Aldosterone Blockade and Heart Failure

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In the fall of 1999, a multicenter, randomized trial examining the effect of spironolactone on morbidity and mortality among patients with severe heart failure was published in the *Journal*.[1] The Randomized Aldactone Evaluation Study (RALES) proved that antagonism of aldosterone had an important role in the management of heart failure, even in patients taking angiotensin-converting–enzyme (ACE) inhibitors. In addition to reducing mortality by 30 percent, small doses of spironolactone resulted in an improvement in ventricular function and enhanced exercise tolerance.[2] The rates of death from progressive heart failure and sudden death from cardiac causes were both diminished by an old, inexpensive medicine. This remarkable study has led to intensified research into the mechanisms whereby aldosterone blockade benefits patients with heart failure, to widespread use of spironolactone in a range of patients with heart failure, and to a new trial involving a novel aldosterone antagonist, eplerenone.[3] Now is a good time to review the reasons why aldosterone blockade may be effective and the types of patients in whom it should be used.

Aldosterone was originally thought to be important in the pathophysiology of heart failure only insofar as it increased the retention of sodium and the loss of potassium. It was also believed that optimal doses of ACE inhibitors would suppress the production of aldosterone, since angiotensin II is a potent stimulus for adrenal aldosterone secretion. In fact, both angiotensin II and aldosterone ultimately escape the effects of long-term ACE inhibition, with aldosterone levels showing a more pronounced rebound.[4] Plasma aldosterone concentrations may reach 20 times the normal level in patients with heart failure, because of both increased production and a decreased rate of hepatic clearance. In addition to being produced by the adrenal glands, aldosterone is synthesized by human vascular cells and has a number of adverse effects on the vasculature.[5] Sustained elevations of angiotensin II and aldosterone concentrations induce abnormal vasomotor reactivity and baroreceptor responsiveness by promoting endothelial dysfunction and oxidative stress. Moreover, intense interest has focused on the role of aldosterone in promoting organ fibrosis. A survival benefit among patients receiving spironolactone in RALES was associated with a reduction in the concentrations of serum markers of collagen synthesis. These and numerous other findings, as reviewed recently,[6] emphasize the importance of tissue collagen turnover and fibrosis in heart failure as critical components in cardiac remodeling.

Ventricular remodeling is the process by which mechanical, neurohormonal, and possibly genetic factors alter ventricular size, shape, and function. Remodeling occurs in several clinical conditions, including myocardial infarction, cardiomyopathy, hypertension, and valvular heart disease. Hallmarks of remodeling include hypertrophy, loss of myocytes, and increased interstitial fibrosis, so that abnormalities of both the cardiomyocytes and the extracellular matrix contribute to systolic and diastolic dysfunction. This remodeling process is complex and multifactorial, and there are multiple opportunities for therapeutic intervention.[7] Current evidence from randomized trials supports the premise that drug therapy with beta-adrenergic antagonists, ACE inhibitors, and angiotensin-receptor blockers reduces morbidity and mortality among patients with heart failure due to left ventricular systolic dysfunction by halting or reversing the remodeling effect.

Aldosterone antagonists influence remodeling as well, as evidenced by the study by Pitt et al.[3] reported in this issue of the *Journal*, in which patients with a left ventricular ejection fraction of 40 percent or lower and symptoms of heart failure were randomly assigned to receive eplerenone an average of seven days after they had had a myocardial infarction. Eplerenone is an aldosterone antagonist, approved in the United States for use in hypertension, that selectively blocks the mineralocorticoid receptor and not the glucocorticoid, progesterone, and androgen receptors. It is the latter receptors that mediate the side effects, especially the painful gynecomastia and sexual dysfunction, that are seen with spironolactone. During a mean follow-up of 16 months, the relative risk of death was reduced by 15 percent among patients receiving eplerenone. There was a salutary effect on mortality from cardiovascular causes as well, primarily driven by a statistically significant reduction in the risk of sudden death in the eplerenone group. The risk of hospitalization for heart failure was reduced by 15 percent with eplerenone; increases in blood pressure were significantly smaller in the eplerenone group. There was a significantly greater increase in the serum creatinine concentration in the eplerenone group than in the placebo group, but the difference between groups was clinically small. Serious hyperkalemia occurred in 5.5 percent of patients in the eplerenone group, as compared with 3.9 percent of patients in the placebo group.

Taken together, these two trials of aldosterone blockade have enrolled more than 8000 patients with systolic dysfunction and symptoms of heart failure. The authors of the current report on the Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) underscore the fact that the patients in this study were receiving optimal treatment with an ACE inhibitor or angiotensin-receptor blocker (in 87 percent of patients), a beta-blocker (in 75 percent), aspirin, a lipid-lowering agent, and coronary reperfusion therapy. In RALES, in contrast, beta-blockers were used in only about 11 percent of patients, although ACE inhibitors were given to 94 percent. Other characteristics of the study populations were different as well and are worth scrutinizing so that the appropriate target populations for these therapies can be determined. The left ventricular ejection fraction in the RALES trial averaged 25 percent; in EPHESUS, the ejection fraction was higher, at 33 percent. One-year mortality among the patients assigned to placebo was 25 percent in RALES and 13.6 percent in EPHESUS. The difference in mortality may reflect the variations in the severity of heart failure at enrollment, the level of systolic dysfunction (which was more profoundly depressed in RALES), or the number of additional effective therapies administered (a higher number in EPHESUS).

Which patients should receive an aldosterone antagonist, and which drug should be used? The guidelines of the American College of Cardiology and the American Heart Association for the management of heart failure recommend that low-dose spironolactone be considered in patients with recent or current symptoms of systolic heart failure at rest despite the use of digoxin, diuretics, an ACE inhibitor, and a beta-blocker.[8] The guidelines further specify that the use of spironolactone for patients with mild-to-moderate heart failure has not been tested and urge caution in prescribing spironolactone for patients with base-line elevations of potassium or creatinine concentrations. Despite these recommendations, published data and many anecdotes suggest that spironolactone has been widely used in patients with heart failure without consideration of their functional class or ejection fraction and without optimization of background treatment with ACE inhibitors and beta-blockers.[9] Many patients treated with spironolactone are distinctly dissimilar from the patients in RALES, and the effect of the therapy in these patients is unknown. Ironically, during the same period when the number of prescriptions for spironolactone increased, there were ongoing reports of the underuse of

beta-blockers after myocardial infarction and inappropriate use of calcium-channel blockers — practices associated with increased rates of rehospitalization, death, or both.[10]

The introduction of eplerenone, a selective aldosterone antagonist with reportedly less cumbersome adverse effects than spironolactone, could theoretically increase the inappropriate use of this class of drug. Eplerenone will undoubtedly be more costly than generic spironolactone. Although the study populations in RALES and EPHESUS were different, all participants had been screened carefully for renal insufficiency and hyperkalemia. Every patient had symptomatic systolic dysfunction and was receiving therapy that was considered optimal at the time of the study. There is nothing in the results of the trials to suggest that eplerenone should be used preferentially before treatment with spironolactone has been tried. It is also critical to emphasize that hyperkalemia is just as likely to occur with eplerenone therapy as it is with spironolactone therapy.

The addition of aldosterone antagonists to the regimens of patients with left ventricular systolic dysfunction and ongoing symptoms of heart failure despite optimal treatment with ACE inhibition and beta-blockers can substantially reduce overall mortality and the rate of sudden death in this vulnerable population. Physicians are understandably eager to apply this lifesaving therapy in their own patients but should acknowledge that real-world practice has to begin with evidence-based medicine. The use of aldosterone antagonists may be well worth the expense or extra effort required to monitor the potential adverse effects, but patients who are treated with them should be screened — and their cases managed — as carefully as those in the published studies. Supplementary trials are needed to determine whether this class of drug will be efficacious in patients with less severe symptoms, or in those with heart failure due to primarily diastolic dysfunction.

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Aldosterone — Villain or Bystander?

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The two primary regulators of aldosterone secretion are potassium and the renin–angiotensin system. The latter is involved in volume homeostasis, with high salt intake suppressing the renin–angiotensin system and aldosterone levels and low salt intake having the opposite effect. Secondary hyperaldosteronism, a physiologic response to dietary salt restriction, promotes renal sodium conservation. In this setting, hyperaldosteronism is a bystander that has no cardiovascular consequences. Hyperaldosteronism emerges as villain in persons whose dietary salt intake is normal if the production of aldosterone is inappropriate for the level of sodium intake, resulting in excessive renal sodium retention, potassium wasting, hypertension, and cardiovascular damage (see Figure).

Defects in the regulatory relationship between the renin–angiotensin system and aldosterone production occur by means of two mechanisms: autonomous secretion of aldosterone by the adrenal cortex secondary to a neoplasm or bilateral hyperplasia (primary aldosteronism) or hyperaldosteronism secondary to the activation of the renin–angiotensin system, such as that caused by renal-artery stenosis (secondary aldosteronism). Traditionally, hypertension in the setting of hyperaldosteronism has been thought to be due to the expansion of extracellular volume, resulting from excessive renal resorption of sodium.

During the past decade, a revised hypothesis has evolved, featuring an expanded role of aldosterone in the pathogenesis of cardiovascular disease. First, the oft-quoted low prevalence of primary aldosteronism among persons with essential hypertension (0.5 to 1 percent) has been challenged. Recent studies have reported that 8 to 15 percent of persons with essential hypertension fulfill the biochemical criteria for primary aldosteronism. Most of these persons have mild hyperaldosteronism, usually idiopathic bilateral hyperplasia; most do not have hypokalemia.[1] Thus, the presence of a normal potassium level does not rule out primary aldosteronism.

Second, new research has focused on the actions of aldosterone in target organs beyond the kidney. In the 1950s, Selye and others realized that aldosterone had nonepithelial effects such as the induction of inflammatory processes, collagen formation, fibrosis, and necrosis. Recent studies in various animal models have confirmed the occurrence of cardiac and renal damage in nonepithelial target tissues.[2] Clinical trials in humans (the Randomized Aldactone Evaluation Study [RALES] and the Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study [EPHESUS]) have also demonstrated a beneficial effect of mineralocorticoid-antagonist treatment on survival in patients with heart disease. In animal models, aldosterone-induced injury was not observed with low salt intake, even though the aldosterone levels were frankly elevated. Thus, the level of aldosterone alone may not be useful in determining its potential causative role in cardiovascular disease. Rather, when aldosterone is produced in inappropriate amounts for the level of sodium intake, it becomes villainous.

In light of the pleiotropic cardiovascular toxicity of aldosterone, the benefits of aldosterone inhibition as demonstrated in clinical trials, and the likelihood that primary aldosteronism is the most frequent secondary form of hypertension, there has been renewed interest in this hormone. In this issue of the *Journal*, Vasan and colleagues (pages 33–41) attempt to extend these observations, hypothesizing that a single morning measurement of aldosterone in a cohort of normotensive subjects from the Framingham Offspring Study would correlate with the risk of blood-pressure–related outcomes (the development of hypertension or an increase in blood pressure by one or more categories as defined by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) approximately four years later. A sodium index, calculated as the number of millimoles of sodium per gram of creatinine in a spot urine sample, was used to assess dietary salt intake.

The results indicated a monotonic modest association between the aldosterone level and the risk of an increase in blood pressure. The risk of an increase by one blood-pressure category or the development of hypertension was significant only in the highest quartile of serum aldosterone and only

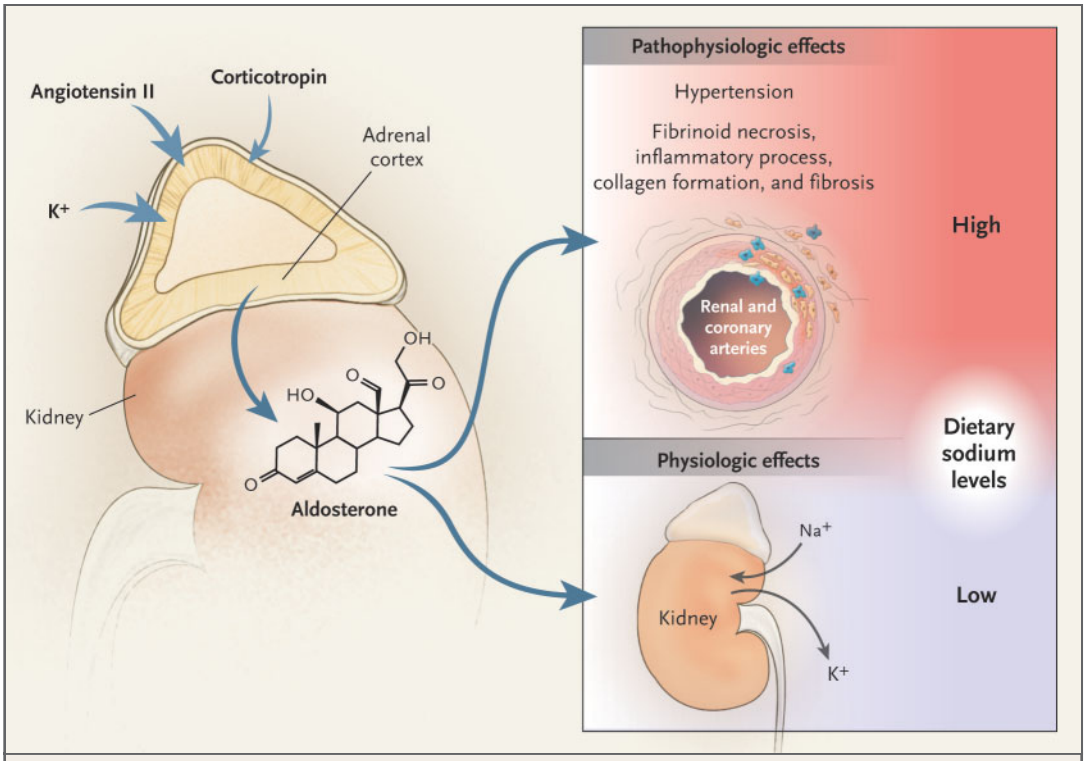

Figure. Physiologic and Pathophysiologic Effects of Aldosterone on the Kidney and Heart in Relation to Dietary Salt Levels.

among participants with a sodium index above the median. The authors conclude that increased aldosterone levels within the physiologic range predispose normotensive persons to the development of elevated blood pressure. Yet the mean level of aldosterone in the highest quartile — 19 ng per deciliter (range, 14 to 72) — should be viewed as clearly elevated in a person with normal salt intake. It would have been helpful if the authors had presented the sodium index in each of the quartiles, as well as that in participants with very high aldosterone levels. It is likely that some participants in the highest quartile had mild primary aldosteronism; the authors acknowledge that this is an alternative explanation, but they dismiss this possibility, since the trend toward an increasing risk of the blood-pressure–related outcomes was observed from the second quartile of aldosterone upward. However, when they tried to adjust for aldosterone levels and the urine sodium index, formal testing showed that the interaction was not statistically significant.

As the authors acknowledge, there are a number of limitations to their study. Diagnosing hyperaldosteronism requires knowledge of the level of salt intake as well as the functional status of the renin–angiotensin system. Since aldosterone production is also positively regulated by potassium balance and momentarily by corticotropin, a random measurement of plasma aldosterone has no value unless it is interpreted in the context of dietary sodium intake as well these regulatory factors. The sodium balance was assessed by means of a spot urine sample rather than a 24-hour collection. Potassium and plasma renin activity levels were not measured; therefore, the ratio of the plasma aldosterone level to the plasma renin activity level could not be calculated, and patients could not be classified as having primary or secondary hyperaldosteronism.

Nevertheless, if we assume that all the participants had an ample sodium intake, the association between the highest aldosterone levels and the increase in blood pressure in this study suggests that the aldosterone levels were inappropriate for the salt intake. If so, one potentially important interpretation of these data is that the risk of

the development of hypertension in some persons is related to the presence of underlying mild primary hyperaldosteronism. Thus, in these persons, aldosterone may indeed be a villain rather than a bystander in a society in which dietary sodium intake is high.

Dr. Williams reports having received consulting fees from Pharmacia, Novartis, Biogen, and Eli Lilly, as well as lecture fees from Pfizer.

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BECOMING A PHYSICIAN

Journal Clubs — Science as Conversation

Joe Wright, B.A.

I had forgotten about it amidst the other tasks of medical-student life: exams, patient write-ups, the shirt I needed to iron. But an e-mail from my fellow student John reminded me that it was my turn to lead the journal club for our HIV–AIDS interest group. I had no idea what article I would bring. I bumbled through PubMed in search of a paper, wandering through several topics before landing on an article about the high prevalence of chlamydia in China,[1] along with an editorial[2] arguing for a particular strategy for preventing a new explosion of human immunodeficiency virus (HIV) infection. I wasn't sure that I could lead a good discussion on this article, but time was up, so I picked it and hoped it would work out. At least in one important sense, it did.

There were only four of us at the session — just barely enough. My fellow journal-club members were puzzled by some of the statistical methods, and I couldn't help much. And I discovered that I'd failed to examine closely the most interesting aspects of the data tables. Nonetheless, I had brought some questions, and I was blessed with thoughtful, talkative colleagues. We talked about infectious disease, social power, and economic development; about whether different factors might drive outbreaks in different regions of the country (thus requiring different intervention strategies); and about how the structure of sexual networks influences the pattern of spread of sexually transmitted diseases. We tried to get through the data ourselves without relying on the interpretations in the abstract or the editorial.

A few days later, Kanu, a journal-club regular, e-mailed us a link to a news article about the Chinese economy, saying, "Thought you guys might be interested, considering our conversation the other day." And it was then that I remembered the genius of journal club: I *was* interested in reading this rather dry article about Chinese economics and politics, because now I had a context and a purpose for the information.

Moreover, in the process of looking for an article, I had learned still more. For instance, while looking through the literature on sexually transmitted diseases, I had called my friend Dan (who had been in charge of the first journal club I'd attended) to ask him about network theory in research on sexually transmitted diseases. I had read an interesting review article about GB virus C (which would become the topic of another journal-club meeting when a new research article came out[3]). I had learned a bit about the economic and physical geography of China. I had remembered that *Chlamydia trachomatis* is an obligate parasite.

None of this knowledge — except the stray fact about *C. trachomatis* — will help me on any exams. Nor did our group come up with any particularly helpful ideas about AIDS to offer to the Chinese people. We developed no 10-point plan for stopping HIV epidemics. It might appear as if we accomplished nothing. But by struggling through the article together, we became more awake to the world around us and more immersed in the scientific project of exploring it.

When I was younger, I generally encountered