

Three Perspectives on Aldosterone's Role in Cardiovascular Disease: Salt's Not the Only Bad Guy

The 50th anniversary of the discovery of aldosterone was celebrated in 2003, yet for the first three decades after its discovery, the role of mineralocorticoids in relation to cardiovascular disease was thought to be limited to that of salt retention and its consequences. Renewed interest in aldosterone starting at the basic research level culminated in clinical studies leading to important changes in the management of cardiovascular disease. Discussing the latest positions on aldosterone are three renowned scientists, each illustrating the subject from his professional perspective.



Giving the basic scientist's point of view is Celso E. Gomez-Sanchez, M.D., Endocrinologist at the University of Mississippi Medical Center in Jackson, Mississippi.



Giving the clinical scientist's point of view is Gordon H. Williams, M.D., of the Center for Clinical Investigation, Brigham and Women's Hospital in Boston, Massachusetts.



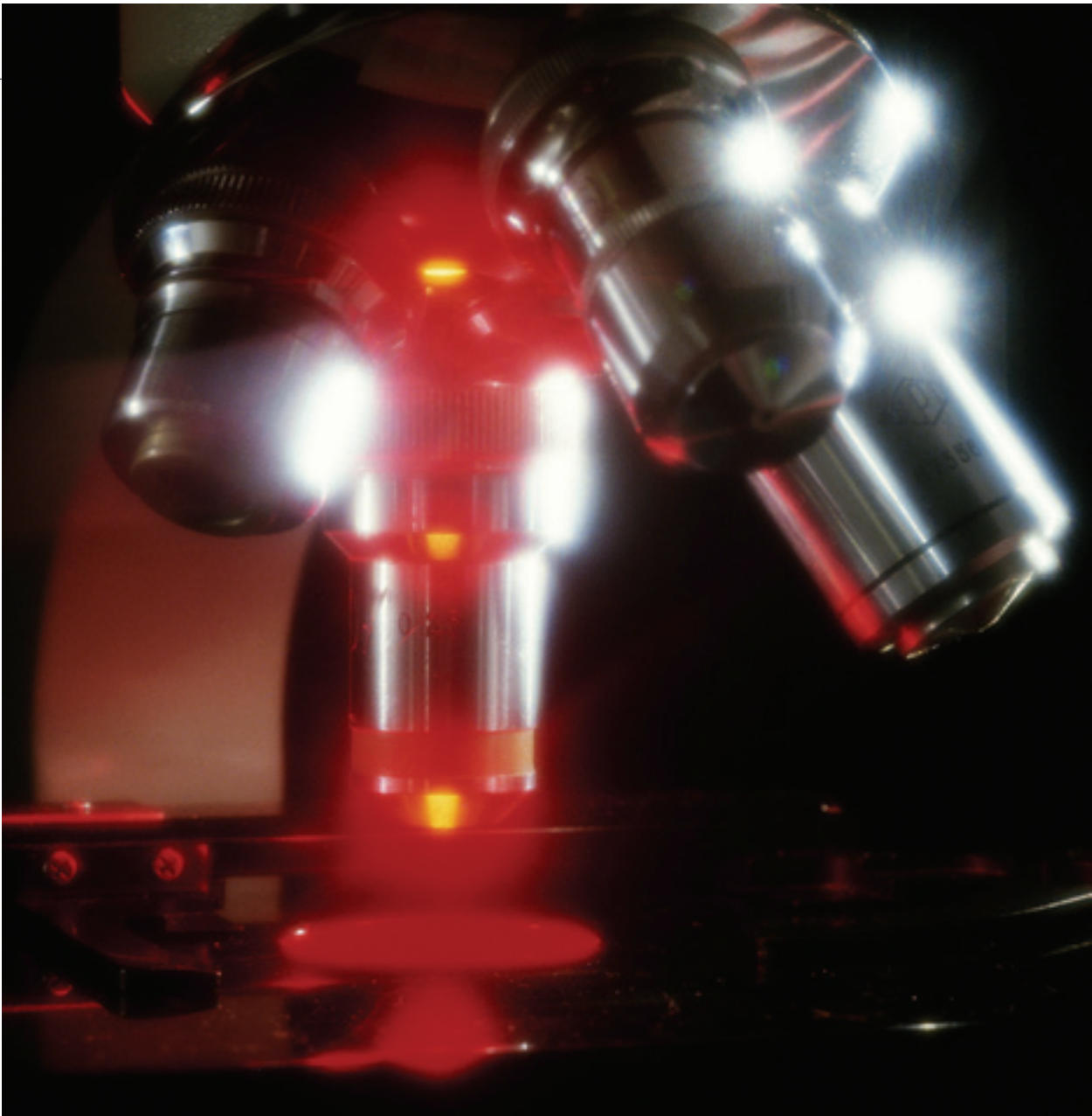
Giving the clinical practitioner's point of view is William F. Young Jr., M.D., of the Mayo Clinic College of Medicine, Mayo Clinic and Mayo Foundation, in Rochester, Minnesota.

From the Basic Scientist: Aldosterone: Beyond the Kidney and Adrenal Gland

Aldosterone's Effects Outside the Kidney

Advances in our understanding of aldosterone's role in cardiovascular remodeling and damage have occurred in several areas. First was the recognition that aldosterone, in addition to increasing vectorial transport of sodium in the kidney collecting ducts, also activates mineralocorticoid receptors in other organs with high concentrations of its receptor, including the heart, vessels and brain, and that these actions work in concert to produce hypertension and cardiovascular remodeling.

The role of brain mineralocorticoid receptors in blood pressure control was demonstrated by chronic infusions of mineralocorticoid agonists and antagonists systemically and intracerebroventricularly. The dose of aldosterone that produces hypertension in rats and dogs when infused into the lateral ventricle is 1/100th the effective systemic dose and increases the blood pressure with similar chronology and intensity (1). Hypertension produced by systemic aldoste-



rone excess in normotensive strains of rats or by a high salt diet in Dahl Salt-Sensitive (SS) rats is prevented by the intracerebroventricular infusion of a mineralocorticoid receptor antagonist at a dose that is ineffective when given systemically (1).

When hypertension of similar amplitude and duration is produced by the systemic or central administration of a mineralocorticoid, the consequences for the heart are very different. Cardiac hypertrophy is associated with the hypertension produced by systemic aldosterone excess, but not with the low doses required for intracerebroventricularly infused aldosterone (1). The intracerebroventricular infusion of a mineralocorticoid antagonist prevents hypertension in rats given a systemic aldosterone excess, but it does not prevent cardiac hypertrophy or fibrosis (2). Thus, cardiovascular actions of mineralocorticoids involve several organs, and the elevation of blood pressure and cardiovascular remodeling are simultaneous and separable effects of aldosterone.

The independence of these two actions is further demonstrated in the Spontaneously Hypertensive rat (SHR) in which mineralocorticoid receptor antagonists at doses that do not lower blood pressure reduce the incidence of cardiovascular and renal injury, stroke and death (3). One of the mechanisms of mineralocorticoid receptor action is the promotion of fibrosis through the endothelial growth factor pathway (4). In addition to direct activation of end organ receptors, aldosterone actions in the brain circumventricular organs modulate myocardial remodeling after experimental myocardial infarction and increase circulating and heart concentrations of proinflammatory cytokines. The central administration of a mineralocorticoid receptor antagonist improves the clinical condition of rats with experimental myocardial infarction and congestive heart failure (5).

Extra-adrenal Synthesis of Aldosterone

The extra-adrenal synthesis of aldosterone in the heart

and brain has been demonstrated, though the relevance of the small amounts produced has been questioned. Mineralocorticoid receptor antagonists are beneficial in some situations, including congestive heart failure and some forms of low renin hypertension, in which plasma aldosterone is not clearly elevated, suggesting deleterious effects are mediated by paracrine or autocrine action. The mRNA for all the steroidogenic enzymes required to form aldosterone from cholesterol are found in the heart and brain (6, 7). Silvestre demonstrated that isolated perfused rat hearts produce aldosterone in a regulated manner (6) and that production of aldosterone by these hearts increases after myocardial infarction (8). Mincees of various brain areas from adrenalectomized rats synthesize aldosterone *de novo* from endogenous and tritiated substrates added to the incubation media (7). Changes in aldosterone concentrations in the heart and brain parallel those of plasma, increasing when rats are given a low sodium diet and decreasing with increasing sodium intake. Adrenalectomized rats given a high sodium diet, as expected, do not have detectable aldosterone in plasma, but the concentrations of aldosterone in their hearts and brains are consistently detectable, albeit very low (9, 10) indicating that some aldosterone is produced in these organs. Such small amounts, if relevant, probably have a paracrine or autocrine role. Partial inhibition of the synthesis of steroids in the brain by the intracerebroventricular administration of trilostane, a 3 β -ol steroid dehydrogenase inhibitor (11), or 19 ethynyl deoxycorticosterone (DOC) (7), prevents the elevation of blood pressure in the salt-challenged Dahl SS rat, suggesting that excessive steroid synthesis in the brain, probably that of aldosterone, is part of the pathogenesis of hypertension in this rat.

Nongenomic Roles of Aldosterone

Another promising area of discovery about aldosterone regulation of cardiovascular function, but one that has been hindered by the lack of tools, is that of the nongenomic effects of aldosterone (12). Some of these may require binding to the mineralocorticoid receptor, others involve direct interaction of aldosterone with intracellular signaling pathways.

In summary, actions of aldosterone in the cardiovascular system are exerted through renal and extra-renal mineralocorticoid receptors within the cardiovascular system and the brain.

From the Clinical Scientist: Clinical Studies Related to Mineralocorticoid Receptor Antagonists

Cumulative data suggest that aldosterone's traditional role as a regulator of sodium volume and potassium homeostasis needs to be expanded. Preclinical data support the concept that activation of the mineralocorticoid receptor

(MR) contributes to vascular disease affecting various target organs, including heart, kidney and brain. Clinical studies affirm these data by documenting beneficial effects of blocking the MR. These studies can be divided into three types: morbidity/mortality, assessment of target organ damage, and mechanisms.

Morbidity/Mortality Studies

The Randomized Aldactone Evaluation Study (RALES) evaluated the effect of adding low-dose spironolactone (25 mg) to standard therapy (angiotensin converting enzyme inhibitors (ACEIs), digoxin and diuretics) in 1,600 patients with NYHA Class 3 or 4 heart failure. Compared to placebo, spironolactone significantly reduced death from all causes (30 percent reduction; $p < 0.001$). The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) had a similar design but a different population (6,642 subjects with heart failure after acute myocardial infarction) and used low-dose eplerenone, a selective MR antagonist). Standard therapy included ACEIs /angiotensin receptor antagonists (ARBs), beta blockers, and diuretics. The eplerenone group had substantial reductions in total mortality (15 percent; $p=0.008$), cardiac mortality/cardiovascular hospitalization (13 percent; $p=0.002$), and sudden cardiac death (21 percent; $p=0.03$). Eplerenone appeared to be particularly effective in reducing sudden cardiac death in individuals with a baseline ejection fraction < 30 percent (relative risk 0.67 (95 percent confidence intervals, 0.5-0.9; $p=0.009$). Thus, low dose inhibition of MR significantly reduces morbidity/mortality in patients with cardiovascular disease.

Mineralocorticoid Receptor Antagonists and Target Organ Damage

In the 4E- (eplerenone, enalapril, eplerenone + enalapril) LVH study, hypertensive patients with documented left ventricular hypertrophy (LVH) by echocardiogram (ECG) were randomized to eplerenone (forced titrated to 200 mg/day), enalapril (forced titrated to 40 mg/day) or enalapril + eplerenone (10 mg of enalapril and eplerenone forced titrated to 200 mg/day). If diastolic blood pressure was not reduced, a diuretic and, if necessary, amlodipine were added. There was a significant reduction in left ventricular mass with each treatment with no difference between the monotherapies, but a significantly greater reduction in the combination treatment group. In a second study, 4E-LVH. Protein excretion was assessed before and after six months of therapy with a significant 45 percent reduction in protein excretion with eplerenone, 63 percent with enalapril, and 74 percent with combination therapy ($p < 0.001$). Combination therapy was significantly more effective than monotherapy. Thus, blockade of the MR or reduction in angiotensin II formation are equally effective in reducing the degree of LVH and level of proteinuria, two

surrogate markers for cardiovascular/renal damage. Strikingly, the combination produces the best results.

In a second diabetic study, subjects were started on enalapril 20 mg/day one month prior to being randomized into placebo, 50 mg of eplerenone or 100 mg of eplerenone groups. Both 50 and 100 mg produced similar 45-50 percent reduction in proteinuria.

Based on the results from the target organ and mortality studies, only a minimal dose of an MR antagonist (25 mg spironolactone or 50 mg eplerenone) is required to produce substantial cardiovascular protection.

Side Effects

Hyperkalemia is associated with MR blockade, specifically in individuals with compromised renal function. In EPHESUS, more eplerenone-treated subjects (15.6 percent) than placebo (11.2 percent) ($p < 0.001$) had serum potassium levels greater than normal. No eplerenone deaths and only one placebo death was attributed to elevated potassium.

In the 4E-proteinuria study, many of the subjects had glomerular filtration rates as low as 30 ml/minute. Approximately 2 percent of enalapril-treated subjects versus 10-11 percent of subjects treated with eplerenone with or without enalapril had hyperkalemia. When 50 mg and 100 mg of eplerenone were added to enalapril, the frequency of hyperkalemia was not significantly different among the three groups. Thus, as anticipated, eplerenone-induced hyperkalemia was dose-related in patients with renal disease.

Potential Mechanisms

Aldosterone levels measured in the Randomized Evaluation of Strategies of Left Ventricular Dysfunction (RESOLVD) pilot study suggested a mechanism by which MR blockade has additional benefit beyond ACEI. During the first 17 weeks, the ARB and an ACEI combination reduced aldosterone levels more than either monotherapy. However at 43 weeks, the aldosterone levels in all groups returned to baseline.

Preclinical studies suggest that MR antagonists reduce vascular inflammation and fibrosis. Two sub-studies of EPHESUS indirectly support these findings. In one, adverse outcome was associated with elevated baseline level of pro-collagen type III amino terminal peptide (PIIINP). Eplerenone significantly reduced PIIINP compared with placebo. Osteopontin, an inflammatory marker, was modified with non-survivors having a higher level than survivors ($p=0.012$). Eplerenone reduced osteopontin ($P < 0.01$). In a



MR antagonist confers substantial advantage...in reducing cardiovascular/renal damage.

sub-study of RALES, similar changes were documented in PIIINP. Increased relative risk of death (2.36; $p=0.03$) was associated with higher baseline levels of PIIINP. After six months of spironolactone, but not placebo, a significant decrease of this marker was documented ($p=0.001$).

Thus, the reported clinical research studies support preclinical data suggesting that an MR antagonist confers substantial advantage beyond what is achieved by ACEIs or ARBs alone in reducing cardiovascular/renal damage. The mechanisms are unclear but likely involve a reduction in inflammation and abnormal collagen formation resulting in decreases in fibrosis and abnormal target organ remodeling.

From the Clinical Practitioner: Aldosterone: More than a Salt-Retaining Hormone—Implications for Managing Patients with Primary Aldosteronism

Clinical Vignette

A 54-year-old man was referred for a secondary hypertension evaluation. He had been hypertensive with poor control for 20 years (e.g., 168/90 mm Hg). His program included daily dose of hydrochlorothiazide 25 mg, doxazosin 12 mg, and metoprolol 100 mg; twice-daily doses of amiloride 5 mg and potassium chloride 20 mEq. He had a six-year history of intermittent hypokalemia. At age 49, he underwent four-vessel coronary artery

bypass grafting surgery. On laboratory evaluation, the plasma aldosterone concentration (PAC) was 33 ng/dL (normal, 1-21), and plasma renin activity (PRA) was <0.6 ng/mL/hr to yield a PAC/PRA ratio > 55 (normal < 20). When the 24-hr urinary excretion of sodium was 214 mEq, the 24-hr urinary aldosterone excretion was 29 mcg (normal < 12). CT scan of the abdomen showed an 8-mm nodule in the lateral limb of the right adrenal gland and a thickened superior portion of the left adrenal gland. Because of the bilateral abnormalities noted on CT and the fact that the small adrenal nodule could represent a nonfunctioning cortical adenoma, adrenal vein sampling was performed and aldosterone hypersecretion was unequivocally localized to the right adrenal gland. The patient underwent laparoscopic right adrenalectomy and an 8x4x3-mm cortical adenoma was found. The PAC was undetectable the day after surgery. Six months later, the patient's blood pressure was well controlled on a two drug program (metoprolol and hydrochlorothiazide), and his hypokalemia was cured. The cause of his coronary artery disease was no doubt multifactorial;

however, was it possible that his longstanding primary aldosteronism (PA) was a contributing factor? Was his future cardiovascular risk decreased by curing his PA?

Background and Definitions

Hypertension, decreased PRA, and increased aldosterone excretion characterize the syndrome of PA, which was first described in 1955 (1). The most common subtypes of PA are bilateral idiopathic hyperaldosteronism (IHA) and aldosterone-producing adenoma (APA). In the past, a diagnosis of PA would only be considered if the patient presented with spontaneous hypokalemia; the diagnostic evaluation required discontinuing anti-hypertensive medications for two weeks. The “spontaneous hypokalemia/no anti-hypertensive drug” diagnostic approach resulted in a predicted PA prevalence rate of <0.5 percent of all hypertensive patients. However, it is now recognized that most patients with PA are not hypokalemic and that screening can be completed with a simple blood test – PAC/PRA ratio – while the patient is taking anti-hypertensive drugs (except aldosterone receptor antagonists) (2-4). The use of the PAC/PRA ratio as a screening test followed by aldosterone suppression confirmatory testing has resulted in higher PA prevalence estimates (5 to 12 percent of all hypertensive patients) (2).

Normalization of circulating aldosterone or aldosterone receptor blockade should be part of managing all patients with primary aldosteronism.

Treatment of Primary Aldosteronism

Unilateral adrenalectomy normalizes hypokalemia and improves hypertension (as in the clinical vignette) in all patients with APA, and hypertension is cured in approximately 30 to 60 percent of these patients (5). Since unilateral or bilateral adrenalectomy seldom corrects the hypertension in patients with IHA, these patients should be treated medically. Therefore, when patients want to pursue a surgical cure, the accurate distinction between the subtypes of PA is a critical step that is reviewed in detail elsewhere (6).

Normalization of blood pressure should not be the only consideration in managing the patient with PA. In addition to the “epithelial” mineralocorticoid receptors (MR) in the kidney and colon, “nonepithelial” MR receptors are present in the heart, brain and blood vessels. Several animal studies indicate that aldosterone exerts deleterious effects when plasma concentrations are inappropriate for salt status, and these effects are detailed in the companion tripoint articles from Drs. Gordon Williams and Celso Gomez-Sanchez.

When matched for age, blood pressure, and duration of hypertension, patients with PA have greater left ventricular mass measurements than patients who have other types of hypertension (e.g., pheochromocytoma, Cushing’s Syndrome, or essential hypertension [EHT]) (7-9). In patients with APA, the left ventricular wall thickness and mass decreases markedly after one year from the time of adrenalectomy; however, this effect is not noted in patients treated medically (10). Studies on small resistance arteries in fat biopsies from patients with PA suggest that unique vascular remodeling may occur (11,12). In addition, myocardial damage, when estimated by thallium-201 myocardial scintigraphy, is more severe in patients with PA than in those with EHT (myocardial damage improves following adrenalectomy) (13). A recent case-control study of 124 patients with PA and 465 patients with EHT (matched for age, gender, systolic and diastolic blood pressure) found that patients presenting with PA from either APA or IHA had a significantly higher rate of cardiovascular events than the matched EHT patients (14). Their findings included a history of stroke in 12.9 percent of patients with PA and 3.4 percent of patients with EHT (odds ratio [OR] = 4.2), nonfatal myocardial infarction in 4.0 percent of patients with PA and in 0.6 percent of patients with EHT (OR = 6.5), and a history of atrial fibrillation in 7.3 percent of patients with PA and 0.6 percent of patients with EHT (OR = 12.1) (14). The occurrence of cardiovascular complications was comparable in both subtypes of PA (14).

Therefore, normalization of circulating aldosterone or aldosterone receptor blockade should be part of managing all patients with primary aldosteronism. Patients with IHA and GRA should be treated medically (15). In addition,

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This is the fifth appearance of the tri-point perspective articles in *Endocrine News*. Past series topics have been:

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- Polycystic Ovary Syndrome
- Diabetes
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Endocrine News staff would like to thank the efforts of Dr. Steven Grinspoon, RAC Co-Chair, and Dr. Ellen Seely, co-editor for their dedication in developing this series for our readers.

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* Archived issues of the Tri-Point series can be found on the *Endocrine News* Web site www.endo-society.org/news/endocrine_news.

patients with APA may be treated medically if this treatment includes MR receptor blockade.

Conclusion

The treatment goal for the patient with primary aldosteronism is to prevent the morbidity and mortality associated with hypertension, hypokalemia, and cardiovascular damage. Because of the deleterious cardiovascular effects of excess aldosterone, normalization of circulating aldosterone or aldosterone receptor blockade should be part of managing all patients with PA. Unilateral laparoscopic adrenalectomy is an excellent treatment option for patients with APA or unilateral hyperplasia. Patients with IHA and GRA should be treated medically. In addition, patients with APA may be treated medically if this treatment includes MR receptor blockade. ■

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