Mechanisms of Disease

Aldosterone in Congestive Heart Failure

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Aldosterone was isolated from blood and urine, its adrenal origin elucidated, and its steroid structure identified nearly 50 years ago. Actions involving the reabsorption of sodium and the release of potassium by epithelial cells in the kidneys, intestine, and sweat and salivary glands led to its designation as a mineralocorticoid. The physiologic importance of aldosterone in preventing the loss of salt and water during periods of dietary sodium deprivation is now clear. Its contribution to the retention of sodium in patients with congestive heart failure, cirrhosis, and the nephrotic syndrome has also been established.1,2 The perception of its pathophysiologic importance in congestive heart failure, however, was minimized during the past 20 years, in part because of the introduction of angiotensin-converting–enzyme (ACE) inhibitors and their presumptive elimination of angiotensin II, a major determinant of aldosterone production by the adrenal glands. Recent evidence has revived interest in aldosterone and its role in congestive heart failure.3-6

The Renin–Angiotensin–Aldosterone System

Evolution to terrestrial life meant leaving behind the sea and its continuous source of salt and water. Water on land, when available, was fresh, and therefore adaptation to land necessitated the development of mechanisms to preserve salinity. An internal source of salinity is provided by extracellular fluid. Each arterial pulse of blood to exchange vessels of the microcirculation represents an onrushing saline tide that maintains a dynamic equilibrium with extracellular fluid. Animals living on land had to become capable of preserving their internal environment, including maintaining osmotic balance and salinity under a wide range of conditions over which they had little control. Kidneys became responsible for regulating the balance of salt and water7-8 by conserving both during periods of deprivation and excreting a dilute urine when water consumption was high. These adaptations required a concentrating and diluting mechanism and were accomplished with the appearance of the loop of Henle. Glomerular filtration in mammals would be maintained within a narrow range despite modifications in the volume and composition of the filtrate. Toward this end, kidneys require a plentiful supply of blood. Renal function is therefore dependent on an adequate cardiac output, of which 25 percent will normally be apportioned to the kidneys. This dependence of renal function on cardiac output explains the vulnerability of patients with heart failure to abnormal renal function, including reduced excretion of salt and water. In heart failure, a competition arises between organs for reduced systemic blood flow. It is particularly evident during exercise, when the vasodilation that appears in working skeletal muscle deprives the kidneys of some of their accustomed blood flow.

Normal regulation of salt and water homeostasis in mammals involves various sensors and controls operating in a negative-feedback loop. These include sensors of renal perfusion and tubular sodium delivery present within the kidney and effector hormones elaborated by endocrine organs. Key among them are renin, released by the juxtaglomerular cells lining afferent renal arterioles and neighboring macula densa cells of the distal tubule9,10 and aldosterone produced by the adrenal glands (Fig. 1). Renin cleaves four amino acids from circulating angiotensinogen, the angiotensin-peptide precursor produced by the liver, to form angiotensin I, a biologically inert decapeptide. Angiotensin-converting enzyme, which is bound to the plasma membrane of endothelial cells, cleaves two amino acids from angiotensin I to form angiotensin II. Angiotensin II has several important actions integral to maintaining circulatory homeostasis, including promoting the constriction of the arterioles within the renal and systemic circulations and the reabsorption of sodium in proximal segments of the nephron. It also stimulates the adrenal cortex to secrete aldosterone, which promotes the reabsorption of sodium (in exchange for potassium) in distal segments of the nephron and in the colon and the salivary and sweat glands. From a teleologic perspective, the evolution of the renin–angiotensin–aldosterone system was a delayed event necessitated by periods of salt deprivation or the loss of salt and water and the need to retain them.9

Variations in renin secretion occur in response to variations in intake of sodium and water; renin se-
cretion is inhibited when salt and water are taken in and activated when they are not.11 There can therefore be periodicity to the activation of this system throughout a given day, depending on the frequency of food intake, or over the course of many days, when periods of starvation alternate with the consumption of food and water. The reductions in renal perfusion that normally occur with the assumption of an upright posture and during ambulation also stimulate renin secretion.12

The renin–angiotensin–aldosterone system preserves circulatory homeostasis in response to a loss of salt and water, such as that which can occur with intense and prolonged sweating caused by high ambient temperatures, vomiting, or diarrheal illness. Plasma concentrations of the system’s effector hormones rise quickly in response to a contraction of intravascular volume and a reduction in renal perfusion. Angiotensin II is the principal stimulator of aldosterone production when intravascular volume is reduced.1,13

Potassium is also a major physiologic stimulus to aldosterone production; aldosterone secretion is integral to potassium homeostasis because aldosterone has the ability to increase potassium excretion in urine, feces, sweat, and saliva.14,15 Aldosterone thereby serves to prevent hyperkalemia during periods of high potassium intake. For example, aldosterone secretion rises after the consumption of foods high in potassium content or after vigorous physical activity that causes the release of potassium from skeletal muscle. The im-

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**Figure 1. The Renin–Angiotensin–Aldosterone System.**

Angiotensinogen, the precursor of all angiotensin peptides, is synthesized by the liver. In the circulation it is cleaved by renin, which is secreted into the lumen of renal afferent arterioles by juxtaglomerular cells. Renin cleaves four amino acids from angiotensinogen, thereby forming angiotensin I. In turn, angiotensin I is cleaved by angiotensin-converting enzyme (ACE), an enzyme bound to the membrane of endothelial cells, to form angiotensin II. In the zona glomerulosa of the adrenal cortex, angiotensin II stimulates the production of aldosterone. Aldosterone production is also stimulated by potassium, corticotropin, catecholamines (e.g., norepinephrine), and endothelins.
portance of aldosterone in potassium homeostasis is most evident in patients with aldosterone insufficiency (Addison’s disease), in whom hyperkalemia is common and can be reversed by treatment with a mineralocorticoid.16

Further evidence of the importance of potassium as a stimulus to aldosterone production comes from studies in genetically manipulated mice that do not express the angiotensin precursor angiotensinogen and therefore have little or no angiotensin II.17 In these animals, dietary sodium deprivation causes hyperkalemia, which, in turn, increases aldosterone secretion, thereby stimulating the reabsorption of salt and water and maintaining extracellular fluid volume. Restriction of both dietary sodium and potassium leads to hypotension and death in these animals.

In addition to their individual effects on salt and water homeostasis, angiotensin II and aldosterone have other endocrine actions relevant to the maintenance of circulatory homeostasis. They contribute to the coagulation of blood, in part through the increased production of plasminogen-activator inhibitor type I and the aggregation and activation of platelets at sites of bleeding;9 they constrict systemic arterioles to preserve arterial pressure in the face of contraction of the intravascular volume;11; and they stimulate thirst.10

Angiotensin II and aldosterone are also involved in regulating inflammatory and reparative processes that follow tissue injury.19,20 In this capacity, they stimulate cytokine production, inflammatory-cell adhesion, and chemotaxis; activate macrophages at sites of repair;21; and stimulate the growth of fibroblasts and the synthesis of type I and III fibrillar collagens, which govern the formation of scar tissue.22

A substance produced by cells within a tissue can exert actions on the same or different cells; these effects are known, respectively, as autocrine and paracrine properties. Recent studies have demonstrated the presence of aldosterone synthase messenger RNA (mRNA) and its activity together with aldosterone production by endothelial and vascular smooth-muscle cells in the heart and blood vessels (Fig. 2).24-26 Once considered the sole province of the zona glomerulosa of the adrenal glands because of the key enzymes involved in its steroidogenesis, the production of aldosterone by the heart is regulated by angiotensin II and by modifications in dietary sodium and potassium. The physiologic importance of locally produced aldosterone is not known, but early findings suggest that it may contribute to tissue repair after myocardial infarction.27

ALDOSTERONE
AND THE PATHOPHYSIOLOGY
OF CONGESTIVE HEART FAILURE

Some 60 years ago, both urine and plasma from patients with congestive heart failure were found to contain a substance with sodium-retaining activity;28; this discovery drew attention to the role of the kidney in the pathogenesis of congestive heart failure. It soon became evident that the initial stages of heart failure involve an expansion of intravascular volume and weight gain that averts volume depletion when relentless salt and water retention produces extravascular volume expansion (e.g., edema). Subsequently, studies of renal hemodynamics revealed marked reductions in renal blood flow with a less severe decline in glomerular filtration and a preserved or even increased filtration fraction.29-32 The retention of sodium is evident not only in urine but also in feces, sweat, and saliva, indicating a widespread avidity for sodium. The salt-active substance mediating many of these changes was initially named electrocortin, but because of its 18-aldehyde steroid structure and adrenal origin it was later renamed aldosterone.33 In heart failure, the presence of increased amounts of aldosterone in urine and plasma correlates with the retention of sodium and water at renal and extrarenal sites.

In normal subjects whose diet contains a normal amount of sodium, the aldosterone secretion rate is 100 to 175 µg (277 to 485 nmol) per day; in patients with congestive heart failure, the aldosterone secretion rate may be as high as 400 to 500 µg (1100 to 1400 nmol) per day.34 Values for plasma aldosterone are in the range of 5 to 15 ng per deciliter (139 to 416 pmol per liter) in normal subjects whose sodium intake is normal and may reach 300 ng per deciliter (8322 pmol per liter) in patients with congestive heart failure — a concentration similar to that in normal subjects whose sodium intake is severely restricted.35 Aldosterone secretion in patients with congestive heart failure is regulated by several major stimuli. These include angiotensin II and elevations in serum potassium concentrations. In normal subjects, corticotropin is thought to play a short-lived, permissive role in stimulating aldosterone production. However, in patients with congestive heart failure, plasma corticotropin concentrations may be chronically increased, resulting in high plasma cortisol concentrations and contributing to the increase in aldosterone secretion.36 Minor stimuli, which may take on additional importance in patients with congestive heart failure, include circulating catecholamines, endotoxins, and arginine vasopressin.

Decreased metabolic clearance of aldosterone by the liver further contributes to increased plasma concentrations of aldosterone in patients with congestive heart failure. In normal subjects, hepatic aldosterone clearance is complete within one passage through the liver, so that little or no aldosterone is found in hepatic venous plasma. Because of the reduced hepatic perfusion in patients with congestive heart failure, aldosterone clearance is also reduced; this problem is exacerbated by upright posture and ambulation. This reduction can account for a severalfold increase...
in plasma aldosterone concentrations. The importance of aldosterone in the pathophysiology of congestive heart failure and other edematous states is supported by the efficacy of aldosterone-receptor–antagonist drugs to ameliorate edema in patients with these conditions.

The importance of aldosterone in promoting edema has been questioned. Normal subjects given aldosterone and patients with primary (renin-independent) hyperaldosteronism (Conn’s syndrome) escape the salt-retaining effects of aldosterone and do not have edema. The mechanisms responsible for this phenomenon have not been elucidated. Unlike normal subjects given aldosterone and patients with primary hyperaldosteronism, patients with congestive heart failure have increases in plasma renin activity and concentrations of plasma angiotensin II. The latter promotes the reabsorption of sodium in proximal segments of the nephron and selectively increases vascular tonicity of efferent renal arterioles. The action of aldosterone on the cells of the distal cortical collecting ducts promotes further reabsorption of sodium, so that urinary sodium retention in congestive heart failure is nearly complete.

In addition to its classic mineralocorticoid properties, which can lead to hypokalemia and hypomagnesemia, aldosterone has other adverse effects that can contribute to the pathophysiology of congestive heart failure. These effects include coronary and renovascular remodeling, endothelial-cell and baroreceptor dysfunction, and inhibition of myocardial norepinephrine uptake, together with reduced heart-rate variability.

Cells in the cortical collecting duct of the distal nephron are a classic target for aldosterone. In addition to stimulating the reabsorption of sodium and

Figure 2. Extraadrenal Production of Aldosterone by Endothelial and Vascular Smooth-Muscle Cells in an Intramyocardial Coronary Artery. Modified from Slight et al. with the permission of the publisher.
the secretion of potassium by these cells, aldosterone has salt-dependent effects on kidney morphology. In normal animals with a normal sodium intake, uninephrectomy is followed by enlargement of nephrons in the remaining kidney, which is caused by hypertension and hyperplasia of distal and collecting-tubule cells.\textsuperscript{46,47} This enlargement results in an increase in the weight and function of the kidney. Similarly, sodium restriction or a diet high in potassium results in an increase in renal mass, caused primarily by an increase in the size of the same cells.\textsuperscript{48-50} The growth of these cells can be prevented by dietary potassium deprivation; by amiloride, an inhibitor of sodium–proton exchange, which increases sodium excretion; or by mineralocorticoid-receptor antagonists.

The morphologic changes in collecting-duct cells in response to aldosterone are temporally and spatially associated with the increased expression of mRNA for \(Na^+\)/\(K^+\)–ATPase and increased activity of the enzyme in the cells. This enzyme acts to maintain the electrochemical gradient of sodium and potassium across these cells, thereby preserving cellular ion content and osmolarity between intracellular and extracellular spaces.\textsuperscript{51} Mineralocorticoid-induced growth of the epithelial cells is linked to this sodium pump and is dependent on the sodium delivered to the epithelial cells and that which enters these cells through sodium channels or a sodium–proton exchange site. Sodium is a necessary modulator of aldosterone-induced \(Na^+\)/\(K^+\)–ATPase expression and activity.\textsuperscript{55,52}

In rats that have undergone uninephrectomy and are treated with deoxycorticosterone or aldosterone together with dietary salt, hypertension develops, as well as nephrosclerosis and perivascular fibrosis of small arteries and arterioles of the heart and systemic organs.\textsuperscript{53} These observations link aldosterone with vascular remodeling by fibrous tissue – an outcome that is preceded by the appearance and replication of inflammatory cells and fibroblasts in the perivascular space of involved vessels. Morphologically indistinguishable remodeling is present in the failing human heart, and these changes appear to have major adverse effects on the heart’s electrical and mechanical function and coronary vasodilator reserve.\textsuperscript{55-57}

Morphologic studies indicate that a chronic excess of mineralocorticoid (plus salt loading) can cause fibrosis in the atria and ventricles (Fig. 3) as well as the kidneys and other organs in humans and animals.\textsuperscript{58-64} Thus, aldosterone may promote the remodeling of organs and fibrosis. Indeed, each effector hormone of the renin–angiotensin–aldosterone system contributes independently to adverse vascular remodeling.\textsuperscript{22,69}

The importance of aldosterone to vascular remodeling has been further demonstrated in studies in which spironolactone was used. In rats that undergo uninephrectomy and are given aldosterone and salt, spironolactone prevents cardiac fibrosis, even when it is given in doses that do not prevent hypertension or left ventricular hypertrophy. Furthermore, cardiac fibrosis associated with the systemic infusion of aldosterone and salt loading is not prevented by the intracerebroventricular infusion of an aldosterone-receptor antagonist that prevents arterial hypertension.\textsuperscript{65,66} Thus, a direct interaction of aldosterone with the target tissue — in this case, the heart — is involved in this remodeling process.

The growth-promoting actions of aldosterone that lead to vascular remodeling are dependent on sodium and suggest that aldosterone may promote the entry of sodium into fibroblasts, in part by activating or recruiting sodium pumps from a preexisting pool (fast adaptation) and inserting these pumps into cell membrane, perhaps by exocytosis. The growth of fibroblasts and the synthesis of collagen also involve the aldosterone-dependent transcriptional regulation of \(Na^+\)/\(K^+\)–ATPase, which requires the interaction of the receptor–ligand complex with a hormone-response element in the promoter region of the gene for this pump (slow adaptation).\textsuperscript{52,70} In rats fed a high-sodium diet and given deoxycorticosterone, there is an increase in the concentrations of mRNA for the \(\alpha_1\) and \(\beta\) subunits of \(Na^+\)/\(K^+\)–ATPase in the heart, aorta, and skeletal muscle; the increase is not related to hypertension and does not occur when deoxycorticosterone is combined with a low-sodium diet.\textsuperscript{71}

**CONGESTIVE HEART FAILURE: A SALT-AVID SYNDROME**

In patients with congestive heart failure, persistent activation of the renin–angiotensin–aldosterone system is inappropriate, given the absence of salt deprivation or intravascular volume contraction, and it has pathologic effects. It induces inappropriate expansion of the intravascular and extravascular volumes and fibrosis of the heart, kidneys, and other organs. These adverse outcomes contribute to the progressive nature of congestive heart failure, with its inexorable downhill clinical course that includes recurrent episodes of symptomatic failure and sudden death from cardiac causes.

Congestive heart failure is a clinical syndrome involving a constellation of symptoms and signs that arise from congested organs and hypoperfused tissues. It begins with impaired ventricular function, but much of what follows is caused by the retention of salt and water.\textsuperscript{72,73} Because of the role of sodium retention, the severity of congestive heart failure cannot be gauged by indexes of systolic or diastolic pump function, as it can be in patients with acute heart failure (e.g., after myocardial infarction). Not all patients with heart failure, defined as chronic ventricular systolic dysfunction, have congestive heart failure. The left ventricular ejection fraction does not predict systemic blood flow or its distribution and therefore cannot predict renal perfusion that results in the activation of the renin–angiotensin–aldoste-
rone system. Patients with a reduced ejection fraction can have compensated heart failure, with exertional dyspnea and fatigue that occur only with heavy muscular work, and no signs of expanded intravascular or extravascular volume. When patients with systolic dysfunction have these symptoms at rest and during mild exertion, they have decompensated heart failure. In patients whose heart failure is compensated, the ratio of sodium to potassium in urine is greater than 1.0, because of the release of natriuretic peptides from the distended atria and ventricles (Fig. 4). Decompensation occurs when there are moderate-to-marked reductions in renal perfusion. Plasma renin activity increases, and the resulting increases in angiotensin II and aldosterone production override the action of the natriuretic peptides. Urinary sodium retention becomes nearly complete (i.e., the sodium:potassium ratio is less than 1.0), and intravascular and extravascular volumes increase.

In an international study (the Randomized Aldactone Evaluation Study [RALES]), conducted in 19 countries on 5 continents and involving more than 1660 patients with moderately severe or severe congestive heart failure, there was a 30 percent reduction in the rate of death from any cause among patients treated with spironolactone (25 mg daily) in combination with an ACE inhibitor and a loop diuretic, as compared with patients who received placebo (Table 1). In addition, there were similar reductions in sudden death from cardiac causes, death from progressive cardiac failure, and hospitalizations related to symptomatic heart failure. The patients enrolled in this trial had base-line serum creatinine concentrations of less than 2.5 mg per deciliter (221 nmol per liter); severe hyperkalemia occurred in less than 2 percent of the patients receiving spironolactone.

These favorable outcomes are likely to be a result of antagonism of several actions, if not all the actions, of aldosterone that contribute to the pathophysiology of congestive heart failure. With regard to the role of aldosterone in promoting organ fibrosis, the results of a recently reported substudy of RALES are of interest. In this substudy, serum markers of collagen synthesis were serially measured in 261 patients. (Markers of collagen synthesis correlate with morphologic evidence of cardiac fibrosis in humans and rats.) Serum concentrations of one of these markers, the N-terminal propeptide of type III procollagen, measured at the time of enrollment, correlated with an increased risk of death and hospitalization. This finding confirms and extends the reported value of this propeptide as an independent predictor of death in patients with either ischemic or idiopathic dilated cardiomyopathy. At six months, in patients in the placebo group, the levels of this and other markers of collagen synthesis were the same as or higher than their base-line levels. The survival benefit among the patients receiving spironolactone was associated with a reduction in serum propeptide concentrations. High doses of spironolactone have also been reported to reduce serum propeptide concentrations in patients with symptomatic heart failure due to ischemic heart disease. Collectively, these findings further emphasize the importance of tissue collagen turnover and fibrosis in heart failure and suggest that spironolactone may attenuate such structural remodeling.

Today’s standard of care for patients with conges-
tive heart failure should therefore include a small dose of an aldosterone-receptor antagonist, given in combination with an ACE inhibitor and a loop diuretic, with or without digoxin. Serum potassium and creatinine should be measured after such combination therapy is initiated and on a regular basis thereafter. Supplemental potassium, used to offset the kaliuresis associated with loop diuretics, should be discontinued when therapy with drugs that decrease aldosterone secretion or action is begun. Given the importance of sodium as a necessary modulator of aldosterone-associated vascular remodeling, it could be argued that dietary sodium restriction should be severe. On the other hand, severe sodium restriction together with diuretic treatment can lead to volume contraction and further activation of the renin–angiotensin–aldosterone system. Hence, the optimal level of daily sodium in patients with congestive heart failure is uncertain.

**CONCLUSIONS**

Survival of mammals that live on land depends on adaptations to life-threatening circumstances such as deprivation of salt and water and marked sweating, vomiting, diarrhea, or tissue injury with hemorrhage. One of these adaptations is the activation of the renin–angiotensin–aldosterone system. In the case of congestive heart failure, however, the activation of this system is maladaptive. What begins with myocardial

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**Figure 4.** Compensated and Decompensated Heart Failure, as Indicated by the Presence or Absence of Urinary Sodium Retention, Together with Symptoms and Signs of Expanded Intravascular and Extravascular Volume.

In compensated heart failure with mild-to-moderate reductions in renal perfusion, natriuretic peptides, such as atrial natriuretic peptide (ANP) released by distended atria, stimulate sodium excretion (decreasing reabsorption, minus sign) so that the urinary sodium:potassium ratio is greater than 1.0. In decompensated heart failure, moderate-to-severe reductions in renal perfusion activate the renin–angiotensin–aldosterone system (RAAS), overriding the action of natriuretic peptides to stimulate nearly complete urinary sodium reabsorption (plus sign), resulting in a urinary sodium:potassium ratio of less than 1.0. Reproduced from Weber and Villarreal with the permission of the publisher.

<table>
<thead>
<tr>
<th>Heart failure</th>
<th>Compensated</th>
<th>Decompensated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impairment in renal perfusion</td>
<td>Mild to moderate</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Urinary sodium:potassium ratio</td>
<td>&gt;1.0</td>
<td>&lt;1.0</td>
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failure eventuates in a clinical syndrome whose consequences are rooted in a marked retention of salt. The undesirable long-term effects of aldosterone in stimulating renal and extrarenal retention of sodium and water (at the expense of potassium excretion) and in the vascular remodeling of the heart and other organs contribute to the progressive nature of heart failure. Although the association between hyperaldosteronism and salt loading with vascular remodeling by fibrous tissue is clear, the cellular and molecular events involved in altering the phenotype, replication, and collagen turnover of fibroblasts require further study.

Pharmacologic interference with the production or action of the hormones of the renin–angiotensin–aldosterone system is an important component in the treatment of patients with congestive heart failure. ACE inhibitors have established efficacy in these patients. Angiotensin-receptor antagonists may also prove of value. Several trials, including that of Cohn et al.,66 are addressing their efficacy and safety. Finally, the RALES trial provided strong evidence for the efficacy of an aldosterone-receptor antagonist in combination with an ACE inhibitor and a loop diuretic in patients with congestive heart failure.

**Table 1. Reduction in the Risk of Death, Death from Cardiac Causes, and Cardiac-Related Illness Among Patients Treated with Spironolactone, as Compared with Placebo, in the Randomized Aldactone Evaluation Study,**

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>PLACEBO (N=841)</th>
<th>SPIRONO- LACTONE (N=822)</th>
<th>RISK</th>
<th>P VALUE</th>
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<tr>
<td>Death</td>
<td>386</td>
<td>284</td>
<td>30</td>
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<tr>
<td>Death from cardiac causes</td>
<td>314</td>
<td>226</td>
<td>31</td>
<td>&lt;0.001</td>
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<tr>
<td>Progression of heart failure</td>
<td>189</td>
<td>127</td>
<td>36</td>
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<tr>
<td>Sudden death</td>
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<tr>
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<td>336</td>
<td>260</td>
<td>30</td>
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<tr>
<td>Aggravation of heart failure</td>
<td>300</td>
<td>215</td>
<td>35</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*pData are from Pitt et al.*

**REFERENCES**


73. Hall CE, Hall O. Hypertension and hypertalism. I. Aldoste-