Cardiorenal syndrome type 1: a literature review

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ABSTRACT

Kidney injury is one of the most common problems in the first two days of treatment for patients with acute heart failure. Renal dysfunction associated with acute heart failure causes fairly high morbidity and mortality. This literature review seeks a variety of literature that helps to explain the relationship between kidney injury and acute heart failure and the factors that play an important role in both of these pathologies. Completion of rapid and prompt diagnosis and treatment from various disciplines of patients with heart failure is important. The laboratories investigation is very important to get an early diagnosis, also determine the complications that occur in patients with acute heart failure. New markers such as Kidney-1 Injury Molecule (KIM-1), Neutrophil Gelatinase-Associated Lipocalin (NGAL), L-type FABP Protein (L-FABP), and Cystatin-C which can be used to detect acute kidney injury (AKI) early in its course hence promote a better clinical outcome and patient prognosis.

Keywords: Acute kidney injury, acute heart failure, cardiorenal syndrome


INTRODUCTION

Acute kidney injury is one of the most common complications in the first 48 hours in patients with acute heart failure. It involves complex pathophysiology and requires multidisciplinary treatment. In addition, the incidence of acute kidney injury can only be detected with serum creatinine markers at least 48 hours after treatment, and it is possible that it already caused permanent damage to renal glomerulus. Acute kidney injury related to the occurrence of acute heart failure has fairly high morbidity and mortality. The incidence of acute heart failure accompanied by acute kidney injury is often also referred to as cardiorenal syndrome.

Acute heart failure is one of the major causes of death. Patients with acute heart failure often come with complaints of severe dyspnea due to pulmonary congestion. Elimination of the excess fluid is the main target of therapy, and the discharge of the fluid is mainly from the kidneys. However, many patients with acute heart failure also experience deterioration of kidney function during the treatment period because indeed the relationship of the heart to the kidneys affects each other. Decreased kidney function due to low perfusion followed by venous congestion in the kidney is the mechanism that causes cellular damage in acute kidney injury (AKI).

ACUTE KIDNEY INJURY IN ACUTE HEART FAILURE

Acute kidney injury is one of the complications of acute heart failure. The relationship between the two important organs serves to maintain hemodynamic stability, both in regulating blood volume and maintaining vascular tone. If there is a disruption in one, there will be dysfunction or damage to the other organs. The relationship between these two organs is shown as distinct clinical pathophysiology called cardiorenal syndrome (CRS). In patients with acute heart failure, the prevalence of deteriorating kidney function reaches 10-40% of total patients. Of these, mortality in 1 year of patients acute heart failure with complications of acute kidney injury ranges from 30%, which is around 1.5 to 2 times if without acute kidney injury. It can be stated that kidney damage is an independent predictor of mortality in patients with heart failure.

According to the 2013 Acute Dialysis Quality Initiative workgroup (ADQI), AKI is divided into five classifications based on the main organ that is dysfunctional, the heart or kidney, or other processes that affect both organs as well as the onset of events (acute or chronic) (Table 1). If the main problem is the heart, and it causes impaired kidney function, then it categorized as type 1 and 2 cardiorenal syndromes, if the main problem is the kidney, then it categorized as type 3 and 4...
**Table 1. Classification and definition of the cardiorenal syndrome from the Consensus Conference of the Acute Dialysis Quality Initiative**

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Clinical Example</th>
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<tbody>
<tr>
<td>CRS type 1 (acute CRS)</td>
<td>Acute heart failure cause acute kidney injury</td>
<td>Acute cardiogenic event that causes cardiogenic shock and acute kidney injury</td>
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<tr>
<td>CRS type 2 (Chronic CRS)</td>
<td>Chronic heart failure cause chronic kidney disease</td>
<td>Chronic heart failure</td>
</tr>
<tr>
<td>CRS type 3 (Acute renocardiac syndrome)</td>
<td>Acute kidney injury causes acute heart failure</td>
<td>Acute kidney damage (decreased cardiac contractility due to uremia, cardiac arrhythmia due to hyperkalemia, lung edema due to fluid overload)</td>
</tr>
<tr>
<td>CRS type 4 (chronic renocardiac syndrome)</td>
<td>Chronic kidney disease caused left ventricle hypertrophy</td>
<td>Chronic kidney disease caused left ventricle hypertrophy, coronary heart disease, and diastolic dysfunction</td>
</tr>
<tr>
<td>CRS type 5 (Secondary CRS)</td>
<td>Presence of systemic comorbid that cause acute or chronic cardiac and renal dysfunction</td>
<td>Amyloidosis, sepsis, diabetes mellitus, anemia and immune system disorders which play a role in the occurrence of AKI.</td>
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Cardiorenal syndrome (CRS) type 1 is most commonly found in patients with acute heart failure, especially acute decompensated heart failure (ADHF), ischemic events (myocardial infarction and cardiac surgery) and also non-ischemic events (valve disorders, aortic dissection, pulmonary embolism, cardiac tamponade). CRS occurs in approximately 40-60% of patients with ADHF based on the current criteria of AKI. In a study of Left Ventricular Dysfunction (SOLVD) study by Ahmad et al., it was shown that a low glomerular filtration rate increased mortality in heart failure patients with left ventricular dysfunction.

There are several variants of CRS type 1 which is divided into 4 subgroups, namely 1) Acute heart failure (de novo) which results in acute kidney injury, 2) Acute heart failure (de novo) which results in chronic kidney injury, 3) acute on chronic decompensated heart failure which causes acute kidney injury (de novo), 4) acute chronic decompensated heart failure resulting in acute on chronic kidney injury. Nevertheless, CRS type 1 is a condition when an acute heart failure that causes acute kidney injury, both in ADHF patients, acute myocardial infarction with symptoms of heart failure or who have decreased ejection of the left ventricular fraction.

The basic mechanism of CRS type 1 is due to a decrease in cardiac output, neurohormonal activation, and the release of vasoactive substances, all of which cause a decrease in perfusion to the kidneys and this causes renal ischemia. Also, high central venous pressure will increase intra-abdominal pressure which ultimately causes venous congestion, sympathetic nerve activation, activation of the renin-angiotensin-aldosterone system and the release of vasoactive substances such as endothelin, anemia and immune system disorders which play a role in the occurrence of AKI.

The mechanism of hemodynamics plays a major role in the occurrence of CRS type 1. Reduced renal artery flow due to decreased cardiac output causes a decrease in the glomerular filtration rate (GFR). If hemodynamics state returned to normal in the early stages, the heart and kidney parameters would also return to normal. Hemodynamic in "cold" conditions are a sign of a decrease in the amount of effective circulating fluid, so that there is a possible decrease in blood flow to the kidneys and activation of the renin-angiotensin-aldosterone system which causes vasoconstriction in renal afferents and decreased effective glomerular perfusion pressure. When there is an increase in central venous pressure (CVP), a "wet" condition will be found in the patient. This condition is also characterized by increased pulmonary and systemic congestion. When CVP increases, interstitial pressure also increases, and kidney tubules collapse so that the glomerular filtration rate also decreases (Figure 1).

The non-hemodynamic mechanisms also play certain roles in the pathogenesis of CRS type 1. The non-hemodynamic mechanisms are the action of the sympathetic nervous system, activation of the renin-angiotensin-aldosterone system, chronic inflammation, and an imbalance between the production of reactive oxygen species (ROS)/nitric oxide (NO) which ultimately contribute to ischemic damage to the renal tubules (Figure 1).

In essence, three main processes promote the occurrence of cardiorenal syndrome type 1. The first is the presence of hemodynamic changes or hemodynamic disorders. Second is the presence of neurohormonal disorders. The third is the existence of other mechanisms related to cardiovascular...
There are four criteria for the definition of AKI based on serum creatinine, and evaluation of glomerular filtration rate according to RIFLE\(^{22}\) (Risk, Injury, Failure, Loss of Kidney Function, and Kidney Disease End-Stage), AKIN\(^{23}\) (Acute Kidney Injury Network), KDIGO\(^{24}\) (Kidney Disease, Improving Global Outcome). It is summarized in Table 2. Essentially, all of these criteria based on the presence of WRF (Worsening Renal Function) or deterioration of kidney function indicated by increased creatinine levels, and a decrease in glomerular filtration rate (Table 2).\(^6\)

Acute kidney injury can also be demonstrated by reduced urine production. Mehta et al. used patient urine production to diagnose acute kidney injury. The criteria divide AKI into 3 stages, stage-1 if urine production ≤0.5 mL/kg per hour for more than 6 hours, stage-2 when urine production is less than 0.5 mL/kg per hour for more than 12 hour, and stage-3 which if the urine production is less than 0.3 mL/kg per hour for more than 24 hours or no urine production at all (anuria) for 12 hours.\(^{23}\)

Recent studies concluded that worsening kidney function occurs in hospitalized patients associated with poor outcome.\(^{16,25,26}\) Voors et al., assess the deterioration of renal function in 30% of patients with acute heart failure patients associated with decreased systolic blood pressure.\(^{27}\) According to Akhter et al., elevated creatinine significantly extend the period of treatment and the effect on long-term mortality.\(^{28}\) According to Chittineni et al., AKI occurs in 21% of patients with congestive heart failure and is associated with increased risk of recurrent.\(^{29}\) According to Damman et al., worsening renal function in patients with acute heart failure both during hospital care and after hospital discharge, independently associated with poor prognosis.\(^{25}\) Blair et al. assessed deterioration of kidney function occurred in 13.8% of patients during treatment and 11.9% after outpatient treatment in heart failure with a decrease in left ventricular ejection function of less than 40%.\(^{30}\) It is somewhat rational to recommend that renal function monitoring is important even after the patients have discharged.

It is important to distinguish kidney deterioration that occurs, whether temporary or permanent, because this affects the long-term prognosis. According to Metra et al., increased serum creatinine caused by artery underfilling and decreased renal perfusion due to the effect of therapeutic diuresis or initiation of therapy or increased doses of angiotensin conversion enzyme blockers or adrenergic receptors (also called vasomotor nephropathy) is usually temporary and is not associated with permanent kidney damage and a poor prognosis.\(^{31}\)

Figure 1. The mechanism, histological correlation, biomarkers, and clinical output of CRS type 1 in acute heart failure.
Table 2. Criteria and definition of acute kidney injury

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Serum creatinine</th>
<th>Duration</th>
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<tr>
<td>KDIGO</td>
<td>• Stage 1: creatinine ≥1.5 times the initial value or increases ≥0.3 mg / dL&lt;br&gt;• Stage 2: creatinine ≥2 times the initial value&lt;br&gt;• Stage 3: creatinine ≥3 times the initial value or increases in creatinine to ≥4.0 mg / dL</td>
<td>The definition of AKI requires a change in creatinine ≥1.5 times of the initial value and occurs in at least 7 days or an increase of 0.3 mg / dL in the first 48 hours.</td>
</tr>
<tr>
<td>AKIN</td>
<td>• Stage 1: increased creatinine 0.3 mg / dL (≥26.2 mol / L) or increase in value up to ≥150% -199% (1.5 to 1.9 times)&lt;br&gt;• Stage 2: increased creatinine up to 200% -299% (≥2 up to 2.9 times) of the initial value&lt;br&gt;• Stage 3: elevated creatinine up to 300% (≥3 times) the initial value or initial creatinine ≥ 4 mg / dL (≥354 mol / L) with an acute rise ≥0,5 mg / dL (44μmol / L) or requiring hemodialysis therapy</td>
<td>Acute creatinine changes occur within the first 48 hours for care</td>
</tr>
<tr>
<td>RIFLE</td>
<td>• At risk: increased creatinine ≥ 1.5 times the initial value or decrease glomerular filtration rate ≤ 25%&lt;br&gt;• Injuries: increased creatinine ≥ 2.0 times the initial value or decrease glomerular filtration rate ≥ 50%&lt;br&gt;• Failure: increased creatinine ≥ 3.0 times the initial value or decrease glomerular filtration rate ≥ 75% or the absolute value of creatinine ≥ 4 mg / dL (≥354 mol / L) with an acute rise at least 0.5 mg / dL (44 mol/L)</td>
<td>Creatinine changed in 1-7 days, began after 24 hours</td>
</tr>
<tr>
<td>WRF</td>
<td>• Increased creatinine ≥ 0.3 mg / dL (26.5 mol / L) of the initial creatinine values</td>
<td>Increased creatinine may occur at any time during treatment</td>
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</table>

The importance of early treatment is early recognition and diagnosis. Due to certain criteria needed 48 hours before establishing the diagnosis, a novel biomarkers of acute kidney injury in urine and blood are needed as an early marker of renal tubular damage. Few candidate markers have been investigated. The various spectrum of the marker has been studied, the functional markers such as plasma and serum creatinine, as well as serum cystatin-c as well as protein markers such as Kidney Injury Molecule-1 (KIM-1), Neutrophil Gelatinase-Associated Lipocalin (NGAL), L-type Fatty Acid Binding Protein (L-FABP), and Interleukin-18 and enzyme markers, namely N-acetyl-β-D-glucosaminidase (NAG) and α-glutathione S-transferase (α-GST). Biomarkers that have shown adequate sensitivity and specificity to renal tubular damage were NGAL, KIM-1, and Cystatin-C.14,32-34

CONCLUSION

Acute heart failure is one of the causes of patients being taken to the hospital, which is often encountered with a fairly high mortality rate. An immediate and appropriate diagnosis and treatment is important for a better clinical outcome. Several limitations of the current criteria of acute kidney injury hinder early intervention. Therefore it is hoped that there will be new markers would support early and faster detection of kidney injury, especially in the setting of acute heart failure.

CONFLICT OF INTEREST

Authors declare no conflict of interest regarding the publication of this article

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