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Mini Review

New Insight in to an Old Therapy for the Treatment of Acute Decompensated Heart Failure and Associated Renal Dysfunction

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Abstract

Acute Decompensated Heart Failure (ADHF) is one of the most common causes of hospital admission and is associated with poor outcome. More than often, currently available treatments including high-dose loop diuretics don't provide patients with adequate decongestion due to either worsening renal function or diuretic resistance resulting in high readmission rate and early mortality. Moreover, the recent trials studying newer strategies such as the mechanical ultrafiltration, low dose dopamine or nesiritide have demonstrated no benefit over diuretic regimens in terms of volume removal or elevation of creatinine leaving no further choice for management of diuretic resistant ADHF patients. Patients with heart failure share the same pathophysiology of decreased effective arterial blood volume as patients with cirrhosis; because of splanchnic vasodilatation in cirrhosis and decreased cardiac output in heart failure with resultant stimulation of the renin-angiotensin-aldosterone system. Hyperaldosteronism plays a major role in the pathogenesis of ascites and contributes to resistance to loop diuretics. Therefore, the use of high doses of aldosterone antagonist (spironolactone up to 400 mg/day) is the main therapy to produce a negative sodium balance in cirrhotic patients with ascites. However, similar approach has not been adopted in ADHF patients to achieve negative sodium balance. This article reviews the pathophysiology of worsening renal function and diuretic resistance associated with the use of loop diuretics, mechanical ultrafiltration and other vasodilator therapies in ADHF patients and identifies the potential role of an old therapy, i.e. aldosterone antagonists in the high dose for management of these patients.

Introduction

In the United States, more than 1 million patients are admitted annually for acute decompensated heart failure (ADHF) [1]. Moreover, despite using higher doses or intravenous diuretics in 90% of ADHF patients, many patients are discharged without adequate decongestion (approximately 50% lose <5 lb and 20% gain weight), resulting in readmission in up to 25% in next 30 days [2] and up to 20% die within 6 months [3]. During the last 10-20 years, several therapies including β-blockers and angiotensin converting enzyme inhibitor (ACEI)/angiotensin receptor blockers (ARB) have been shown to have a beneficial impact on the clinical course of patients with chronic congestive heart failure [4]; however, similar advances have not occurred for the treatment of ADHF.

Limitations of Loop-Diuretic Therapy

The main focus in the management of ADHF is on therapies directly responsible for removal of excess sodium and water. The most widely used therapy at present is higher than usual dose of oral or intravenous loop diuretics including furosemide, torsemide and bumetanide alone or in combination with thiazide like diuretics including chlorthalidone, hydrochlorthiazide or metolazone. However, declining kidney function during diuresis is a common occurrence, and on many occasions patients already present with worsening renal function along with ADHF (cardiorenal syndrome type I). The mechanisms behind these relationships are complex and patient specific. Usually in ADHF, loops diuretics improve cardiac function by decreasing cardiac filling pressure, functional mitral insufficiency, ventricular wall stress, and endomyocardial ischemia [5]. This improved cardiac function results in improved effective arterial blood volume (EABV) resulting in decreased neurhumoral stimulation (sympathetic nervous system, renin-angiotensin-aldosterone system (RAAS), and arginine vasopressin). The decrease in neurohumoral stimulations results in decrease in renal vasoconstriction and thus better renal perfusion and improved natriuresis. However, when the rate of fluid removal in heart failure patients exceeds the estimated rate of fluid mobilization from the interstitium to vascular compartment, volume depletion may ensue in the compartment which is responsible for usual baroreceptor inhibition i.e. EABV, despite persistence of overall hypervolemic state, resulting in further stimulation of the neurohumoral system. This rate of fluid mobilization from the interstitium to vascular compartment varies from patient to patient. A patient with heart failure with no other co-morbidities may tolerate net fluid

loss of 2 liter/day without depleting EABV; however, presence of co-morbidities such as sepsis even mild, or hypoalbuminemia decrease the rate of fluid mobilization secondary to likely associated capillary leak phenomenon. Therefore, when the rate of diuresis exceeds the rate of fluid mobilization, further stimulation of neurohumoral system results in renal vasoconstriction and hence, decreased renal function. The decrease in the dose of diuretics to reduce the rate of diuresis may improve the renal function, however, leads to delay in symptoms relief and prolongation of the hospitalization sometimes resulting in early discharge with inadequate decongestion. The results of the DOSE (diuretic optimization strategies evaluation) trial are supportive of above phenomenon [6]. The DOSE trial was a prospective, randomized, double-blind, controlled trial where patients with ADHF received furosemide intravenously at either a low dose (equivalent to the patient's previous oral dose) or a high dose (2.5 times the previous oral dose) and either as a bolus every 12 hours or continuous infusion. The high-dose strategy was associated with greater diuresis, weight loss and relief from dyspnea but also with transient worsening of renal function. Overall, there were no significant differences in patients' global assessment of symptoms with either of these strategies.

Another limitation with the use of loop diuretics is the development of resistance to the natriuretic effect. Long-term loop diuretic use causes further RAAS activation by inhibiting sodium chloride transport at the macula densa and relative volume depletion. In addition, chronic use of loop diuretics causes enhanced sodium chloride co-transporter expression at distal collecting tubules leading to increased sodium absorption at this site resulting in resistance to natriuretic effect [7]. Addition of thiazide like diuretics overcomes the later problem; however, relative volume depletion causing further RAAS activation and excessive proximal tubular sodium absorption remains an issue.

Results Of The Recent Randomized Controlled Trials For Treatment of ADHF

Recently, many other strategies have been tested for removal of excessive fluid in addition to or in place of diuretics. First, blood based extracorporeal ultrafiltration which requires use of invasive device and anti-coagulation. There are 5 randomized controlled trial comparing ultrafiltration to diuretics in patients with ADHF with mixed results [8-12]. The CARRESS-HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure) is the most recent and rigorously done trial where ultrafiltration was compared with stepped pharmacologic (loop diuretic based) decongestion and specifically targeted patients with worsening kidney function. There was no significant difference in weight loss at 96 hours; however, patients in the ultrafiltration group had more increase in the creatinine level and adverse events compared to stepped pharmacologic group. Second, Nesiritide, it is a human recombinant B-type natriuretic peptide with vasodilating and natriuretic properties and is approved for management of acute heart failure. The recommended dose is a 2-µg/kg bolus followed by infusion at 0.01µg/kg/min. This dose decreases blood pressure and atrial pressures and produces modest improvement in dyspnea, but does not favorably affect clinical outcomes or renal function, potentially because of its hypotensive effects [13,14]. The latest Renal Optimization Strategies Evaluation (ROSE) trial [15] compared with placebo, the addition of low-dose nesiritide (0.005 µg/kg/min without bolus) to diuretic therapy in patients with ADHF and renal dysfunction (glomerular filtration rate [GFR] of 15-60 mL/min/1.73m2 as estimated by the Modification of Diet in Renal Disease equation). This low-dose nesiritide did not worsen renal function but neither enhanced the decongestion. Third, in the same trial, the addition of low-dose dopamine (2 µg/kg/min) was also compared to placebo to usual diuretic therapy. Dopamine is an endogenous catecholamine that, at low doses (≤3 µg/kg/min), may selectively activate dopamine receptors and promote renal vasodilatation [16,17]. This low dose dopamine did not cause any improvement in urinary sodium excretion, weight loss or clinical symptoms, nor in renal outcomes.

The possible explanation for failure to achieve the better outcomes with the above strategies is similar to the use of loop diuretic, i.e. further stimulation of neurohumoral system and RAAS. The heart failure patients have severe underlying secondary hyperreninemic and hyperaldosteronism state due to reduced EABV as a result of decreased cardiac output. Further decrease in EABV either secondary to rapid volume loss from loop diuretics or ultrafiltration, or due to use of vasodilators causes further worsening of this secondary hyperreninemic and hyperaldosteronism state. The elevated RAAS axis causes worsening of renal function and inadequate decongestion due to renal vasoconstriction and enhanced sodium absorption in all the segments of the nephron.

High Dose Aldosterone Antagonist

Given the very poor prognosis of patients with ADHF, the medical community is in dire need of a therapy to improve their outcome. In that regards, aldosterone antagonists such as spironolactone, available since mid-20th century, has significant potential to cause substantial natriuresis without worsening renal function; however, has gained minimal attention. High dose of spironolactone (up to 400-600 mg/day) is commonly used in the management of patients with cirrhosis with ascites, the disorder which shares the same pathophysiology of sodium and water retention as heart failure, which is decreased EABV as a result of systemic vasodilatation with resultant stimulation of neurohumoral axis. Hyperaldosteronism plays a major role in the pathogenesis of ascites as suggested by elevated plasma aldosterone concentrations and marked increases in both of the major aldosterone-sensitive apical transport proteins of renal tubule, namely, the thiazide sensitive sodium chloride cotransporter and the epithelial sodium channel α subunit [18]. The consequence is that much of the sodium that is not reabsorbed in the loop of Henle, secondary to the action of furosemide or other loop diuretics, is subsequently reabsorbed in the distal nephron. In a comparative trial in cirrhotic patients, spironolactone was found to be more effective than furosemide, which exhibited an impaired diuretic response secondary to increased RAAS activity [19]. Thus, patients with marked hyperaldosteronism did not respond to furosemide and required high doses of spironolactone (400 to 600 mg/day). On the basis of these findings, the International Club of Ascites defines diuretic resistance in patients with ascites as those unresponsive to a sodium-restricted diet and high-dose (400 mg/day spironolactone and 160 mg/day furosemide) diuretic treatment.

Aldosterone antagonism is a standard therapy and proven to provide mortality benefit in heart failure, however, in those trials the doses of spironolactone utilized were non-natriuretic and the majority of benefit resulted from the anti-fibrotic actions [20]. In

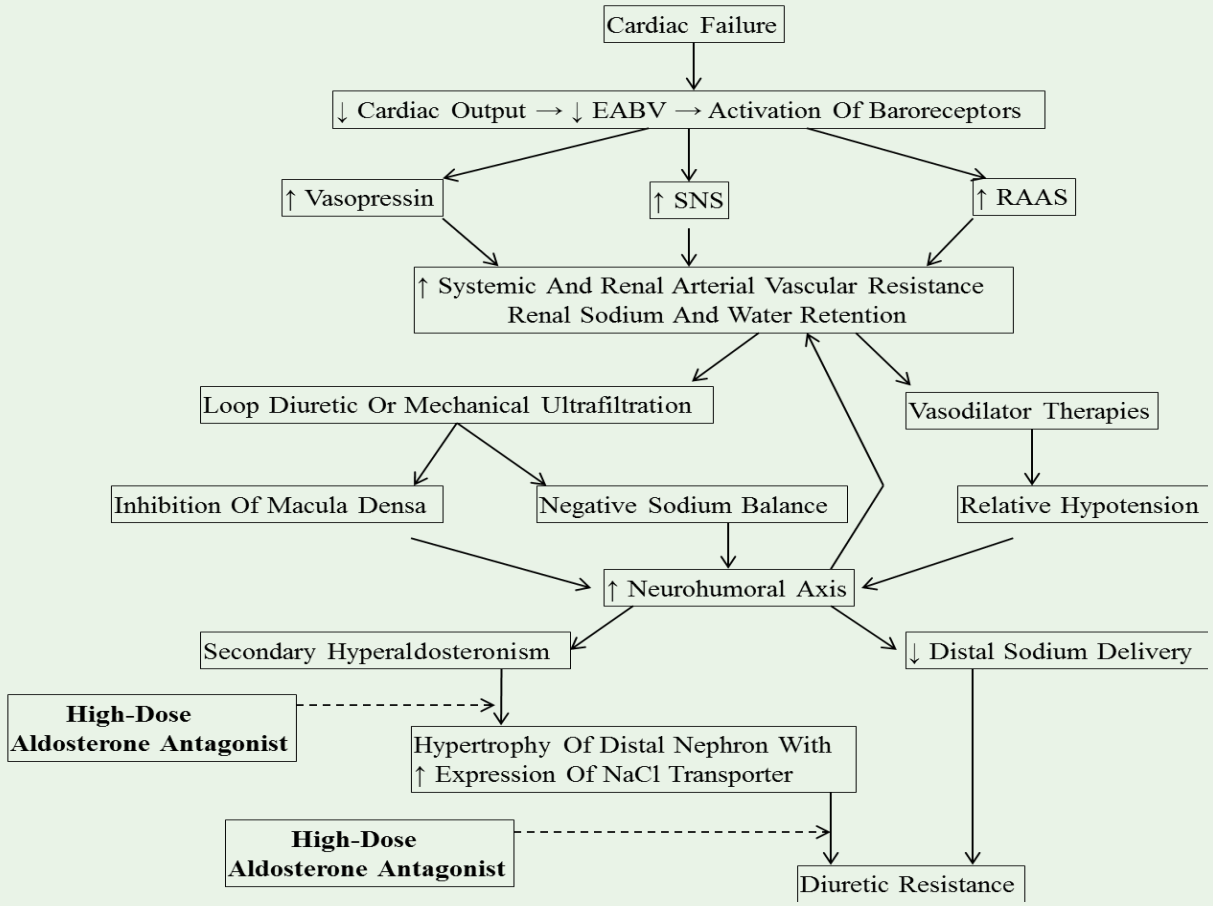

Figure 1: The mechanism of diuretic resistance with potential benefit of aldosterone antagonist. Dotted line indicates inhibition.

context of the similar pathophysiology of diuretic resistance in cirrhosis and HF, aldosterone antagonists in natriuretic-doses (>50 mg of spironolactone) is an alternative attractive diuretic strategy in treating heart failure (Figure 1). In this regard, in a small trial of 6 avidly sodium retaining patients with heart failure, spironolactone 200 mg BID caused a marked increase in sodium excretion and indeed led to sodium balance over a few days with a clinically negligible rise in serum potassium concentration [21]. In another study, 81% of the patients with severe heart failure, who were resistant to high-dose loop diuretics (10 mg of bumetanide) and captopril, responded with increased natriuresis with the use of 100 mg/day spironolactone. At baseline, these resistant patients had higher plasma aldosterone concentrations and low urine Na/K ratio compared with nonresistant patients, thus suggesting the presence of more marked hyperaldosteronism [22]. The authors did not encounter hyperkalemia in any of those patients. The latest addition to this literature has been a relatively large, single center, single-blind trial by Ferreira et al. [23], where addition of spironolactone 50-100 mg/day to the standard ADHF therapy was compared to standard therapy alone in 100 patients. The greater proportion of patients in the spironolactone group were free of congestion, edema, rales, and orthopnea by day 3. The treatment group also had less worsening of renal function and better plasma N-terminal pro brain natriuretic peptide levels with no difference in serum potassium levels compared to standard therapy. In our own experience, addition of spironolactone 100 mg bid to IV furosemide in patients with ADHF and estimated GFR 15-60 ml/min resulted in significant weight loss without hyperkalemia and avoided the need for invasive ultrafiltration [24]. In all of these studies, use of aldosterone antagonist resulted in significant diuresis without significant worsening renal function. Inhibition of the RAAS axis at the downstream rather than its stimulation as caused by loop-diuretics resulting in no impairment of renal blood flow is possible mechanism for preservation of renal function during diuresis. One argument against the use of aldosterone antagonist could be the widely prevalent use of ACEI/ARB in this patient population which should be sufficient to cause the aldosterone suppression. However, there is increasing evidence to suggest that in some patients aldosterone may only transiently be suppressed with ACE inhibition [25-27]. Specifically, in clinical trials of ACEIs and ARBs, plasma aldosterone levels, after an initial decline, have been shown to increase in some patients over the long term. This phenomenon termed “aldosterone breakthrough” can have important clinical consequences given the hormone’s sodium-retaining effect as well as the profibrotic actions on diverse organ systems including heart, blood vessels, and kidney [28].

Nevertheless, the risk of hyperkalemia is high in HF patients treated with high doses of aldosterone antagonists in the presence of ACEIs, and/or ARBs. Inpatient use of high dose spironolactone with frequent electrolyte monitoring is safe. Moreover, the ACEI/ARBs

can be held during hospitalization to allow active diuresis since these drugs confer their protective effects on long term use in chronic heart failure. In addition, decrease potassium secretion due to aldosterone inhibition is balanced by the increased potassium secretion caused by loop-diuretic mediated enhanced tubular flow rate.

Conclusion

Hyperaldosteronism has increasingly been recognized as a risk factor for myocardial and vascular fibrosis and is responsible for loop diuretic resistance. Mineralocorticoid antagonists are the preferred diuretics in cirrhosis and have been shown to have better natriuretic response compared with loop diuretics. Cirrhosis and heart failure have important similarities in the mechanisms of sodium retention including marked hyperaldosteronism. Therefore, natriuretic doses of spironolactone may provide supplementary benefit over and above their effect on myocardial and vascular fibrosis in patients with decompensated heart failure without the associated risk of worsening renal function. This possibility warrants testing in carefully designed randomized controlled trial. Moreover, the potassium losing effect of loop diuretics would also blunt any tendency of mineralocorticoid antagonists to cause hyperkalemia.

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