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Received: 27 August, 2018

Accepted: 09 September, 2018

Published: 11 September, 2018

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Keywords: Acute decompensated heart failure; Diuretics; Worsening renal function; Decongestion; Cardiorenal syndrome; Word count: 4,793

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Review Article

Renal congestion related to worsening renal function in patients with acute decompensated heart failure: Diuretic strategy for acute cardiorenal syndrome

Abstract

Deterioration of renal function in patients with acute decompensated heart failure (ADHF) influences the prognosis, suggesting that ADHF should be managed as an acute cardiorenal syndrome. Close collaboration between cardiologists and nephrologists is frequently crucial for management of this condition. It is noteworthy that renal congestion promotes worsening renal function (WRF). High-dose loop diuretics can cause WRF, but are often necessary for treatment of congestion, which is the main symptom of ADHF. However, it is controversial whether WRF associated with diuretic therapy actually has a poor prognosis. In this review, we focus on the mechanism of renal congestion related to WRF in patients with ADHF and on the current status of WRF. We also review the use of loop diuretics to treat ADHF and chronic heart failure, as well as the current role of selective vasopressin-2 receptor antagonist therapy.

Introduction

Heart failure is clinically a syndrome characterized by symptoms (e.g., dyspnea, exertional intolerance, and fatigue) and signs (e.g., pedal edema, pulmonary crackles, and elevated jugular venous pressure) caused by decreased cardiac output that are attributable to cardiac disorder [1,2]. Acute decompensated heart failure (ADHF) can be defined as the new onset or the recurrence of symptoms and signs of heart failure, requiring urgent evaluation and treatment [1-4]. The recurrence of ADHF causes cardiac injury and chronic heart failure (CHF) which lead to asymptomatic cardiac dysfunction, and then to worsening symptoms, absolutely requiring management and treatment of heart failure [1-4].

ADHF is the most frequent cause of hospitalization in the United States and Europe [1,2]. It is associated with high in-hospital and post-discharge mortality rates and a high readmission rate. Symptoms due to congestion are predominant in patients with ADHF and only 10-20% of these patients have symptoms related to low cardiac output [3-5]. It has been suggested that the treatment strategy for ADHF should involve management of this condition as acute cardiorenal syndrome. Recently, there has been concern about

worsening renal function (WRF) because of renal congestion in ADHF rather than prerenal acute kidney injury (AKI) due to low cardiac output. Persisting signs of congestion and renal dysfunction have been consistently reported to be among the most important prognostic variables for ADHF [2,6-12]. WRF is usually defined as an increase of serum creatinine by ≥ 0.3 mg/dL compared with the admission value. WRF occurs in approximately one third of patients admitted with ADHF and is associated with a longer hospital stay, a higher readmission rate, and worse short-term and long-term survival [10,12-18]. Renal congestion participates in the development of WRF [19], and patients with heart failure who remain on long-term treatment with high-dose loop diuretics have a poor prognosis [20-22]. The objective of administering loop diuretics differs between ADHF and CHF, with diuretics being used to achieve decongestion in ADHF versus use for management of the fluid balance in CHF.

In this review, we focus on the mechanism of renal congestion related to WRF in ADHF and on current understanding of WRF. We also review the use of loop diuretics for ADHF and CHF, and the potential of treatment with a selective vasopressin-2 receptor antagonist that does not activate the renin-angiotensin-aldosterone (RAA) system.

Mechanism of renal congestion related to WRF in patients with ADHF

In patients with heart failure, elevation of the inferior vena cava pressure due to fluid retention causes an increase of renal venous pressure, resulting in congestion of the kidney. Because the kidney is an encapsulated organ, renal congestion leads to elevation of the interstitial pressure with compression of the renal vasa recta and tubules, leading to reduction of renal medullary blood flow and the glomerular filtration rate (GFR), followed by development of renal ischemia and reduced Na^+ diuresis. In patients with heart failure and kidney disease, renal damage can be readily exacerbated, leading to marked fluid retention. Conversely, fluid retention associated with ADHF causes renal congestion, which is a factor in promoting renal damage (Figure 1). Thus, a vicious circle can develop in ADHF where renal congestion is complicated by renal ischemia that results in a further decline of renal function [23–26].

Is WRF actually problematic?

Worsening renal function (WRF) during treatment of ADHF is frequently defined as an absolute increase of serum creatinine by ≥ 0.3 mg/dl, and several studies have shown that it is an important adverse prognostic factor [27]. Elevation of central venous pressure (CVP) is associated with renal impairment and is independently related to all-cause mortality in a broad spectrum of patients with cardiovascular disease [27]. An increase of renal venous pressure leads to a decline of GFR, which is probably mediated by decreased renal perfusion. On the other hand, it has been reported that larger early net fluid loss is associated with a lower risk of WRF, but not with greater reduction of right atrial pressure (RAP), suggesting that RAP is not a reliable indicator of the extent of decongestion and the risk of WRF [28], although changes of the fluid balance generally influence both CVP and RAP. Interestingly, a change of GFR by $\geq 20\%$ in either direction (better or worse renal function) during treatment of ADHF has been reported to identify a patient population with advanced disease and a poor prognosis [29]. At present, it is controversial whether WRF is necessarily associated with a worse prognosis in patients with heart failure because publication bias was suggested by funnel plot assessment in a meta-analysis [30]. Thus, we cannot

discriminate between WRF with or without adverse prognostic consequences. However, funnel plot analysis showed no evidence of publication bias for the relation between baseline chronic kidney disease (CKD) and mortality in the same report, indicating that baseline CKD is a prognostic factor for patients with heart failure [30]. Elevation of serum creatinine may be strongly influenced by deterioration of renal hemodynamics caused by heart failure-related changes and diuretic therapy in patients who have baseline CKD, and may be a marker of more severe heart failure rather than actual WRF [31].

A conclusion has not been reached about the prognostic influence of WRF in relation to the left ventricular ejection fraction (LVEF), when patients who have heart failure with preserved ejection fraction are compared to those having heart failure with reduced ejection fraction (cut-off LVEF of 50%) [32,33]. In patients with ADHF, occurrence of WRF is more closely related to age, diuretic dosage, and underlying diseases (including CKD, diabetes, and hypertension) than to LVEF [30]. However, the influence on WRF of diuretics and RAA system inhibition by angiotensin II receptor blockers (ARBs) and/or angiotensin-converting enzyme inhibitors (ACEIs) is reported to be related to LVEF [34,35].

Diuretics are employed to promote excretion of excess body fluid with salt when treating ADHF, although diuretic therapy activates factors promoting fluid retention, such as the RAA system, catecholamines, and vasopressin, eventually leading to progression of renal dysfunction with exacerbation of fluid retention. Long-term use of high-dose loop diuretics by patients with heart failure is associated with a poor prognosis [20–22,36,37], providing the negative impression that loop diuretics may dose-dependently promote WRF [38].

However, it was recently reported that effective decongestion by loop diuretics resulted in a better prognosis for ADHF patients, even if WRF showed exacerbation [39, 40], and the benefits of effective decongestion are assumed to overcome the disadvantages of WRF [23–26]. In patients with ADHF, venous congestion is the most important hemodynamic factor driving WRF, and it depends on elevation of CVP rather than a decrease of cardiac output [23]. Thus, decongestion may be favorable for maintenance of renal function. Interestingly, when patients with or without WRF were compared, there were no significant differences in the length of hospital stay, the mortality rate, or the readmission rate [41].

Effect of Na^+ diuretics (loop diuretics) on ADHF

High-dose loop diuretics are preferentially used to achieve decongestion in patients with acute cardiorenal syndrome. On the other hand, such treatment is associated with WRF and the development of AKI. The cause of WRF was traditionally regarded as a decrease of the effective circulating blood volume due to reduction of cardiac output by heart failure and volume depletion by high-dose diuretic therapy [19]. However, renal congestion derived from blood pooling in the inferior vena cava and renal veins has also been shown to be an important hemodynamic mechanism of WRF [23–26]. CKD is a common condition [42,43] and is related to the pathophysiology of

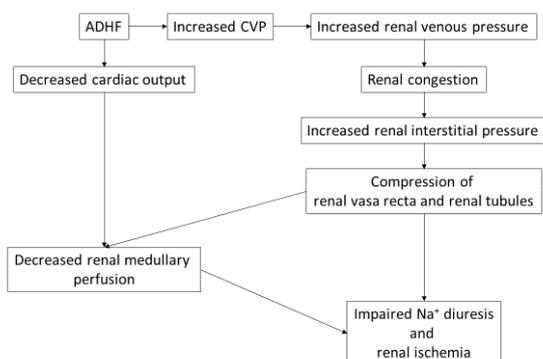


Figure 1: Impairment of Na^+ diuresis and development of renal ischemia secondary to renal congestion associated with ADHF. ADHF, acute decompensated heart failure; CVP, central venous pressure.

worsening ADHF, with the combination of CKD and ADHF resulting in resistance to diuretic therapy (including high-dose diuretics) and a decline of renal function. It is known that the effect of diuretic therapy can be attenuated during treatment due to the “diuretic breaking phenomenon” and diuretic resistance [44,45]. Na⁺ retention occurs due to activation of the RAA system after short-acting loop diuretics promote fluid excretion (diuretic breaking phenomenon). In addition, long-term administration of loop diuretics promotes Na⁺ retention in the distal tubules and collecting ducts located downstream of the ascending limb of the loop of Henle, while hypokalemia related to long-term administration reduces Na⁺ secretion into the renal tubules, and delivery of loop diuretics to the renal tubules is impaired because drug absorption is affected by intestinal tract edema and renal blood flow is decreased secondary to reduction of the effective circulating blood volume (diuretic resistance). In ADHF patients, both diuretic resistance and the diuretic dose are factors with an independent influence on the prognosis [22].

It has been reported that the loop diuretic dose, presence of WRF, and persistent pulmonary congestion at discharge influence the prognosis of ADHF [21,40,46,47]. Therefore, it seems important to achieve early decongestion in ADHF patients before aiming at prognostic improvement for CHF, although we currently lack evidence that loop diuretics improve the long-term prognosis.

Diuretic strategy for maintaining renal function in patients with CHF

In the management of CHF, it is important to maintain renal function without causing exacerbation of heart failure because deterioration of renal function is an adverse prognostic factor for CHF patients [48–50]. It is necessary to inhibit activation of the RAA system, as well as managing the fluid balance to prevent volume overload [i.e., excessive preload on the heart]. The RAA system has an important role in regulating renal hemodynamics [51]. A decrease of cardiac output due to heart failure leads to reduced renal blood flow, but GFR is maintained by contraction of the efferent arterioles in response to angiotensin II [52–54]. Inhibition of the RAA system by treatment with ARBs or ACEIs results in dilation of the efferent arterioles and promotes the maintenance of long-term renal function regardless of an early decline in GFR [55–57] that occurs due to the decrease of intraglomerular pressure derived from the effect of reduced afterload on intraglomerular hemodynamics. Reducing the daily dosage of loop diuretics or the number of doses by using long-acting agents is important for minimizing RAA system activity, and combined administration with ARBs or ACEIs is recommended.

Effect of a water diuretic (selective vasopressin-2 receptor antagonist) that does not activate the RAA system on ADHF

Tolvaptan is a selective vasopressin-2 receptor antagonist that does not activate the RAA system [58] and maintains renal hemodynamics [59], suggesting that it may be useful for renal protection. Tolvaptan can be expected to promote renal

decongestion by decreasing the inferior vena cava pressure via reduction of fluid overload, in addition to maintaining renal medullary blood flow, which has a renoprotective effect due to prevention of renal medullary ischemia and inhibition of RAA system activation.

There have been increasing reports about tolvaptan, and evaluation of its usefulness for decongestion in ADHF was decided in 2017 [60,61]. The EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan, tolvaptan dose of 30mg/day) trial in 2007 and the AQUAMARINE (Answering the Question of Tolvaptan’s Efficacy for Patients With Acute Decompensated Heart Failure and Renal Failure, tolvaptan dose of 15mg/day) study in 2016 investigated tolvaptan in patients with HFrEF and revealed early improvement of congestion symptoms. However, two clinical trials reported in 2017, the TACTICS-HF (Targeting Acute Congestion with Tolvaptan in Congestive Heart Failure, tolvaptan dose of 30 mg/day) trial and the SECRET of CHF (Study to Evaluate Challenging Responses to Therapy in Congestive Heart Failure, tolvaptan dose of 30mg/day) trial, did not show improvement of congestion symptoms despite increased fluid excretion [60–63]. The prevalence of WRF among patients receiving tolvaptan was comparable to that among those receiving control therapy, except in the TACTICS-HF trial. These findings did not support the use of tolvaptan for early decongestion in ADHF based on cost and limited efficacy, thereby ending a debate that has been ongoing for approximately 10 years since the EVEREST trial was reported in the United States [64]. The open-label AQUAMARINE study in Japan included subjects with a higher LVEF relative to the double-blind trials of patients with HFrEF [63]. Thus, investigation of tolvaptan in patients with HFpEF may be considered.

There is currently no evidence as to whether adding tolvaptan to a loop diuretic for fluid management in CHF contributes to maintenance of renal function in patients with chronic cardiorenal syndrome. Further investigation may be justified from the viewpoint of reducing afterload on the kidney and renal protection, because treatment that has a diuretic effect without reducing renal blood flow is theoretically desirable.

Conclusion

In ADHF patients, WRF is associated with renal congestion. Treatment of ADHF aimed at decongestion should be the top priority before considering the long-term prognosis. When the prognostic significance of WRF is assessed, including its influence on the hospital stay, medical costs, in-hospital or post-discharge mortality, and short-term or long-term readmission rates, studies that stratify patients by their background characteristics are necessary because the influence of WRF may vary according to factors such as the age and underlying diseases.

Acknowledgment

We would like to thank Yamada Translation Bureau, Inc. for reviewing the English manuscript.

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