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DISCUSSION

Cardioprotection by Aldosterone Receptor Antagonism in Heart Failure: 1. The Role of Aldosterone in Heart Failure[1]

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Abstract—In recent years, understanding of the role of aldosterone has expanded beyond the known classic effects of promoting renal sodium retention and potassium and magnesium loss. It is now well documented that aldosterone causes myocardial and perivascular fibrosis, blocks the myocardial uptake of norepinephrine, and increases plasminogen activator inhibitor levels. In conjunction with angiotensin II, aldosterone causes vascular damage, endothelial dysfunction, and decreased vascular compliance. Thus, the renin–angiotensin–aldosterone system (RAAS) plays a major role in the development of both hypertension and heart failure and is, therefore, a key target for therapeutic interventions. Commonly prescribed medications for control of hypertension and congestive heart failure are inhibitors of the RAAS, including angiotensin converting enzyme inhibitors (ACE-Is) and angiotensin II (A-II) receptor antagonists. A well-documented increase in aldosterone levels occurs over several months during chronic treatment with an ACE-I or an A-II receptor antagonist. Such suppression of circulating aldosterone, however, is transient, as exemplified by the term "escape" used to describe the phenomenon. This rebound of aldosterone even occurs when patients receive both an ACE-I and an A-II receptor antagonist. In addition, ACE-Is and A-II receptor antagonists are less effective in controlling blood pressure in the estimated 60% of hypertensive patients who are salt- (volume-) sensitive and more prone to hypertension-associated morbidity, such as black patients and type 2 diabetics. Thus, chronic and complete blockade of aldosterone action requires an aldosterone receptor antagonist. The Randomized Aldactone Evaluation Study (RALES) trial results in patients with severe heart failure (New York Heart Association class III or IV) and a left ventricular ejection fraction of no more than 35% showed that administration of a subhemodynamic dose of spironolactone (25 mg/day) as an add-on therapy to ACE-Is plus standard treatment resulted in a significant mortality reduction due to decreases in both death from progressive heart failure and sudden cardiac death. These findings support the pivotal role of aldosterone in the pathophysiology of progressive heart failure. Although it is an effective antialdosterone agent, widespread use of spironolactone in humans is limited by its tendency to produce undesirable sexual side effects. At standard doses, impotence and gynecomastia can be induced in men, whereas premenopausal women may experience menstrual disturbances. Data on a selective aldosterone receptor antagonist, eplerenone, show that it appears promising for the effective blockade of aldosterone and its harmful effects without the sexual disturbances of spironolactone. Recently, eplerenone was successfully introduced for the treatment of hypertension and heart failure. A growing number of experimental studies are finding a broader role for aldosterone in driving the pathophysiology of both heart failure and hypertension. When added to conventional therapy, aldosterone receptor blockers show benefits in addition to those conferred by ACE-Is and/or A-II receptor blockers.

Heart failure is one of the most frequent causes of hospitalization in the world and is both a deadly and a costly diagnosis. Its incidence continues to increase, which reflects not only the aging of the overall population and attendant high rates of coronary artery disease and hypertension but also improved survival rates after initial acute coronary events.

Congestive heart failure is a complex clinical syndrome with uncertain underlying pathology. Long-term outcomes in patients with heart failure have improved, but this is due to symptom control with pharmaceutical intervention, most notably, angiotensin-converting enzyme inhibitor (ACE-I) therapy, and not treatment of an underlying disease process. Congestive heart failure, a syndrome arising from hypoperfused tissues and congested organs, has its pathophysiological origins in salt-avid kidneys [1–3]. The kidneys become adversaries of the heart, lungs, and liver. A house divided; homeostasis lost. The reason for this dysfunctional relation between organs that normally cooperate to preserve circulatory balance is an activation of the renin–angiotensin–aldosterone system (RAAS) [4]. The RAAS plays a major role in the development and progression of both hypertension and heart failure and is, therefore, a key target for therapeutic intervention. Elevations in plasma angiotensin II and aldosterone concentrations are physiological when they preserve sodium and water homeostasis in response to sodium and volume contraction. In the absence of these circumstances, sustained activation of the RAAS is inappro-

[1] This article was submitted by the authors in English.

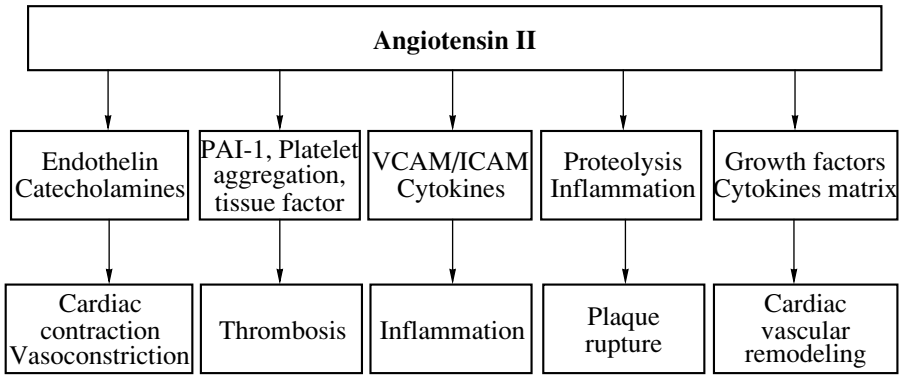


Fig. 1. Angiotensin.

priate and pathological. This is the case in heart failure, where the potent actions of angiotensin and aldosterone overwhelm the ability of natriuretic peptides released by the distended heart to maintain euvolemia and compensation [3]. Consequences of long-term activation of the RAAS in patients with congestive heart failure include a progressive remodeling of the heart and vascular system mediated, in part, by the induction of various cytokines and growth factors [5–8].

Aldosterone is one of the key hormones in the RAAS. In the past, the role of aldosterone in the pathophysiology of heart failure has been underestimated because angiotensin-converting enzyme (ACE) inhibition–related reductions in angiotensin were thought to eliminate aldosterone production. Such suppression of circulating aldosterone, however, is transient, as exemplified by the term used to describe the phenomenon, "escape" [9]. In addition, treatment with an aldosterone receptor blocker in conjunction with an ACE-I has been considered relatively contraindicated because of the potential for serious hyperkalemia. Consequently, aldosterone receptor blockers are used infrequently in patients with heart failure.

It is now well known that the role of aldosterone has expanded beyond the known classic effects of promoting renal sodium retention and potassium and magnesium loss [10, 11]. Aldosterone causes myocardial and perivascular fibrosis, blocks the myocardial uptake of norepinephrine, and increases plasminogen activator inhibitor levels [12]. In addition, aldosterone promotes baroreceptor dysfunction and vascular damage and impairs arterial compliance [13, 14]. Treatment with the aldosterone receptor blocker spironolactone at a daily dose of 12.5–25 mg in conjunction with standard doses of an ACE-I, a loop diuretic, and (in some cases) digoxin is pharmacologically effective and well tolerated, decreases atrial natriuretic peptide concentrations, and does not lead to serious hyperkalemia [15]. On the basis of this information, the Randomized Aldosterone Evaluation Study (RALES) was performed [16]. The overall risks of death due to progressive heart failure and sudden death from cardiac causes were reduced by approximately 30% among spironolactone-treated patients, prompting the early termination of the study. The combined endpoint analysis of cardiac mortality and cardiac hospitalization demonstrated a 32% reduction in risk in the spironolactone group compared to the placebo group ($p < 0.001$).

The following sections will describe the role of aldosterone and aldosterone antagonism in heart failure and will also show that results from clinical studies clearly indicate that the beneficial effects of selective and nonselective aldosterone antagonists in patients with heart failure are additive to those of ACE-Is and angiotensin II (A-II) blockers.

Cardiovascular disease and the RAAS. Cardiovascular disease is linked by a chain of events that progresses from one to another, ultimately, to end-stage organ failure. These events can be interrupted by therapy. Therefore, early intervention is very important to interrupt, at any one of these points, the progression to end-stage heart disease. It turns out, based on many different studies, that cholesterol is an important factor, and the statin data are very impressive. But the other mediator is definitely the RAAS.

Throughout the entire cardiovascular continuum, the RAAS plays an important role. In addition to the hemodynamic and renal effects of angiotensin, the RAAS has direct tissue effects; i.e., by activating this receptor in this tissue, the RAAS can exert vascular and cardiac remodeling and renal remodeling effects that have long-term implications, both in cardiovascular pathophysiology and in end-organ damage.

It appears that the RAAS, through its direct tissue effect, in addition to the hemodynamic effect, can cause inflammation, thrombosis, remodeling, and plaque rupture (Fig. 1). This has been the basis for more aggressive treatment plus inhibition of the RAAS by blocking angiotensin receptors or ACE. More recently, novel information emerged about the other mediator of the RAAS, aldosterone. In the context of the RAAS, the role of aldosterone has been underestimated. We have always thought aldosterone to be a substance that causes salt and water retention by acting on the distal

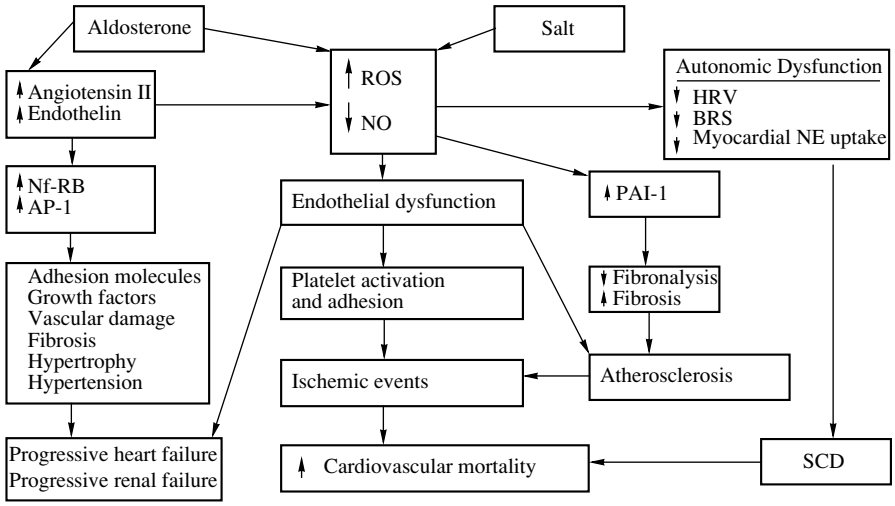


Fig. 2. Nonrenal effects of aldosterone.

tubule. There is now strong evidence that aldosterone should be recognized as an important factor in the development and progression of heart failure. In patients with congestive heart failure, plasma aldosterone concentrations may reach 20 times the normal level [1, 17].

Two pathophysiological mechanisms contribute to the increased concentrations. The first is an increase in the rate of aldosterone production by the adrenal glands, largely as a result of increased plasma angiotensin concentrations, which stimulate adrenal zona glomerulosa cells by binding to angiotensin I receptors. The second mechanism is a decreased rate of hepatic aldosterone clearance, which causes plasma aldosterone concentrations to triple or quadruple. The primary determinant of aldosterone metabolism is hepatic blood flow. In patients with congestive heart failure, the rate of aldosterone clearance by the liver falls to 25–50% of the normal rate, with commensurate reductions in hepatic perfusion [18, 19].

The role of aldosterone in heart failure. Although much attention has been focused on the role of renin and angiotensin II in heart failure, the role of aldosterone in this progressive disease has been overlooked until recently. The main reasons for the heightened interest in the role of aldosterone in heart failure, which will be discussed separately, are the following (Fig. 2):

evidence of aldosterone receptors and protecting enzyme 11β-HSD and synthesis of aldosterone in the heart and vasculature, independent of adrenal–renal aldosterone activity;

evidence of several extrarenal aldosterone mechanisms involved in the progression of heart failure;

evidence of aldosterone escape during ACE-I therapy;

association of such escape or "rebound" with higher mortality.

All these lines of reasoning led to the RALES hypothesis that aldosterone receptor antagonism could reduce mortality in heart failure [20].

Myocardial and vascular aldosterone synthesis. Other investigators have now used similar mRNA probes and high-precision biochemical techniques (e.g., high-performance liquid chromatography with mass spectrometry and polymerase chain reaction) to confirm the presence of extrarenal aldosterone receptors [21, 22].

In addition to finding receptors, these researchers have also documented the synthesis of aldosterone itself within many of the same cardiovascular tissues. For example, it was found in [22] that the main enzyme necessary for aldosterone synthesis is actively expressed in human pulmonary tissue [21, 22].

Further, these investigators were able to demonstrate that locally produced aldosterone heightened smooth muscle sensitivity to overstimulation by angiotensin II, which has been linked to the development of thickened vessel walls in hypertension or after angioplasty [21]. Following this lead, another researcher has now shown that aldosterone may potentiate this angiotensin II vascular action by increasing the number of angiotensin II receptors on blood vessels. If documented in more studies, such local "paracrine" or "autocrine" actions of aldosterone could eventually be shown to be central to the regulation of vascular tone, as well as the vascular and cardiac remodeling that occur in heart failure (fibrosis, left ventricular hypertrophy (LVH)) [5].

In summary, findings of a complete self-contained "system" of aldosterone synthesis and binding within cardiovascular tissues imply that aldosterone has local tissue effects independent of the circulating renin–angiotensin–aldosterone system. This concept is supported, for example, by a recent study showing that aldosterone production within the rat heart essentially

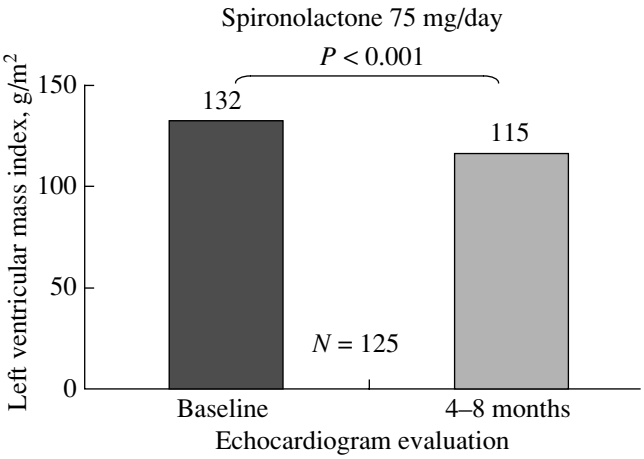


Fig. 3. Spironolactone promotes LVH regression [32].

constitutes a local "steroidogenic" system that is independent of the adrenal–renal circulatory aldosterone system [23].

Aldosterone stimulates myocardial fibrosis. One of the primary suspected mechanisms of aldosterone-associated cardiac damage is myocardial fibrosis. For years, however, researchers have attempted to separate the direct fibrotic effects of hormones such as aldosterone and angiotensin II from their hemodynamic effects.

In [24], to test the relative contributions of a circulating hormone such as aldosterone and a mechanical factor such as hypertension to the process of myocardial fibrosis, three different rat models of increased blood pressure and LVH were created (Fig. 3). They examined both the pressure-overloaded, hypertrophied left ventricle and the normotensive, nonhypertrophied right ventricle (Fig. 4) [5].

The authors concluded that myocardial fibrosis is under the control of aldosterone, while hypertrophy of cardiac myocytes depends more on mechanical factors such as hypertension.

Several other independent lines of evidence now point to aldosterone as a unique trigger for myocardial fibrosis.

Aldosterone-producing adrenal tumors are associated with myocardial fibrosis, and the increased left ventricular (LV) wall thickness and decreased early diastolic filling observed under such conditions are corrected by removal of the tumor [25]. Aldosterone treatment unrelated to hypertension produced fibrosis in the right and the left atria, the aorta, and the pulmonary artery [12].

In animals, aldosterone administration led to an increase in expression of collagen mRNA in both the right and the left ventricles [26], and cardiac fibrosis was found to be related to aldosterone receptor binding in the heart and not to hypertension. Collagen synthesis

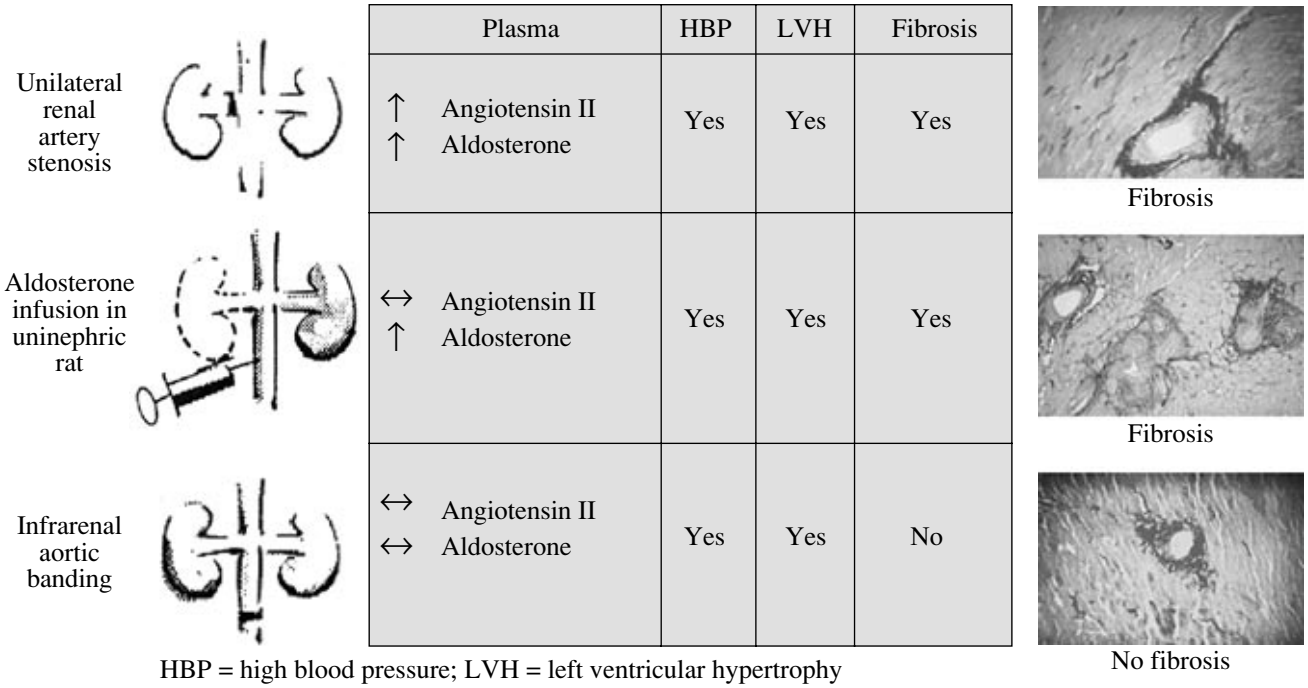
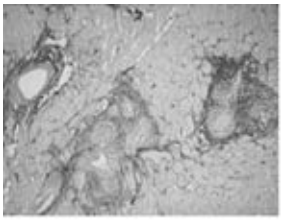


Fig. 4. Aldosterone stimulates myocardial fibrosis (adapted from [5]). Top row: In the first model, one renal artery was occluded. Circulating angiotensin II and aldosterone each increased and fibrosis appeared in both ventricles. Middle row: In the second model, plasma aldosterone was increased while angiotensin II was suppressed. Again, fibrosis was produced in both ventricles. Bottom row: In the third model, however, when circulating aldosterone and angiotensin II levels remained normal, no fibrosis developed in either ventricle.

Aldosterone infusion in uninephric rat

Treatment	HBP	LVH	Fibrosis
Control (aldosterone active)	Yes	Yes	Yes
Low-dose spironolactone	Yes	Yes	No
High-dose spironolactone	No	No	No



Fibrosis

No fibrosis

HBP = high blood pressure; LVH = left ventricular hypertrophy

Fig. 5. Spironolactone prevents myocardial fibrosis (adapted from [23]). Top row: In this rat model involving unilateral nephrectomy, a high-sodium diet, and aldosterone administration, animals receiving no spironolactone developed hypertension, LVH, and fibrosis of both right and left ventricles and atria, despite suppression of angiotensin II. Middle row: In the group receiving low-dose spironolactone, high blood pressure and LVH were evident but myocardial fibrosis was not. Bottom row: In the high-dose spironolactone group, neither LVH, nor hypertension, nor myocardial fibrosis developed, suggesting that collagen accumulation and myocardial structural remodeling associated with heart failure may be prevented by blockade of aldosterone receptors with spironolactone.

of cultured cardiac fibroblasts is increased in response to aldosterone.

The association between aldosterone and myocardial fibrosis is clear. Fibrosis includes both a reactive component involving intramural coronary arteries (perivascular fibrosis) and reparative, microscopic scarring in response to cardiac myocyte necrosis [5, 12].

Spironolactone prevents myocardial fibrosis. Aldosterone receptor blockade with spironolactone can prevent experimentally induced myocardial fibrosis (Fig. 5) [24].

Aldosterone correlates with LVH. One key piece of evidence is the finding that aldosterone levels are independently associated with increased left ventricular mass—itself one of the most foreboding prognostic signs in heart failure [27].

In [28], a significant positive correlation between plasma aldosterone levels and left ventricular mass as measured by echocardiography was documented (Fig. 6). The effect was independent of arterial blood pressure.

Similar parallels between aldosterone levels and left ventricular mass have been noted in other studies involving hypertensive patients [29] and healthy populations [30] as well as in patients with aldosterone-producing tumors [25, 29], in whom surgical removal of the adenoma resulted in regression of the LVH.

In related findings, genetic variations in aldosterone synthase mRNA have recently been shown to influence left ventricular diastolic function in healthy individuals [31].

Spironolactone promotes LVH regression. Treatment with spironolactone not only improves measures of LV function in hypertension but also appears to result in LVH regression.

In this study [32], investigators used echocardiographic measurements to determine the effects of spironolactone on LVH in patients with mild to moderate essential hypertension (Fig. 3).

The researchers analyzed the echocardiograms of 125 patients (35 men and 90 women, aged 26–80 years) who (1) had a baseline echocardiogram with evidence of LVH, defined as a left ventricular mass index (LVMI) of >131 g/m^2 in men and >100 g/m^2 in women; (2) took spironolactone, 75 mg/day, for 2 months; (3) had normalized blood pressure after 2 months of therapy; and (4) had a second echocardiogram 4–8 months after the initial examination [32].

As shown in Fig. 3, a statistically significant 13% reduction in LVMI from baseline was seen with spironolactone treatment (115 + 29 g/m^2 vs. 132 + 25 g/m^2, $p < 0.001$). The reduction in LVMI was achieved through lessening of both LV diameter and LV wall thickening [32].

Spironolactone, 75 mg/day, significantly reduced LVMI and normalized blood pressure in patients with mild to moderate essential arterial hypertension and

evidence of LVH. These effects would also be beneficial in patients with heart failure.

Myocardial fibrosis correlates with diastolic dysfunction. Another key measure of LV activity is the filling volume during different phases of the heart cycle. As assessed and calculated by echocardiography, low volumes during the rapid filling phase are considered a possible sign of diastolic dysfunction.

Results of a study in normotensive (n = 6) and hypertensive subjects (n = 28, 10 with and 18 without LVH) [33] have shown that the rapid filling volume correlated significantly with the degree of myocardial fibrosis as assessed by right ventricular endomyocardial biopsy. This filling volume parameter also correlated with wall thickness (as assessed by biventriculography), a more traditional marker of early-stage heart failure.

Other echocardiographic indicators of diastolic function (e.g., the quotients of the LV rapid filling and end-diastolic volume and stroke volume) were also positively correlated with myocardial fibrosis.

These results indicate that myocardial interstitial fibrosis is related, at least in part, to deteriorating heart function. Furthermore, diastolic dysfunction associated with fibrosis is evident even in patients with mild and moderate hypertension, indicating that fibrosis may be a precursor of systolic dysfunction and heart failure.

Aldosterone correlates with decreased large artery compliance. Another potentially harmful effect of aldosterone is decreased arterial compliance, a pathophysiological sign that has been linked with chronic heart failure and, specifically, with detrimental hemodynamic effects such as increased arterial impedance and cardiac afterload [34].

In a recent study, 13 patients with New York Heart Association (NYHA) class II heart failure who had been taking captopril, furosemide, and digitalis for at least three months were compared to a control group of healthy subjects [35]. Treatment with ACE-Is in the heart failure patients was associated with increased aldosterone levels and reduced arterial compliance of the aorta and its major side branches [35].

The authors concluded that ACE inhibition therapy did not effectively suppress aldosterone and that the increased aldosterone levels reduced arterial compliance. This, in turn, could lead to worsening of heart failure due to increased impedance of ventricular outflow [35].

Aldosterone promotes hypokalemia and hypomagnesemia. As already discussed, the role of aldosterone in causing magnesium and potassium loss is well established. It is the unique action of this mineralocorticoid in the late distal tubule and collecting duct that leads to sodium retention and enhanced potassium and magnesium excretion. Patients with hypertension or heart failure often have depleted stores of these serum and muscle electrolytes due to the disease process itself, which includes excess compensatory aldosterone stimulation. In addition, these patients may be taking thiazide or loop diuretics, which aggravate the electrolyte derangement.

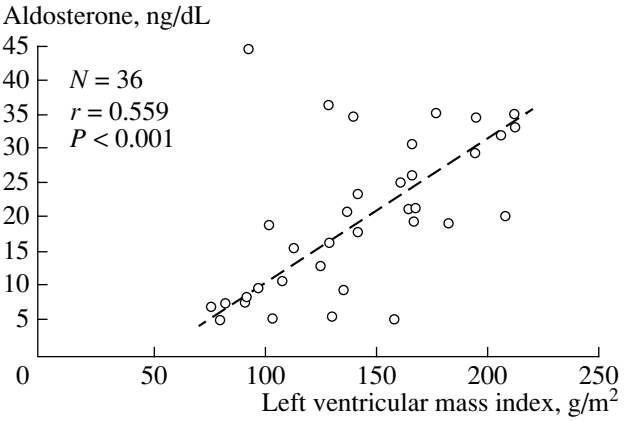


Fig. 6. Aldosterone correlates with left ventricular hypertrophy [28].

In one study, for example, patients receiving conventional diuretic therapy were shown to have reduced skeletal magnesium and potassium levels even though they were taking potassium supplements [36]. Patients receiving spironolactone, on the other hand, demonstrated significantly increased skeletal concentrations of both electrolytes.

The link between hypokalemia and hypomagnesemia and severe ventricular arrhythmia and sudden cardiac death is well established [37, 38]. In fact, in the 1990s, half of patients with heart failure died suddenly and unexpectedly, presumably from ventricular fibrillation [39]. This represents a fundamental shift from the 1950s, when most patients with heart failure died from pulmonary edema, a complication that is now well managed with the use of diuretics. This shift highlights the importance of arrhythmia, including factors such as electrolyte levels.

The fact that enalapril did not reduce the incidence of sudden cardiac death in the CONSENSUS and SOLVD trials [40, 41] may indicate that ACE-Is fail to produce a beneficial effect on electrolyte levels even though they may initially suppress aldosterone levels.

Beyond the established link between hypomagnesemia and ventricular arrhythmia, other lines of evidence point to nonarrhythmic roles for magnesium depletion in enhanced cardiac mortality, perhaps related to coronary vasospasm or endothelial cytotoxicity [42].

Aldosterone inhibits myocardial uptake of [^{3}H] Norepinephrine in rats. Potentiating the peripheral constrictor effects of catecholamines may be just one consequence of aldosterone's effect on catecholamines [9]. In the myocardium, sympathetic overactivation may be another important consequence of excess aldosterone.

Aldosterone clearly blocks the myocardial reuptake of labeled norepinephrine in animals [43]. Excess extracellular catecholamines in the myocardium may induce arrhythmia and ischemia (due to increased coronary tone). Thus, prevention of catecholamine reuptake by aldosterone, which has structural similarities with corticosterone, a classic inhibitor of extraneuronal reuptake, could exacerbate the arrhythmogenic and proischemic effects of these catecholamines [9].

Spironolactone: cardioprotective effects increase myocardial norepinephrine uptake. Other potentially cardioprotective effects of aldosterone receptor blockade were assessed in a study of 42 patients with mild to moderate heart failure. All patients in the study also received diuretics and ACE-Is.

Following up on an animal study that showed that aldosterone suppressed myocardial uptake of radiolabeled norepinephrine, Barr *et al.* [43] gave either placebo or spironolactone, 50–100 mg/day, to patients with heart failure and then used scintigraphy to assess the uptake of ^{123}I metaiodobenzylguanidine (MIBG) in the myocardium. This is an established method for measuring cardiac catecholamine neuronal uptake. Spironolactone significantly increased cardiac norepinephrine uptake, which is considered a better prognostic marker for overall cardiac mortality in heart failure than plasma norepinephrine [43].

These results show that spironolactone enhances removal of the sympathetic stimulator norepinephrine from the cardiovascular system. Because this stimulator normally acts to increase coronary tone or alter cardiac rhythm, the enhanced uptake caused by spironolactone may prevent arrhythmia.

The same study showed that spironolactone significantly reduced the number of ventricular premature beats (arrhythmia) as measured by 24-h Holter ECG monitoring. Compared to patients receiving placebo, the patients on spironolactone therapy had 20% fewer of these erratic beats ($P < 0.05$).

Aldosterone escape despite ACE inhibition and angiotensin II blockade. Drugs that block the angiotensin II receptor have recently been developed in an attempt to avoid the side effects associated with ACE-Is [44].

Several angiotensin II blockers have been approved for use in hypertension (e.g., losartan, candesartan). No major studies have found evidence that angiotensin II receptor antagonists are superior to ACE-Is in treating heart failure. These agents are therefore generally reserved for patients who cannot tolerate ACE-Is due to angioedema or intractable cough [45]. In a recent pilot study, investigators found no significant difference in exercise capacity or risk of cardiac events in 768 patients treated with candesartan, enalapril, or a combination [46].

The pilot study also documented a pattern of aldosterone escape similar to that noted following treatment with ACE-Is [47, 48]. Whether in combination with the ACE-I or alone, the angiotensin II receptor blocker produced a sizable increase in plasma aldosterone levels in heart failure patients after 43 weeks of treatment [49].

These results support the hypothesis that aldosterone synthesis can be triggered by agents other than angiotensin II, for example, plasma potassium, ACTH, endothelin, and prostaglandins [50]. Thus, disruption of either the synthesis of angiotensin II (via ACE inhibition) or the binding of angiotensin II (via agents such as candesartan) does not appear to prevent the tendency for aldosterone to increase with heart failure progression.

Limitations of angiotensin converting enzyme inhibitors and angiotensin receptor blockers in cardiovascular medicine. There is no question that ACE-Is have been one of the major developments in cardiovascular medicine in the second half of the 20th century, but they are not the final answer. A confirmation of this statement is provided by an analysis of the following two trials:

About half of the subjects in a study of left ventricular dysfunction [41] who were treated with an ACE-I, enalapril, ultimately died or were hospitalized for worsening heart failure.

The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) [40] in patients with NYHA class IV heart failure was the first trial of ACE inhibition in heart failure, and a quarter of the patients who were treated with enalapril died during a six-month follow-up period. In this study, there were 51 patients who died and 68 who survived.

Irrespective of treatment, baseline plasma aldosterone was an important predictor of outcome. In the patients who died, the aldosterone plasma concentration was about 30% higher than in those very ill NYHA class IV patients who survived. That means that the treatment with ACE-Is and/or angiotensin receptor blockers in patients with heart failure needs a further drug partner to block the "escaping" aldosterone.

This is a lead-up to the Randomized Aldactone Evaluation Study (RALES), which will be described in the second part.

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