

## Sodium Retention in Heart Failure and Cirrhosis Potential Role of Natriuretic Doses of Mineralocorticoid Antagonist?

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**Abstract**—Patients with cirrhosis and heart failure (HF) share the pathophysiology of decreased effective arterial blood volume because of splanchnic vasodilatation in cirrhosis and decreased cardiac output in HF, 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. Hyperaldosteronism also has increasingly been recognized as a risk factor for myocardial and vascular fibrosis. Therefore, low-dose aldosterone antagonists are being used in patients with HF for cardioprotective action. However, the doses (25 to 50 mg/day) at which they are being used in cardiac patients as reported in the Randomized Aldactone Evaluation Study are not natriuretic. It is likely, therefore, that the mortality benefit relates primarily from their effect on cardiac and vascular fibrosis. Resistance to commonly used loop diuretics is frequently present in patients with advanced HF. In patients with decompensated HF with volume overload who are loop diuretic resistant, ultrafiltration may be the only available option. This is, however, an invasive procedure. For these patients, natriuretic doses of aldosterone antagonists (spironolactone >50 mg/day) may be a potential option. The competitive natriuretic response of aldosterone antagonists is related to activity of the renin-angiotensin-aldosterone system: the higher the renin-angiotensin-aldosterone system activity, the higher the dose of aldosterone antagonist required to produce natriuresis. This article will discuss the potential use of natriuretic doses of aldosterone antagonists in patients with HF, including the potential side effect of hyperkalemia. (*Circ Heart Fail.* 2009;2:370-376.)

**Key Words:** spironolactone ■ neurohumoral axis ■ cardiorenal syndrome ■ edematous states

Heart failure (HF) has emerged as a disease with significant public health implications. There are ~5 million patients with HF in the United States, and >400 000 new cases are diagnosed annually.<sup>1</sup> Given the increased use of angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs),  $\beta$ -blockers, and low-dose aldosterone antagonists, and device therapies such as cardiac resynchronization therapy, the mortality curve for patients with chronic HF has been attenuated somewhat<sup>2–6</sup>; however, the risk of death within 5 years of diagnosis is still >50%.

Cirrhosis and HF are disorders with a common pathophysiology of decreased effective arterial blood volume with resultant stimulation of the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system, and arginine vasopressin causing increased sodium and water retention. This arterial underfilling is caused by splanchnic vasodilatation in cirrhosis and decreased cardiac output in HF. In cirrhotic patients with refractory ascites, the standard of first-line care is mineralocorticoid antagonist (eg, spironolactone in doses up to 400 mg/day). However, natriuretic doses of aldosterone antagonists have not been examined in patients with HF.

Since the introduction of the Randomized Aldactone Evaluation Study (RALES),<sup>6</sup> the use of aldosterone antagonists in

patients with HF has increased worldwide. However, the reduction in the risk of death in the study does not seem to be due to an effect of spironolactone on sodium retention because in their dose-finding study 25 mg of spironolactone daily had no apparent effect on sodium retention score, urinary sodium excretion, or body weight.<sup>7</sup> Therefore, it is likely that spironolactone in this dose is primarily cardioprotective. The present article will review the potential role of natriuretic doses of aldosterone antagonist in patients with HF.

### Common Pathophysiology of Cardiac Failure and Cirrhosis

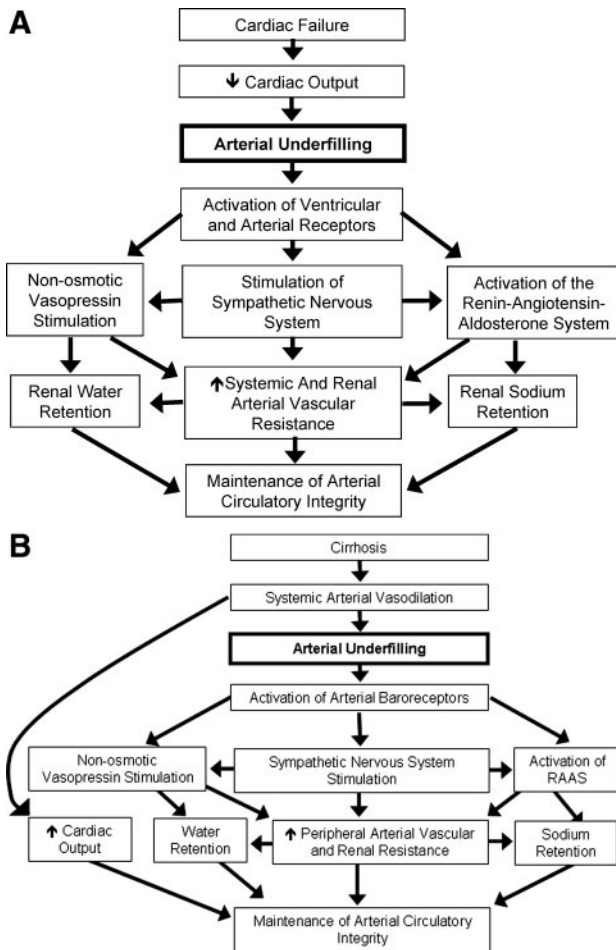
During the last 3 decades, an understanding of the pathogenesis of edematous disorders has evolved.<sup>8–11</sup> Estimates of circulating blood volume distribution indicate that ~85% of blood circulates on the low-pressure, venous side of the circulation, whereas an estimated 15% of blood is circulating in the high-pressure arterial circulation. Although there are low-pressure receptors on the venous side of the circulation, body fluid volume regulation primarily involves the integrity of the arterial circulation as the primary modulator of renal water and sodium regulation. Underfilling of the arterial

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**Figure 1.** Clinical conditions in which a decrease in cardiac output (A) and systemic arterial vasodilation (B) cause arterial underfilling with resultant neurohumoral activation and renal sodium and water retention. Reproduced with permission from *J Am Soc Nephrol.* 2007;18:2028–2031.

circulation can occur secondary to either a decrease in cardiac output (Figure 1A) or a relative underfilling caused by systemic arterial vasodilation as seen in cirrhosis, high-output failure (eg, beriberi, thyrotoxicosis), and pregnancy (Figure 1B).<sup>12</sup> This hypothesis of body fluid regulation is only applicable in the absence of renal parenchymal disease, thus excluding edema associated with chronic renal diseases and/or nephrotic syndrome. Normally, a tonic inhibition of nonosmotic vasopressin release and central sympathetic outflow is present via afferent vagal and glossopharyngeal neural pathways. With a decrease in arterial baroreceptor stretch during low-output cardiac failure or systemic arterial vasodilation, there is nonosmotic vasopressin release<sup>10,13,14</sup> and an increase in sympathetic tone.<sup>15</sup> The enhanced sympathetic tone increases RAAS activity via renal  $\beta$ -adrenergic stimulation<sup>16</sup>; both the sympathetic and angiotensin pathways increase systemic vascular resistance and renal sodium and water retention to maintain circulatory integrity by attenuating the arterial underfilling. The increased nonosmotic vasopressin release stimulates V1a receptors on vascular smooth muscle cells to increase vascular resistance and V2 receptors in the collecting duct to increase renal water reabsorption.

The effect of angiotensin to stimulate aldosterone and the failure to escape from the renal sodium retaining effect of aldosterone contributes to edema formation.

Thus, patients with HF and cirrhosis share a common pathophysiology of arterial underfilling secondary to decreased cardiac output and decreased systemic vascular resistance, respectively, with eventual stimulation of neurohumoral axis and sodium and water retention. Although these compensatory mechanisms cause acute hemodynamic improvement, chronic activation of these systems contributes to an increased cardiac preload, increased cardiac afterload, increased myocardial workload, arrhythmia, and decreased myocardial relaxation in patients with HF with exaggerated renal vasoconstriction. The resultant renal vasoconstriction and sodium and water retention lead to ascites and hepatorenal syndrome in advanced cirrhosis and cardiorenal syndrome in patients with HF.

### Activation of the RAAS in HF

RAAS activation in patients with HF has been shown to correlate directly with mortality. Angiotensin II is known to cause myocardial remodeling,<sup>17</sup> and the resultant increase in aldosterone may increase myocardial fibrosis and necrosis in the heart.<sup>18</sup> Moreover, angiotensin II is known to be a potent stimulator of the sympathetic nervous syndrome.<sup>19</sup> There is also experimental evidence for angiotensin generation in the central nervous system during cardiac failure, as evidenced by an increase in angiotensin concentration in the cerebrospinal fluid. Increased angiotensin and decreased nitric oxide in the brain have been implicated as mediators of the blunting of baroreceptor sensitivity in experimental HF.<sup>20</sup> The increase in renal sympathetic tone, secondary to this baroreceptor perturbation, would be expected to cause sodium retention by several mechanisms.<sup>21</sup> Angiotensin and adrenergic nerve stimulation both activate receptors on the proximal tubule epithelium, which enhances sodium reabsorption.<sup>22,23</sup> Furthermore, the resultant decreased sodium delivery to the distal nephron impairs the normal escape mechanism from the sodium-retaining effect of aldosterone. Vasoconstriction of the glomerular efferent arteriole by angiotensin II in HF also alters net Starling forces in the peritubular capillary by decreasing hydrostatic and increasing oncotic pressure in a direction to enhance sodium reabsorption.<sup>24</sup>

Aldosterone may cause cardiovascular injury by mechanisms independent of its salt retention and hypertensive effects.<sup>25–27</sup> Aldosterone activates mineralocorticoid receptors in nonepithelial tissues and, in the presence of high sodium intake causes oxidative stress, endothelial dysfunction, inflammation, and fibrosis leading to cardiovascular and renal injury.

### Comparison of Risk Factors for Poor Survival in Advanced Cardiac Failure and Cirrhosis

Several common markers have been proposed to predict poor survival in patients with HF and cirrhosis. Increased neurohormonal stimulation and renal failure have been the most notable and portend the worst prognosis. In HF, elevated plasma norepinephrine, arginine vasopressin, renin activity, endothelin, and B-type natriuretic peptide have been shown to

be significant predictors of outcome in multivariate analyses in different trials.<sup>28–35</sup> Elevated plasma aldosterone is also associated with higher mortality in HF.<sup>32</sup> Results of the multicenter Cooperative North Scandinavian Enalapril Survival Study in patients with severe HF, New York Heart Association class IV, demonstrated that elevated plasma aldosterone levels were associated with increased 6-month mortality. This higher mortality rate occurred in patients with abnormally high plasma levels of angiotensin II and renin.<sup>32</sup> Furthermore, this research demonstrated that when levels of aldosterone, angiotensin II, or renin were reduced with ACEIs, there was a concomitant reduction in mortality.<sup>36</sup> In multiple studies, any detectable decrease in renal function has also shown to increase mortality in patients with HF.<sup>37–39</sup>

Similar to HF, cirrhosis is a heterogeneous disease with the same pathophysiology of arterial underfilling and increased neurohormones including aldosterone. Plasma aldosterone concentrations are elevated in both severe HF and cirrhosis.<sup>40,41</sup> In both HF and cirrhosis, patients with resistance to loop diuretics have been found to have much higher plasma aldosterone concentration, and they have better natriuresis with mineralocorticoid antagonist therapy.<sup>41,42</sup> Moreover, patients with increased plasma renin activity and increased aldosterone and norepinephrine levels have a high probability of developing hepatorenal syndrome that predicts high mortality in the absence of liver transplantation.<sup>43,44</sup>

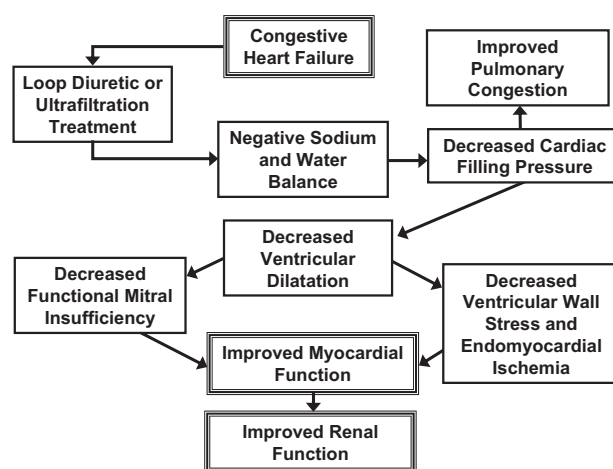
## Role of Diuretics in the Management of Cirrhosis and Cardiac Failure

### Cirrhosis With Ascites

Management of ascites is based on improving the renal sodium excretion with diuretics and dietary sodium restriction. Large-volume paracentesis and transjugular intrahepatic portosystemic shunts are also useful in managing patients with refractory ascites.

### Spironolactone and Loop Diuretics

Loop and distal diuretics are the basic drugs for the treatment of ascites. Although pharmacological studies indicate that the natriuretic potency of loop diuretics is much greater than that of more distal diuretics, the administration of relatively high doses of furosemide (up to 160 mg/day) to nonazotemic cirrhotic patients causes a satisfactory natriuresis in only 50% of patients.<sup>45,46</sup> Mechanisms involved in this poor diuretic effect include reduced tubular secretion of furosemide into the lumen, decreased delivery of fluid to the loop of Henle secondary to enhanced proximal sodium reabsorption, and finally, hyperaldosteronism. 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  $\alpha$  subunit.<sup>42</sup> 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 patients with cirrhosis, spironolactone was found to be more effective than furosemide, which exhibited



**Figure 2.** Mechanisms in congestive HF whereby negative sodium and water balance by loop diuretics or ultrafiltration therapy may improve myocardial and renal function. Reproduced with permission from *J Am Coll Cardiol*. 2006;47:1–8.

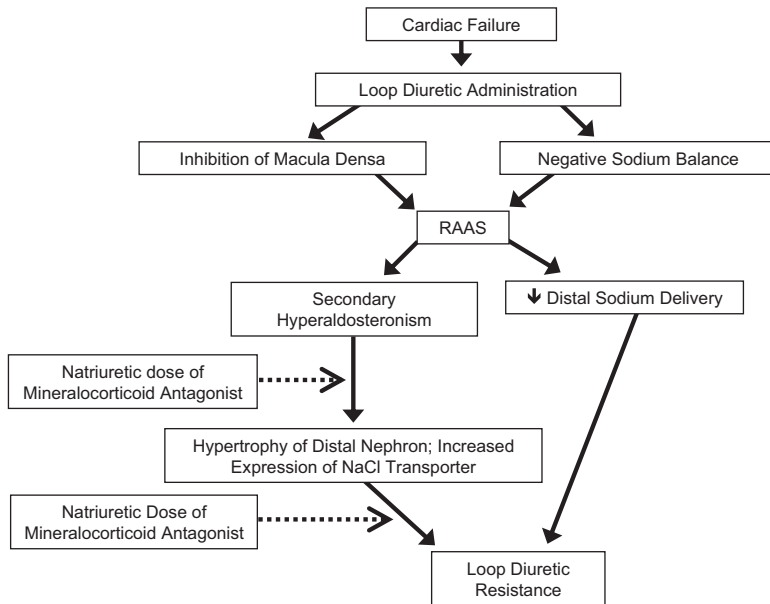
an impaired diuretic response secondary to increased RAAS activity. Thus, patients with marked hyperaldosteronism did not respond to furosemide and required high doses of spironolactone (400 to 600 mg/day).<sup>45</sup> On the basis of these findings, the International Club of Ascites defined diuretic 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.

### Cardiac Failure

Current therapy has focused on improving symptoms and hemodynamics. Nevertheless, the length of hospital stay, although variable in different countries, has remained relatively stable for patients with acute decompensated HF.

### Diuretics

In patients with symptomatic HF, there is little question about the positive role of providing symptomatic relief from pulmonary and peripheral congestion. However, the use of loop diuretics in HF may be a double-edged sword. There have not been any large randomized controlled trials that have evaluated the safety of loop diuretics in HF. There is, however, a meta-analysis of 3 small randomized trials that concludes a benefit of diuretics on mortality.<sup>47</sup> The use of diuretics in some cardiac failure patients occasionally may lead to deterioration of renal function. Loop diuretics also may improve cardiac function by decreasing cardiac filling pressure, functional mitral insufficiency, ventricular wall stress, and endomyocardial ischemia (Figure 2). In some patients, this may also lead to improved renal function. However, when the rate of fluid removal in cardiac failure patients exceeds the estimated rate of fluid mobilization from the interstitium to vascular compartment (>12 to 14 mL/min), intravascular volume depletion may ensue with resultant decreased cardiac preload and cardiac index. This leads to further stimulation of the neurohumoral system (sympathetic nervous system, RAAS, and arginine vasopressin) with renal vasoconstriction, sodium and water retention, and deterioration of renal function. Moreover, in addition to the inhibition of the NaK<sub>2</sub>Cl cotransporter in the thick medullary ascending loop of Henle,



**Figure 3.** Mechanisms of diuretic resistance with potential benefit of mineralocorticoid antagonism. Dotted line indicates inhibition.

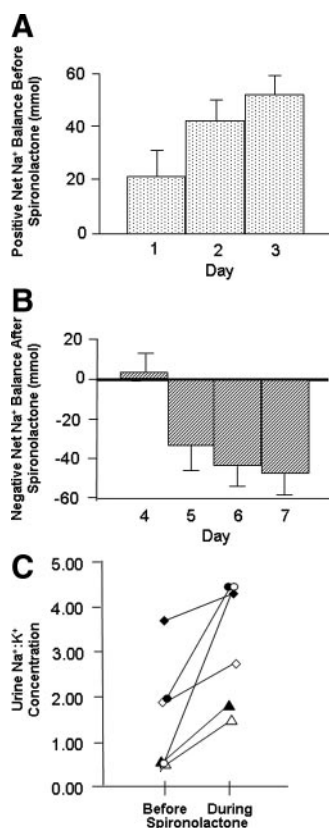
loop diuretics also block sodium chloride transport at the macula densa, which directly stimulates the RAAS independent of renal sodium loss.<sup>48</sup> Activation of the RAAS has been shown to be a major factor in the occurrence of diuretic resistance<sup>49</sup> (Figure 3). In a porcine study of tachycardia-induced HF, furosemide administration shortened the time to left ventricular dysfunction and elevated serum aldosterone concentrations compared with placebo independent of detectable differences in cardiac preload.<sup>50</sup> In addition, chronic administration of loop diuretics has been shown to cause hypertrophy of the distal nephron and increase expression of the sodium chloride cotransporter, effects that can be reversed by a mineralocorticoid antagonist.<sup>49,51</sup>

Thus, loop diuretics may cause worsening of already increased RAAS activation and secondary hyperaldosteronism in patients with HF. Furthermore, there is failure to escape from the sodium-retaining effect of aldosterone because of persistent activation of the renin-angiotensin and sympathetic systems causing enhanced proximal tubular sodium absorption and decreased distal sodium delivery. As a result of failure to escape from the sodium-retaining effect of aldosterone, the natriuretic effect of loop diuretics is blunted by increased reabsorption distally at the collecting tubular site of aldosterone action. Thus, inhibition of mineralocorticoid receptors, in addition to loop diuretics, may cause a significant natriuresis. This could be crucial in the management of pulmonary and peripheral edema in patients with HF, as occurs with cirrhosis. In the RALES, a dose of 25 to 50 mg had no apparent natriuretic effect as evidenced by no change in total body weight, sodium retention score, or urinary sodium excretion.<sup>7</sup> In patients with cirrhosis, the natriuretic response to spironolactone is related to activity of the RAAS. In cirrhosis studies, patients with marked hyperaldosteronism causing resistance to furosemide may require high doses (up to 400 mg/day) of spironolactone to reverse this diuretic resistance. The same resistance to loop diuretics may be true for patients with HF who share a pathophysiology of arterial

underfilling similar to that of cirrhotic patients. In this regard in a small trial of 6 avidly sodium retaining patients with HF, doses of spironolactone (200 mg BID in the study) that were adequate to block an increased endogenous concentration of plasma aldosterone 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 (Figure 4).<sup>52</sup> In another study, 81% of the patients with severe HF, 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.<sup>41</sup> The authors did not encounter hyperkalemia in any of those patients. In a study by Braunwald et al,<sup>53</sup> spironolactone (100 mg/day) increased sodium excretion in all 3 cardiac patients who were studied. Although natriuretic doses of spironolactone are standard therapy in the management of patients with cirrhosis, there has been no large clinical trial evaluating the role of natriuretic doses of mineralocorticoid antagonist in patients with HF.

The Acute Decompensated HF National Registry reports that most HF hospitalizations are because of congestion in patients refractory to oral diuretics.<sup>54</sup> Despite using intravenous diuretics in 90% of these patients with HF, the average hospitalization for decompensated HF is 4.3 days, with 42% of the patients discharged with unresolved symptoms, 50% losing  $\leq 5$  pounds, and 20% gaining weight during the hospitalization.<sup>54</sup> Thus, unresolved congestion may contribute to high readmission rates.<sup>54</sup> Approximately 25% to 30% of these patients with HF develop diuretic resistance, defined as reduced diuresis and natriuresis in response to a constant high dose of loop diuretics.<sup>55</sup> Current pharmacological therapies for diuretic resistance in HF have limited success. Ultrafiltration using either central or peripheral venous access is an attractive option to manage the volume overload in these patients.<sup>56</sup> However, it is an invasive procedure and offers





**Figure 4.** Diuretics, digoxin, and ACEIs were withdrawn 4 days before admission to General Clinical Research Center. The subjects were placed on a constant daily diet of 100 mEq sodium and 60 mEq potassium. A (dotted bars), Positive cumulative sodium balance in the 6 patients (4 ischemic heart disease, 1 idiopathic cardiomyopathy, and 1 aortic valvular disease). B (cross-hatch), In the same patients, significant negative cumulative sodium balance during 200 mg BID spironolactone ( $P<0.01$ ). C, Increase in urine  $\text{Na}^+:\text{K}^+$  concentration ratio during spironolactone in all 6 patients ( $P<0.05$ ), a finding compatible with aldosterone antagonism. Mean plasma potassium increased from  $3.86\pm 0.2$  mEq/L to  $4.1\pm 0.2$  mEq/L during spironolactone treatment ( $P<0.05$ ). Mean systolic blood pressure ( $112\pm 7$  mm Hg versus  $110\pm 5$  mm Hg,  $P=\text{NS}$ ) and creatinine clearance ( $87\pm 7$  mL/min versus  $87.2\pm 8$  mL/min, NS) did not change with spironolactone treatment. Plasma hANP decreased significantly with spironolactone ( $147\pm 58$  versus  $83\pm 30$  mg/L,  $P<0.05$ ). Fluid intake was not restricted, and a mean of 2 kg weight loss occurred. Reproduced with permission from *Am J Nephrol*. 1991;11:441–446.

only transient improvement, and patients generally need hospitalization to receive this therapy. Thus, use of natriuretic doses of mineralocorticoid antagonists may be a better alternative to reverse diuretic resistance secondary to hyperaldosteronism.

There is, however, the danger of hyperkalemia in patients with HF treated with natriuretic doses of mineralocorticoid antagonists, particularly in the presence of ACEIs, ARBs, and/or  $\beta$ -blockers. ACEIs and ARBs are not used in patients with cirrhosis, but because of their beneficial effects on survival and hospital readmission, they are standard therapy in the management of HF. However, if mineralocorticoid antagonists are used in conjunction with loop diuretics, their renal potassium-losing effect may counterbalance the potassium-retaining properties of mineralocorticoid antago-

nists. The main mechanism behind mineralocorticoid antagonist-induced hyperkalemia is decreased potassium secretion in the collecting tubules. In contrast, loop diuretics increase distal sodium delivery, and the resultant enhanced tubular flow rate increases potassium secretion at collecting duct sites. In the RALES, the median potassium concentration increased only by 0.30 mmol/L.<sup>6</sup> Similarly, in the Eplerenone Neurohormonal Efficacy and Survival trial, the incidence of serious hyperkalemia was no different between the eplerenone and placebo groups.<sup>57</sup> The mineralocorticoid antagonist doses in these studies were nonnatriuretic. However, the subsequent Canadian epidemiological study reported increases in hyperkalemia-associated morbidity and mortality after the publication of RALES.<sup>58</sup> The relationship with the RALES can be questioned, however, because nonnatriuretic doses should not inhibit the passive secretion of potassium in the collecting duct.

Because hypomagnesemia, as may occur with loop diuretics, has the potential for causing arrhythmias, the magnesium-sparing property of spironolactone and eplerenone could be beneficial in this area. Although the serum magnesium concentration may increase with natriuretic doses of mineralocorticoid antagonist, hypermagnesemia is rare.<sup>59</sup>

#### Potential Need of Aldosterone Antagonist in Presence of Angiotensin Inhibition

Although interruption of RAAS with ACEIs and ARBs improves morbidity and mortality in HF, there is increasing evidence to suggest that in some patients aldosterone may only transiently be suppressed with ACE inhibition.<sup>60–63</sup> 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.<sup>64</sup> In this setting, the addition of aldosterone antagonists to conventional heart and kidney failure regimens may improve clinical outcomes. On the basis of this information, the addition of aldosterone inhibition to ACEIs in the RALES<sup>6</sup> and Eplerenone Neurohormonal Efficacy and Survival<sup>57</sup> trial reduced the morbidity and mortality in patients with reduced cardiac ejection fractions, thus the use of low-dose aldosterone antagonist is recommended by American College of Cardiology in selected patients.

#### Conclusion

Hyperaldosteronism has increasingly been recognized as a risk factor for myocardial and vascular fibrosis. Loop diuretics are the mainstay of therapy for HF but are associated with worsening of hyperaldosteronism. Mineralocorticoid antagonists are the preferred diuretics in cirrhosis and have been shown to have better natriuretic response compared with loop diuretics. Cirrhosis and HF have important similarities in the mechanisms of sodium retention, including marked hyperaldosteronism. However, in patients with HF, only a low dose of spironolactone, which has no natriuretic response, has been studied. Natriuretic doses of spironolactone may provide

supplementary benefit over and above their effect on myocardial and vascular fibrosis. This possibility warrants testing in patients with HF, particularly in carefully designed randomized controlled pilot trial. Moreover, the potassium-losing effect of loop diuretics would also blunt any tendency of mineralocorticoid antagonists to cause hyperkalemia.

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### References

- Center for Disease Control and Prevention. Heart failure fact sheet. Available at [www.cdc.gov/cvhl/library/fs\\_heart\\_failure.htm](http://www.cdc.gov/cvhl/library/fs_heart_failure.htm). Accessed September 10, 2008.
- Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, Messenger J. Cardiac resynchronization in chronic heart failure. *N Engl J Med*. 2002;346:1845–1853.
- Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. *N Engl J Med*. 1987;316:1429–1435.
- Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med*. 2001;345:1667–1675.
- Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. 1996;334:1349–1355.
- Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. 1999;341:709–717.
- Effectiveness of spironolactone added to an angiotensin-converting enzyme inhibitor and a loop diuretic for severe chronic congestive heart failure (the Randomized Aldactone Evaluation Study [RALES]). *Am J Cardiol*. 1996;78:902–907.
- Schrier RW. Pathogenesis of sodium and water retention in high-output and low-output cardiac failure, nephrotic syndrome, cirrhosis, and pregnancy (2). *N Engl J Med*. 1988;319:1127–1134.
- Schrier RW. Body fluid volume regulation in health and disease: a unifying hypothesis. *Ann Intern Med*. 1990;113:155–159.
- Schrier RW, Abraham WT. Hormones and hemodynamics in heart failure. *N Engl J Med*. 1999;341:577–585.
- Schrier RW. Water and sodium retention in edematous disorders: role of vasopressin and aldosterone. *Am J Med*. 2006;119:S47–S53.
- Schrier RW. Decreased effective blood volume in edematous disorders: what does this mean? *J Am Soc Nephrol*. 2007;18:2028–2031.
- Bichet D, Szatalowicz V, Chaimovitz C, Schrier RW. Role of vasopressin in abnormal water excretion in cirrhotic patients. *Ann Intern Med*. 1982;96:413–417.
- Szatalowicz VL, Arnold PE, Chaimovitz C, Bichet D, Berl T, Schrier RW. Radioimmunoassay of plasma arginine vasopressin in hyponatremic patients with congestive heart failure. *N Engl J Med*. 1981;305:263–266.
- Bichet DG, Van Putten VJ, Schrier RW. Potential role of increased sympathetic activity in impaired sodium and water excretion in cirrhosis. *N Engl J Med*. 1982;307:1552–1557.
- Berl T, Henrich WL, Erickson AL, Schrier RW. Prostaglandins in the beta-adrenergic and baroreceptor-mediated secretion of renin. *Am J Physiol*. 1979;236:F472–F477.
- Hirsch AT, Pinto YM, Schunkert H, Dzau VJ. Potential role of the tissue renin-angiotensin system in the pathophysiology of congestive heart failure. *Am J Cardiol*. 1990;66:22D–30D.
- Weber KT. Aldosterone in congestive heart failure. *N Engl J Med*. 2001;345:1689–1697.
- Brooks VL. Interactions between angiotensin II and the sympathetic nervous system in the long-term control of arterial pressure. *Clin Exp Pharmacol Physiol*. 1997;24:83–90.
- Zucker IH, Schultz HD, Li YF, Wang Y, Patel KP. The origin of sympathetic outflow in heart failure: the roles of angiotensin II and nitric oxide. *Prog Biophys Mol Biol*. 2004;84:217–232.
- Schrier RW. Role of diminished renal function in cardiovascular mortality: marker or pathogenetic factor? *J Am Coll Cardiol*. 2006;47:1–8.
- Bell-Reuss E, Trevino DL, Gottschalk CW. Effect of renal sympathetic nerve stimulation on proximal water and sodium reabsorption. *J Clin Invest*. 1976;57:1104–1107.
- Myers BD, Deen WM, Brenner BM. Effects of norepinephrine and angiotensin II on the determinants of glomerular ultrafiltration and proximal tubule fluid reabsorption in the rat. *Circ Res*. 1975;37:101–110.
- Schrier RW, De Wardener HE. Tubular reabsorption of sodium ion: influence of factors other than aldosterone and glomerular filtration rate. 2. *N Engl J Med*. 1971;285:1292–1303.
- Funder JW. Aldosterone, mineralocorticoid receptors and vascular inflammation. *Mol Cell Endocrinol*. 2004;217:263–269.
- Rudolph AE, Rocha R, McMahon EG. Aldosterone target organ protection by eplerenone. *Mol Cell Endocrinol*. 2004;217:229–238.
- Weber KT. Aldosteronism revisited: perspectives on less well-recognized actions of aldosterone. *J Lab Clin Med*. 2003;142:71–82.
- Wei CM, Lerman A, Rodeheffer RJ, McGregor CG, Brandt RR, Wright S, Heublein DM, Kao PC, Edwards WD, Burnett JC Jr. Endothelin in human congestive heart failure. *Circulation*. 1994;89:1580–1586.
- Benedict CR, Shelton B, Johnstone DE, Francis G, Greenberg B, Konstam M, Probstfield JL, Yusuf S. Prognostic significance of plasma norepinephrine in patients with asymptomatic left ventricular dysfunction. SOLVD Investigators. *Circulation*. 1996;94:690–697.
- Cohn JN, Rector TS. Prognosis of congestive heart failure and predictors of mortality. *Am J Cardiol*. 1988;62:25A–30A.
- Francis GS, Cohn JN, Johnson G, Rector TS, Goldman S, Simon A. Plasma norepinephrine, plasma renin activity, and congestive heart failure: relations to survival and the effects of therapy in V-HeFT II. The V-HeFT VA Cooperative Studies Group. *Circulation*. 1993;87:VI40–VI48.
- Swedberg K, Eneroth P, Kjekshus J, Wilhelmssen L. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. CONSENSUS Trial Study Group. *Circulation*. 1990;82:1730–1736.
- Cohn JN, Levine TB, Olivari MT, Garberg V, Lura D, Francis GS, Simon AB, Rector T. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl J Med*. 1984;311:819–823.
- Benedict CR, Johnstone DE, Weiner DH, Bourassa MG, Bittner V, Kay R, Kirlin P, Greenberg B, Kohn RM, Nicklas JM. Relation of neurohumoral activation to clinical variables and degree of ventricular dysfunction: a report from the Registry of Studies of Left Ventricular Dysfunction. SOLVD Investigators. *J Am Coll Cardiol*. 1994;23:1410–1420.
- Latini R, Masson S, Anand I, Salio M, Hester A, Judd D, Barlera S, Maggioni AP, Tognoni G, Cohn JN. The comparative prognostic value of plasma neurohormones at baseline in patients with heart failure enrolled in Val-HeFT. *Eur Heart J*. 2004;25:292–299.
- Swedberg K, Eneroth P, Kjekshus J, Snapinn S. Effects of enalapril and neuroendocrine activation on prognosis in severe congestive heart failure (follow-up of the CONSENSUS trial). CONSENSUS Trial Study Group. *Am J Cardiol*. 1990;66:40D–44D.
- Gottlieb SS, Abraham W, Butler J, Forman DE, Loh E, Massie BM, O'Connor CM, Rich MW, Stevenson LW, Young J, Krumholz HM. The prognostic importance of different definitions of worsening renal function in congestive heart failure. *J Card Fail*. 2002;8:136–141.
- Krumholz HM, Chen YT, Vaccarino V, Wang Y, Radford MJ, Bradford WD, Horwitz RJ. Correlates and impact on outcomes of worsening renal function in patients > or =65 years of age with heart failure. *Am J Cardiol*. 2000;85:1110–1113.
- Smith GL, Vaccarino V, Kosiborod M, Lichtman JH, Cheng S, Watnick SG, Krumholz HM. Worsening renal function: what is a clinically meaningful change in creatinine during hospitalization with heart failure? *J Card Fail*. 2003;9:13–25.
- Arroyo V, Bosch J, Mauri M, Ribera F, Navarro-Lopez F, Rodes J. Effect of angiotensin-II blockade on systemic and hepatic haemodynamics and on the renin-angiotensin-aldosterone system in cirrhosis with ascites. *Eur J Clin Invest*. 1981;11:221–229.
- van Vliet AA, Donker AJ, Nauta JJ, Verheugt FW. Spironolactone in congestive heart failure refractory to high-dose loop diuretic and

- low-dose angiotensin-converting enzyme inhibitor. *Am J Cardiol*. 1993; 71:21A–28A.
42. Fernandez-Llama P, Ageloff S, Fernandez-Varo G, Ros J, Wang X, Garra N, Esteve-Font C, Ballarin J, Barcelo P, Arroyo V, Stokes JB, Knepper MA, Jimenez W. Sodium retention in cirrhotic rats is associated with increased renal abundance of sodium transporter proteins. *Kidney Int*. 2005;67:622–630.
  43. Gines A, Escorsell A, Gines P, Salo J, Jimenez W, Inglada L, Navasa M, Claria J, Rimola A, Arroyo V. Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites. *Gastroenterology*. 1993;105:229–236.
  44. Ruiz-del-Arbol L, Monescillo A, Arocena C, Valer P, Gines P, Moreira V, Milicua JM, Jimenez W, Arroyo V. Circulatory function and hepatorenal syndrome in cirrhosis. *Hepatology*. 2005;42:439–447.
  45. Perez-Ayuso RM, Arroyo V, Planas R, Gaya J, Bory F, Rimola A, Rivera F, Rodes J. Randomized comparative study of efficacy of furosemide versus spironolactone in nonazotemic cirrhosis with ascites: relationship between the diuretic response and the activity of the renin-aldosterone system. *Gastroenterology*. 1983;84:961–968.
  46. Pinzani M, Daskalopoulos G, Laffi G, Gentilini P, Zipser RD. Altered furosemide pharmacokinetics in chronic alcoholic liver disease with ascites contributes to diuretic resistance. *Gastroenterology*. 1987;92: 294–298.
  47. Faris R, Flather M, Purcell H, Henein M, Poole-Wilson P, Coats A. Current evidence supporting the role of diuretics in heart failure: a meta-analysis of randomised controlled trials. *Int J Cardiol*. 2002;82: 149–158.
  48. He XR, Greenberg SG, Briggs JP, Schnermann J. Effects of furosemide and verapamil on the NaCl dependency of macula densa-mediated renin secretion. *Hypertension*. 1995;26:137–142.
  49. Abdallah JG, Schrier RW, Edelstein C, Jennings SD, Wyse B, Ellison DH. Loop diuretic infusion increases thiazide-sensitive Na(+)Cl(–) cotransporter abundance: role of aldosterone. *J Am Soc Nephrol*. 2001; 12:1335–1341.
  50. McCurley JM, Hanlon SU, Wei SK, Wedam EF, Michalski M, Haigney MC. Furosemide and the progression of left ventricular dysfunction in experimental heart failure. *J Am Coll Cardiol*. 2004;44:1301–1307.
  51. Ellison DH, Velazquez H, Wright FS. Adaptation of the distal convoluted tubule of the rat: structural and functional effects of dietary salt intake and chronic diuretic infusion. *J Clin Invest*. 1989;83:113–126.
  52. Hensen J, Abraham WT, Durr JA, Schrier RW. Aldosterone in congestive heart failure: analysis of determinants and role in sodium retention. *Am J Nephrol*. 1991;11:441–446.
  53. Braunwald E, Plauth WH Jr, Morrow AG. A method for the detection and quantification of impaired sodium excretion. Results of an oral sodium tolerance test in normal subjects and in patients with heart disease. *Circulation*. 1965;32:223–231.
  54. Adams KF Jr, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, Berkowitz RL, Galvao M, Horton DP. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J*. 2005;149:209–216.
  55. Ellison DH. Diuretic therapy and resistance in congestive heart failure. *Cardiology*. 2001;96:132–143.
  56. Haas GJ, Pestritto VM, Abraham WT. Ultrafiltration for volume control in decompensated heart failure. *Heart Fail Clin*. 2008;4:519–534.
  57. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 2003;348:1309–1321.
  58. Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, Redelmeier DA. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med*. 2004;351:543–551.
  59. Thomason JD, Rockwell JE, Fallaw TK, Calvert CA. Influence of combined angiotensin-converting enzyme inhibitors and spironolactone on serum K<sup>+</sup>, Mg<sup>2+</sup>, and Na<sup>+</sup> concentrations in small dogs with degenerative mitral valve disease. *J Vet Cardiol*. 2007;9:103–108.
  60. Duprez DA, De Buyzere ML, Rietzschel ER, Taes Y, Clement DL, Morgan D, Cohn JN. Inverse relationship between aldosterone and large artery compliance in chronically treated heart failure patients. *Eur Heart J*. 1998;19:1371–1376.
  61. Borghi C, Boschi S, Ambrosioni E, Melandri G, Branzi A, Magnani B. Evidence of a partial escape of renin-angiotensin-aldosterone blockade in patients with acute myocardial infarction treated with ACE inhibitors. *J Clin Pharmacol*. 1993;33:40–45.
  62. Cleland JG, Dargie HJ, Hodsman GP, Ball SG, Robertson JJ, Morton JJ, East BW, Robertson I, Murray GD, Gillen G. Captopril in heart failure: a double blind controlled trial. *Br Heart J*. 1984;52:530–535.
  63. Biollaz J, Brunner HR, Gavras I, Waeber B, Gavras H. Antihypertensive therapy with MK 421: angiotensin II–renin relationships to evaluate efficacy of converting enzyme blockade. *J Cardiovasc Pharmacol*. 1982; 4:966–972.
  64. Bombardier AS, Klemmer PJ. The incidence and implications of aldosterone breakthrough. *Nat Clin Pract Nephrol*. 2007;3:486–492.