Review of aldosterone- and angiotensin II-induced target organ damage and prevention

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Abstract

Aldosterone is well recognized as a cause of sodium reabsorption, water retention, and potassium and magnesium loss; however, it also produces a variety of other actions that lead to progressive target organ damage in the heart, vasculature, and kidneys. Aldosterone interacts with mineralocorticoid receptors to promote endothelial dysfunction, facilitate thrombosis, reduce vascular compliance, impair baroreceptor function, and cause myocardial and vascular fibrosis. Although angiotensin II has been considered the major mediator of cardiovascular damage, increasing evidence suggests that aldosterone may mediate and exacerbate the damaging effects of angiotensin II. While angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers reduce plasma aldosterone levels initially, aldosterone rebound, or 'escape' may occur during long-term therapy. Therefore, aldosterone blockade is required to reduce the risk of progressive target organ damage in patients with hypertension and heart failure. This may be achieved nonselectively with spironolactone or with use of the selective aldosterone blocker eplerenone. While both agents have been demonstrated to be effective antihypertensive agents, eplerenone may produce improved target organ protection as witnessed in a variety of clinical settings, without the antiandrogenic and progestational effects commonly observed with spironolactone.

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1. Introduction

Hypertension is a major risk factor for cardiovascular disorders, including stroke, heart failure, vascular disease, and end-stage renal disease. In addition to elevated blood pressure, other factors, such as aldosterone and angiotensin II, contribute to the target organ damage seen in hypertensive patients. Therefore, treatment must provide target organ protection in addition to lowering elevated blood pressure [1,2]. Historically, angiotensin II has been viewed as a primary factor causing tissue damage, and angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) were thought to protect against its detrimental effects on target organs, including the cardiovascular system [3]. However, substantial evidence has emerged to show that aldosterone plays an independent and relatively equivalent role in the development of cardiovascular tissue damage. Although ACE inhibitors and ARBs reduce aldosterone levels during acute therapy, the suppression of aldosterone is variable and unsustained over the long term [3,4]. If not inhibited, aldosterone can cause a wide range of pathophysiologic actions and compounds the effects of angiotensin II and other products of the renin–angiotensin–aldosterone system (RAAS) [4,5]. This review presents recent evidence demonstrating the important concomitant roles of aldosterone and angiotensin II in target organ damage, including cardiovascular disease, as well as comparison of the therapeutic benefits of and differences between spironolactone and eplerenone.

2. Aldosterone and angiotensin II in target organ damage

Aldosterone, the release of which is stimulated by angiotensin II, potassium, and to a lesser extent, adrenocor-
tropic hormone (ACTH), is primarily produced in the outer zona glomerulosa of the adrenal gland. Somatostatin, heparin, atrial natriuretic factor, and dopamine inhibit aldosterone synthesis. Aldosterone binds to mineralocorticoid receptors in renal epithelial cells that results in sodium reabsorption, potassium excretion, and passive water retention in the sodium-replete state [4]. Human tissue cultures [6] and animal models [7,8] have established that aldosterone synthase (CYP11B2), the enzyme responsible for the last step in aldosterone biosynthesis, has been identified in the heart, blood vessels, and brain, suggesting that aldosterone also may be produced in these tissues (where mineralocorticoid receptors are present) [9–11]. An additional enzyme, 11β-hydroxysteroid dehydrogenase (11β-HSD), that regulates the binding of aldosterone to the mineralocorticoid receptor, also has been identified in human heart samples [12,13]. Interestingly, it has been demonstrated that the control mechanisms responsible for aldosterone production in the adrenal cortex and cardiovascular tissue (i.e., angiotensin II, low sodium/high potassium diet, ACTH) are similar [14–16]. With excess aldosterone, both renal and extrarenal mineralocorticoid receptors are activated, leading to a number of pathophysiologic effects that may result in hypertension, heart failure, and other cardiovascular disorders (Fig. 1) [1–11].

The trophic effects of aldosterone are complex and intertwined with those produced by angiotensin II. Each plays a major role in cardiac remodeling, regulating collagen turnover and fibrous tissue formation (particularly following a myocardial infarction), and their cardiovascular and adrenal production is activated through a neurohormonal reaction during heart failure [17]. Although the mechanisms for aldosterone-induced damage are only beginning to be fully recognized, based on the most current findings, the following sections attempt to summarize its effects in individual physiologic systems.

2.1. Cardiovascular disease

Cardiovascular disease is associated with a prothrombotic state, and elevated plasminogen activator inhibitor type 1 (PAI-1) is a risk factor for serious cardiovascular events. [18] Aldosterone may contribute to prothrombotic conditions by increasing PAI-1. Brown et al. [19] noted that PAI-1 antigen concentrations correlated with serum aldosterone levels in salt-depleted normotensive subjects even in the presence of an ACE inhibitor. In a recent study, [20] PAI-1 and aldosterone levels also were correlated in hypertensive patients at baseline and during treatment with hydrochlorothiazide. Treatment with spironolactone, a nonselective aldosterone blocker (i.e., also has progestational and antiandrogenic effects), abolished this correlation, implicating mineralocorticoid receptor activation in the regulation of PAI-1 expression [20].

2.2. Myocardial fibrosis in animal models

Myocardial fibrosis and remodeling are characteristic of heart failure and left-ventricular hypertrophy (LVH), and there is good evidence that aldosterone may be implicated. In animal models of hypertension and hyperaldosteronism, myocardial fibrosis was observed in the hypertrophied left ventricle as well as in the nonhypertrophied right ventricle of rats [21,22]. Aldosterone, when administered with a high-
sodium diet, also produced fibrosis in both left and right rat atria [23]. Spironolactone prevented myocardial fibrosis in both ventricles, irrespective of the development of hypertension or LVH [21]. Aldosterone elicits a dose-dependent increase in cardiac fibroblast collagen synthesis in the presence of a high-salt diet that is thought to contribute to these profibrotic actions [21]. The effect is not observed in the presence of a low-salt diet, underscoring the importance of the balance of salt with mineralocorticoids in this pathology [24].

Aldosterone-induced fibrosis is associated with vascular injury. In a rabbit model of vascular injury, aldosterone increased neointimal thickening in the aorta and iliac artery that was inhibited by treatment with spironolactone [25]. Furthermore, in stroke-prone spontaneously hypertensive rats (SHRSP), aldosterone infusion augmented proteinuria and increased the incidence of thrombotic and proliferative lesions in the arterioles and glomeruli [26,27]. Spironolactone protected against proteinuria and the vascular lesions without affecting systolic blood pressure or fluid and electrolyte balance. Spironolactone also protected against cerebrovascular lesions and reduced symptomatic evidence of stroke in these animals [26].

### 2.3. Myocardial fibrosis in human studies

Observations in patients with heart failure and hypertension support these experimental findings. In patients with heart failure, increased myocardial expression of aldosterone synthase (CYP11B2) was associated with greater myocardial fibrosis and severity of LVH, suggesting a role for locally synthesized aldosterone [28]. Large clinical trials involving patients with left-ventricular dysfunction receiving ACE inhibitors have found that aldosterone production is correlated with mortality [29,30]. In a study of the effects of circulating aldosterone on cardiac structural and functional changes, the response to salt-induced aldosterone suppression was compared in patients with mild essential hypertension and normotensive adults [31]. In the hypertensive patients, suppression was attenuated and the serum aldosterone concentrations correlated with left-ventricular mass on echocardiography. This effect was independent of 24-h ambulatory blood pressure. [31] It has been suggested that there is a genetic predisposition for the development of aldosteronism given the right environmental stimuli (e.g., increased sodium intake) [32,33].

### 2.4. Endothelial dysfunction and arterial compliance

Several mechanisms have been proposed to explain the negative effects of aldosterone on vascular smooth muscle cells (VSMC), endothelial cells, and vascular matrix in hypertensive individuals. Although these proposed mechanisms have merit, one in particular has gained widespread acceptance. Kornel [10] proposed that glucocorticoids and mineralocorticoids, mediated through receptors, control the contractility of VSMC through increasing transport capacities for Na⁺ and Ca²⁺. The reduction of endothelium-dependent vasodilation by acetylcholine, through aldosterone inhibition of nitric oxide release, has been proposed as the mechanism by which endothelial dysfunction occurs [34]. The untoward effects of aldosterone on the vascular matrix have been established to be caused by a disproportionate increase in collagen content or fibrosis due to long-term elevations in circulating mineralocorticoids [34].

Aldosterone-induced profibrotic effects lead to reduced arterial compliance and impaired baroreflex activity and, consequently, to impaired autonomic control of cardiac and vascular function in patients with hypertension and heart failure [34]. In heart failure patients, chronically treated with captopril, furosemide, digoxin, and aspirin, plasma aldosterone concentrations correlated inversely with arterial compliance in the aorta and its major proximal branches [35]. A similar correlation was observed in patients with primary aldosteronism. The reduced arterial compliance was further correlated with baroreflex function [36].

Evidence of endothelial dysfunction was seen in isolated renal artery segments and aortic rings from rats exposed to a model of excessive mineralocorticoid receptor stimulation. In animals treated with spironolactone, normal endothelial function was restored [37,38]. Similarly, in rabbits fed a proatherosclerotic diet, treatment with spironolactone normalized superoxide formation and improved endothelial function [39]. In healthy male volunteers, aldosterone has been shown to cause acute endothelial dysfunction [40].

### 2.5. Sodium resorption

In healthy individuals, the actions of aldosterone on sodium reabsorption are generally transient [41]. However, in the presence of hypertension or heart failure, aldosterone may cause sodium retention continuously, resulting in edema and the loss of potassium and magnesium, which can contribute to ventricular arrhythmias. Aldosterone also potentiates catecholamine action by blocking norepinephrine uptake by the myocardium [42]. The resulting sympathetic activation may contribute to myocardial dysfunction and tachyarrhythmias [41].

### 2.6. End-stage renal disease

Finally, aldosterone plays an important role in progressive renal disease through hemodynamic effects and direct cellular actions [43]. In rats, subtotal renal ablation produced adrenal hypertrophy and increased aldosterone levels more than 10-fold relative to sham-operated controls [44]. These effects were accompanied by greater degrees of proteinuria and glomerulosclerosis than seen with the sham-operated controls. The elevated aldosterone levels and pathologic changes were blocked by ACE inhibitors, but infusion of aldosterone in the presence of ACE blockade restored proteinuria and glomerulosclerosis to levels seen in
the untreated renal-ablation group. As noted previously, aldosterone infusion produced proteinuria and severe renal injury in the salt-replete SHRSP and reversed the protective action of captopril in this model [26,27].

3. Aldosterone mediates angiotensin II-induced damage

3.1. Cardiovascular damage

The role of angiotensin II in cardiovascular disease is well documented and is considered to be a major mediator of cardiovascular damage. Recently, experimental and clinical research has focused on the concomitant role of aldosterone. In addition to the independent hypertensive actions of aldosterone, evidence suggests that aldosterone mediates and exacerbates angiotensin II-induced cardiovascular damage. Aldosterone has been shown to induce upregulation of angiotensin II receptors in VSMC in a time- and concentration-dependent manner and increase angiotensin II-mediated signal transduction while preventing angiotensin II-induced receptor downregulation and desensitization [45]. The effect of aldosterone on the number of angiotensin II receptors was attenuated by spironolactone, suggesting that this effect was mediated by mineralocorticoid receptors in the VSMC. Preincubation of aortic rings with aldosterone leads to near doubling of angiotensin II-induced contractile responses, whereas KCl-induced contraction is unaffected [46]. It also has been suggested that subtle changes in glucocorticoid metabolism may play a role in increasing aldosterone production via ACTH-induced adrenocortical hyperplasia [32].

3.2. Renal damage

Using saline-drinking SHRSP, Rocha et al. [27] demonstrated that angiotensin II per se was not sufficient to cause vascular and glomerular damage, unless aldosterone also was present. When aldosterone was infused in the presence of captopril, the nephroprotective effect of captopril was abolished. These effects of aldosterone in promoting renal damage were independent of changes in blood pressure, but were highly dependent on the presence of salt.

Two further studies also support the role of aldosterone in mediating angiotensin II-induced renal injury. In a preliminary study, selective aldosterone blockade with eplerenone prevented the development of proteinuria and renal lesions but not severe hypertension in SHRSP [47]. In the follow-up study, angiotensin II infusion increased aldosterone levels and reversed the protective effects of captopril on proteinuria and renal damage. However, selective aldosterone blockade, given in conjunction with captopril and angiotensin II infusion, markedly attenuated proteinuria and renal damage [47]. In adrenalectomized SHRSP, infusion of angiotensin II was no longer able to increase plasma aldosterone levels or cause proteinuria or renal lesions; administration of aldosterone to adrenalectomized rats was followed by the reappearance of proteinuria and renal damage [48]. Together, these studies suggest that aldosterone, via activation of mineralocorticoid receptors, plays an important role in mediating angiotensin II-induced renal injury in the SHRSP model.

Further evidence of the role of aldosterone in mediating myocardial and renal vascular damage was demonstrated in a rat model that combined elevated blood pressure, moderately high salt intake, RAAS activation with angiotensin II, and blunted nitric oxide production [49]. The administration of the nitric oxide synthase inhibitor Nω-nitro-L-arginine methyl ester in conjunction with a short-term angiotensin II infusion to rats drinking 1% NaCl caused hypertension, cardiac hypertrophy, severe biventricular myocardial necrosis, proteinuria, and fibrinoid necrosis of renal and cardiac vessels. Adrenalectomy, salt depletion, or selective aldosterone blockade markedly reduced cardiac and renal damage in this model without significantly affecting hypertension, whereas aldosterone infusion in adrenalectomized, glucocorticoid-replaced animals restored cardiac and renal damage. Both aldosterone and 1% NaCl provided insights in this model, since selective aldosterone blockade with eplerenone or a low-salt diet was effective in preventing cardiac damage [50]. In addition, Rocha et al. recently demonstrated that blocking aldosterone, either by adrenalectomy or by treatment with eplerenone, prevented myocardial damage produced by high-salt intake and elevated angiotensin II [51].

Aldosterone blockade also was evaluated in rats that were double transgenic for the human renin and angiotensinogen genes [52]. In this model, angiotensin II production led to the development of hypertension, cardiac hypertrophy, vasculopathy, and fibrosis, with 50% mortality by 7 weeks. In these transgenic animals, plasma aldosterone levels were increased by about 20-fold. Treatment with spironolactone prevented death and vasculopathy and reversed cardiac hypertrophy independent of blood pressure lowering. Nonselective aldosterone blockade with spironolactone prevented angiotensin II-mediated upregulation of basic fibroblast growth factor, activation of the transcription factors AP-1 and NF-κB, and ameliorated extracellular matrix protein production in the heart. These findings strongly suggest that aldosterone activation of mineralocorticoid receptors is necessary for cardiac damage induced by angiotensin II [52].

4. Aldosterone blockers

4.1. Nonselective aldosterone blockade with spironolactone

The role of aldosterone in the pathogenesis of cardiovascular disease in humans was firmly established by the results of the Randomized Aldactone Evaluation Study (RALES) [53]. The RALES enrolled 1663 patients with
severe heart failure (New York Heart Association [NYHA] class III or IV) and a left-ventricular ejection fraction < 35% who were being treated with an ACE inhibitor, a loop diuretic, and in most cases, digoxin. Patients were randomly assigned to additionally receive either spironolactone (25 mg daily) or placebo. RALES was terminated early because spironolactone showed a clear survival benefit on an interim analysis. After a mean follow-up of 24 months, spironolactone reduced all-cause mortality by 30% relative to placebo ($P<0.001$). A survival benefit was seen in all subgroup analyses. Other benefits of spironolactone therapy included a 35% lower risk of hospitalization for worsening heart failure as well as significant symptomatic improvement in terms of NYHA functional class (both $P<0.001$) [53].

The therapeutic role of spironolactone in treating patients with mineralocorticoid hypertension has been well established. It is also indicated for chronic heart failure and ascites. In heart failure patients, spironolactone suppresses vascular ACE beyond traditional ACE inhibitor therapy in combination with a loop diuretic, an effect that was demonstrated in a study of 10 patients with NYHA II and III congestive heart failure (spironolactone dose 25–50 mg/day) [55].

As has been demonstrated by the work of Bauersachs et al. [54], the addition of spironolactone to ACE inhibition in rats with heart failure results in improvements in endothelial vasomotor dysfunction that can be attributed to the normalization of nitric oxide-mediated relaxation through the beneficial modulation of nitric oxide balance and superoxide anion formation. A randomized, placebo-controlled, double-blind study [55] of 10 patients with NYHA classes II–III chronic heart failure, who were receiving standard diuretic/ACE inhibitor therapy, further substantiated the results demonstrated by animal models and the RALES. The results of this study, verified by significantly increased forearm blood flow response to acetylcholine (vs. placebo, $P<0.001$) showed that the addition of spironolactone 50 mg/day for 1 month improved endothelial dysfunction (i.e., improved acetylcholine-mediated endothelium-dependent vasodilation), increased nitric oxide bioactivity, and inhibited vascular angiotensin I and II conversion in patients with heart failure [55].

The observation that aldosterone contributes to ventricular arrhythmia in heart failure patients was supported by the results of a study published by Ramires et al. [56]. In patients with systolic dysfunction and NYHA class III heart failure secondary to dilated or ischemic cardiomyopathy, spironolactone added to standard medical management with an ACE inhibitor, furosemide, and digoxin significantly reduced ventricular premature complexes and episodes of nonsustained ventricular tachycardia [56].

In patients with raised aldosterone/renin ratios, who failed to suppress plasma aldosterone with salt loading and fludrocortisone, the use of spironolactone ($n=28$) was evaluated for a mean period of 12.9 months [57]. As is widely accepted, raised ratios are indicative of nonsuppression of plasma aldosterone, which suggests primary aldosteronism. Although at baseline, patients were taking a mean of 2.1 antihypertensive agents, 57% had DBP>90 mm Hg and 39% had SBP>160 mm Hg. Of the 27 patients who completed therapy, 96% achieved a DBP<90 mm Hg, while 78% achieved a SBP<160 mm Hg. The mean number of antihypertensive agents used in the study declined to 0.7 with the addition of spironolactone. In fact, 48% of patients actually were treated with spironolactone monotherapy and achieved a BP of $\leq 140/90$ mm Hg. Lim et al. [57] do note, however, that the use of spironolactone in patients with raised aldosterone/renin ratios should be avoided unless the presence of adrenal adenomas is excluded.

4.2. Selective aldosterone blockade with eplerenone

Eplerenone is the first selective aldosterone blocker with specificity for the mineralocorticoid receptor. The efficacy and safety of eplerenone as monotherapy or in combination regimens for the treatment of hypertension has been evaluated in a number of large randomized, double-blind, controlled trials compared either with placebo or active treatment [58–67].

As monotherapy, once-daily eplerenone 25–200 mg produced dose-dependent reductions in systolic and diastolic blood pressure compared with placebo in patients with essential hypertension [67]. Comparative trials with other antihypertensive agents have found eplerenone to be at least as effective as other agents in a wide range of patient populations. Eplerenone 50–200 mg once daily was as similarly effective as enalapril 10–40 mg once daily in patients with essential hypertension [58] and asamlodipine 2.5–10 mg once daily in older patients with systolic hypertension [63]. In patients with low-renin hypertension, eplerenone 100–200 mg once daily was more effective than losartan 50–100 mg once daily [60]. Similar results were obtained in another study in which eplerenone 50–200 mg once daily was at least as effective as losartan 50–100 mg once daily with superior efficacy among African-American and low-renin subgroups [61]. Combination trials have demonstrated further blood pressure lowering when eplerenone is used as add-on therapy or when a second agent is added to first-line eplerenone [64–66]. Agents that have been successfully used in combination with eplerenone include ARBs, ACE inhibitors, calcium channel blockers, β-blockers, and diuretics.

Several studies also have demonstrated that eplerenone provides end-organ protection. In patients with hypertension and left-ventricular hypertrophy, eplerenone 100 mg once daily produced reductions in left-ventricular mass similar to that produced by enalapril 40 mg once daily [59]. The concomitant use of both agents produced an additional reduction in left-ventricular mass. In patients with hypertension, eplerenone 50–200 mg reduces proteinuria as measured by the urinary albumin/creatinine ratio (UACR) [58,61–63]. In one study, eplerenone (50–200 mg once
daily) decreased UACR by 21.6% in patients with essential hypertension compared with a decrease of 18.2% for losartan 50–100 mg daily and with an increase of 5.2% for those receiving placebo [61]. The difference between each drug and placebo was statistically significant, but there was no significant difference between active treatments. In elderly patients with systolic hypertension, eplerenone 50–200 mg once daily reduced UACR significantly more than did amlodipine 2.5–10 mg/day (52% vs. 10%, \( P=0.04 \)) [63]. Two studies, including one in patients with diabetic nephropathy and hypertension, also have shown eplerenone to produce significantly greater decreases in UACR than enalapril [58,62]. In the study in diabetic patients, eplerenone 50–200 mg once daily reduced UACR to a greater extent than did enalapril 10–40 mg once daily (62% vs. 45%, \( P=0.015 \)) [62]. The combination of eplerenone plus enalapril produced a further significant reduction in UACR (72%) compared with either drug alone (\( P=0.018 \) vs. eplerenone and \( P<0.001 \) vs. enalapril) [62].

Eplerenone also has been shown to decrease mortality and morbidity in patients with left-ventricular dysfunction and heart failure after an acute myocardial infarction [68]. In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival (EPHESUS) study, 6642 patients on optimized standard therapy (including ACE inhibitor or ARB, \( \beta \)-blocker, aspirin, diuretics) were randomized to receive eplerenone 25–50 mg once daily or placebo. Patients receiving eplerenone achieved statistically significant reductions in the relative risks for death (15%), cardiovascular death (17%), and death for cardiovascular cause or hospitalization for cardiovascular events (13%) compared with placebo-treated patients. The decreased risk of death was due in large part to a 21% decreased risk of sudden death from cardiovascular causes. The benefits of treatment were consistently seen across a wide range of predefined subgroups of patients [68].

4.3. Safety of aldosterone blockade

With regard to the adverse event profile from the RALES, gynecomastia and breast pain were reported to have occurred in 10% of men who received spironolactone as compared to 1% with placebo. As a result, 10 men discontinued treatment with spironolactone. Although median creatinine and potassium concentrations did not change in the placebo group, they did increase by 0.05–0.10 mg/dl and 0.3 mmol, respectively, with spironolactone. Fourteen patients (2%) in the spironolactone group experienced serious hyperkalemia [53]. Breast tenderness was also reported to have occurred in another study of patients being treated with spironolactone. Lim et al. reported that three patients complained of breast tenderness but continued treatment with spironolactone [57].

The most significant adverse event reported with the use of eplerenone to date has been hyperkalemia [61–68]. In the study by Pitt et al. [68], the occurrence of severe hyperkalemia was 5.5%, although the authors note that the risk of severe hyperkalemia significantly increased in patients with decreased creatinine clearance at baseline (<50 ml/min). The majority of other reports of potassium elevation in previously identified studies occurred with concomitant medication, including verapamil and chlorthalidone (one patient each) [66], \( \beta \)-blockers and calcium channel blockers [65], ACEs and ARBs [64], and enalapril [62], making it difficult to draw a direct causal relationship. Other reported adverse events with eplerenone, considered to be possibly treatment related, include coughing (3.1%) [59], headache (11.6–16.4%) [63,67], and nonspecific pain (6%) [63,67].

5. Conclusion

Aldosterone/salt imbalance is detrimental to patients with hypertension and heart failure and can lead to progressive tissue damage in the heart, vasculature, and kidneys. Moreover, published evidence suggests that aldosterone exacerbates the tissue-damaging effects of angiotensin II. Although ACE inhibitors and ARBs reduce plasma aldosterone initially, aldosterone levels rebound, or ‘escape,’ during long-term therapy. As a result, aldosterone again becomes available to continue causing progressive cardiovascular tissue damage. Therefore, the blockade of aldosterone, the final product of the RAAS, reduces the risk of progressive target organ damage in patients with hypertension and heart failure. While spironolactone will continue to have its place in therapy, the evidence suggests that selective aldosterone blockade is preferential when long-term, combination therapy is required in order to minimize adverse effects.

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