity and sensitivity and may be considered as specific tools to help in the diagnosis and to get a prognosis for patients with HF. Reflecting distinct pathophysiological pathways and types of cellular insults, they should be very useful in the future with conventional laboratory tests to decrease mortality and morbidity of CRS.

Acute heart failure (AHF) is the leading cause of hospitalizations in patients aged 65 and over and represents a significant economic cost [3]. The prevalence of HF is about 2% in Europe and in the United States [3]. The time window between renal insult and development of acute kidney injury (AKI) in AHF can vary.

AKI is often diagnosed too late, only when the effects of the insult become evident with a loss or decrease of renal function. The development of renal injury is responsible for the increasing mortality of patients with HF [4]. AKI is indeed an independent risk factor for 1-year mortality in acute decompensated heart failure (ADHF) patients [5]. According to certain databases, renal dysfunction is the most frequent comorbidity in AHF patients, associated with high in-patient mortality [6].

Type 1 CRS occurs in approximately 25% to 33% of patients admitted with ADHF, depending on the criteria used [7].

The mortality rate for ADHF is dependent of the presence or absence of impairment renal function. Annual mortality rates are 26% in patients without renal dysfunction, 41% in patients with any impairment of renal function and 51% in patients with moderate to severe impairment [8].

## 2. Definition–Classification

Combined disorders of heart and kidney are classified as cardiorenal syndromes [1]. The primary failing organ can either be the heart or the kidney, and the syndrome is divided into five distinct subtypes. In **types 1** and **2, CRS**, worsening of HF in acute (type 1) or chronic HF (type 2), leads to worsening kidney function. In **types 3** and **4** (termed acute and chronic reno-cardiac syndromes, respectively), AKI or chronic kidney disease (CKD) leads to worsening HF. In **type 5 CRS**; systemic conditions cause simultaneous dysfunctions of the heart and kidney [1].

A patient with known HF, who is admitted to hospital for an episode of ADHF and either a mild elevation in serum creatinine at baseline or a temporary need for dialysis, would be classified as type 1 CRS since the HF was the initial, predominant problem and the renal failure the consequence [5]. Because of the complexity of interaction between acute heart and kidney failure, type 1 CRS is subdivided into 4 categories [7]:

- De novo cardiac injury leading to de novo kidney injury
- De novo cardiac injury leading to acute-on-chronic kidney injury

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- Acute-on-chronic cardiac decompensation leading to de novo kidney injury
- Acute-on-chronic cardiac decompensation leading to acute-on-chronic kidney injury

CRS type 1 is characterized as the development of AKI in a patient with acute cardiac illness. The acute cardiac insults commonly include acute coronary syndrome (ACS), ADHF, cardiogenic shock and can appear in the post procedure of cardiopulmonary bypass surgery. There is evidence to support a multiple pathophysiological mechanism, resulting in a clinical syndrome characterized by a rise in serum creatinine, oliguria, diuretic resistance, and in many cases, worsening of ADHF symptoms.

The new criteria for the diagnosis of AKI include a minor change in renal function, including a rise in creatinine of 0.3 mg/dL in 48 h or 0.5 mg/dL in 7 days and a decrease in urinary output of at least 0.5 ml/kg/h for at least more than six consecutive hours [4]. In addition, these new criteria suggested that the diagnosis of AKI should be based on a reduction of kidney function occurring within a time window of 48 hours [9]. Early detection of AKI is not possible with the use of plasma creatinine and there is a need for more precise markers, able to show renal damage while it is happening.

In most cases, patients with AHF are admitted with clinical signs and symptoms of congestion and fluid overload. Loop diuretics, used to induce a diuresis in these congested patients, are often associated with a subsequent decrease in glomerular filtration rate (GFR), and cause a creatinine increase that is apparent within 48 to 72 h.

Numerous factors can independently predict the development of WRF at the admission of patients with clinical manifestations of ADHF. These factors include baseline renal function, history of coronary artery disease, hypertension, diabetes mellitus, and history of prior HF [10]. In addition, the presence of systolic hypertension, tachycardia, pulmonary edema, and the use of high doses of diuretics at admission were independently related to the development of type 1 CRS during treatment [11].

## 3. Physiopathology

It is well known that HF is characterized by complex interactions between cardiac, renal, and vascular systems, mediated through hemodynamic, neuro-hormonal mechanisms and endothelial dysfunction. The kidney plays a crucial role to maintain hemodynamic balance, which is often disrupted in HF patients [12].

The acute cardiac insult often results in reduced cardiac output (CO), which leads to decreased renal perfusion pressure, increased renal venous resistance, and as a consequence reduced GFR. When AHF is characterized by diminished left ventricular systolic function and poor CO, compensatory mechanisms are stimulated, such as an activation of the renin–angiotensin–aldosterone system (RAAS), the sympathetic nervous system (SNS), and a production of other local mediators, which interact to maintain the fluid volume [13]. Endothelial dysfunction contributes to vasoconstriction and increased afterload. The imbalance between these compensatory mechanisms, unable to maintain adequate CO, results in volume overload. Furthermore, decreased renal perfusion, in addition to nephrotoxic agents and over-diuresis, eventually leads to AKI in such patients [7].

As the rise of serum creatinine takes some time to become apparent, novel techniques such as the use of biomarkers have received considerable attention in the diagnosis and prognosis of patients with WRF secondary to HF. These biomarkers are secreted in response to increased stress and are studied in trials to monitor the progression and the severity of the disease. Currently, these new biomarkers are not used as bedside tools yet.

### 3.1. Renal dysfunction in acute HF

As already mentioned, a deep interaction exists between the heart and the kidneys, altered in patients with AHF leading to CRS type 1. The mechanism of renal insult is different in case of low or high CO. The paragraph below details the hemodynamics and neuro-hormonal abnormalities involved in this interaction (see Fig. 1).

#### 3.1.1. Hemodynamic dysfunction

Studies have demonstrated that the majority of patients brought to hospital because of pulmonary congestion have normal or even high blood pressure (140 mm Hg or higher systolic blood pressure). Only 2% of the patients had a systolic blood pressure of 90 mm Hg or lower [14]. Renal function can be maintained with a CO as low as 1.5 l/min/$m^2$ [15]. The fall in renal function in case of AHF is related to the reduction of left ventricular function only in 20% of the cases.

When low CO appears, a systemic venous congestion and renal arteriolar vasoconstriction develop. They increase central venous pressure and further reduce renal blood flow. Renal hypoperfusion triggers the SNS and activates the RAAS to maintain plasma volume by retaining sodium and water [16].

Venous congestion is one of the most important hemodynamic determinants of CRS and is due to a decrease of effective arterial blood volume (EABV). It has been associated with the development of renal dysfunction in the setting of ADHF, with normal or low CO. In HF patients, increased central venous pressure (CVP) can be transmitted to the kidney circulation by the glomerular efferent arteriole. Renal efferent vasoconstriction, increased peritubular capillary oncotic pressure and reduced peritubular capillary hydrostatic pressure lead to kidney flow redistribution. Furthermore, renal congestion also activates both the RAAS and the SNS and induces tubulointerstitial inflammation. This inflammation increases the peritubular oncotic pressure too. The association of increasing peritubular oncotic pressure and decreasing in peritubular hydrostatic pressure induces a fall of GFR. [17]. Damman et al. found that higher CVP was inversely related to GFR and independently associated with all-cause mortality [18]. This effect is probably due to an increase in renal venous pressure, which decreases the arteriovenous pressure gradient across the kidney [19]. The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial found no relationship with baseline hemodynamic parameters like CO, pulmonary capillary wedge pressure, or systemic vascular resistance (SVR) and baseline renal function. Only venous or right atrial pressure was significantly but weakly correlated with serum creatinine and GFR [20]. Venous congestion also leads to the development of visceral oedema and ascites with increased intra-abdominal pressure (IAP). Elevated IAP is prevalent in patients with ADHF and is also associated with impaired renal function [21].

Moreover, it is frequently observed that renal dysfunction may complicate the treatment course of HF because of the use of diuretics. Even if the use of intravenous loop diuretics often decreases venous congestion, the cost to pay is a WRF within a few days of hospitalization. Although loop diuretics provide prompt diuresis and relief of congestive symptoms, they provoke a marked activation of the SNS and RAAS systems, resulting in reno-vascular reflexes and sodium retention. They are thus considered as a primary precipitant of CRS. This places the patient with ADHF at risk for CRS in a narrow therapeutic management.

#### 3.1.2. Neurohormonal activation

The RAAS has thus an important role in the initiation and maintenance of vascular, myocardial, and renal dysfunction leading to oedema in HF [7]. This activated mechanism occurs as an initial protection mechanism for renal hypoperfusion, which leads to stimulation of angiotensin II. This peptide is also known to be a stimulator of the SNS, which increases SVR and congestion. Angiotensin II has direct trophic effects on cardiomyocytes and renal tubular cells that promote cellular hypertrophy, apoptosis, and fibrosis [22]. Constriction of afferent arterioles by angiotensin II and the SNS reduces renal blood flow and GFR, and causes increased proximal tubular sodium reabsorption (see Fig. 1).