The present and future role of aldosterone blockade

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Abstract

Angiotensin-converting enzyme (ACE) inhibitor therapy only partially suppresses aldosterone production and 'aldosterone escape' occurs in up to 40% of patients with congestive heart failure (CHF). The RALES and EPHESUS studies show clearly that even in the presence of ACE inhibitor therapy, aldosterone contributes to mortality in CHF. There are many mechanisms for this. Firstly, aldosterone contributes to endothelial dysfunction and attenuates endothelium-dependent vasodilatation, at least partly by reducing nitric oxide bioavailability. Aldosterone also promotes myocardial fibrosis and cardiac remodelling by enhancing collagen synthesis, resulting in increased myocardial stiffness and increased left ventricular mass. These mechanisms mediated by aldosterone contribute to increased risk of ventricular arrhythmias and sudden cardiac death. Inhibition of aldosterone's effect on mineralocorticoid receptors should now be considered standard therapy in populations of CHF patients. Aldosterone blockers also reduce the blood pressure in all types of hypertensive patients and may have an additional role as add-on therapy in hypertension, especially to lessen target organ damage.

Key words: aldosterone, congestive heart failure, spironolactone, eplerenone, hypertension.

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Introduction

Plasma aldosterone levels can be up to 20-fold higher in untreated patients with chronic heart failure (CHF) compared to normal controls.[1]

The advent of angiotensin-converting enzyme (ACE) inhibitor therapy for congestive heart failure therefore led initially to the feeling that any adverse effects of aldosterone would be ameliorated by ACE inhibitors. Increasingly, however, it is becoming evident that following an acute fall in aldosterone in response to administration of an ACE inhibitor, the level of aldosterone rises again, and indeed, returns to baseline in some patients, a phenomenon known as 'aldosterone escape'.

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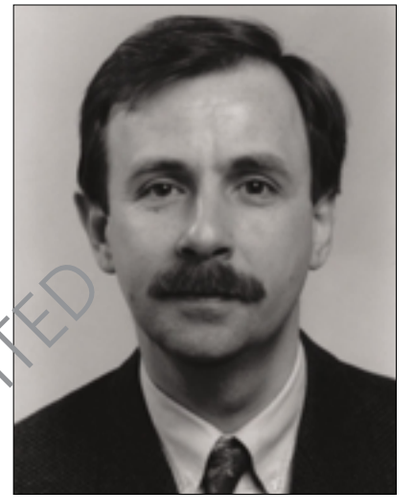

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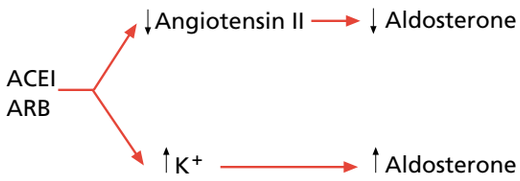
Aldosterone concentrations greater than 144 pg/ml have been reported in up to 40% of patients with symptomatic CHF[2] despite use of an ACE inhibitor. In one study, 14 patients with CHF showed only a mean fall of 20% in plasma aldosterone levels after six weeks' treatment with captopril.[3] Aldosterone levels have also been shown to increase progressively in patients given an ACE inhibitor following acute myocardial infarction[4] or for essential hypertension.[5]

Even when an ACE inhibitor is given in combination with an angiotensin II receptor antagonist, aldosterone levels remain uncontrolled. In RESOLVD (Randomised Evaluation of Strategies for Left Ventricular Dysfunction pilot trial),[6] patients with CHF given both enalapril and candesartan had a significant fall in aldosterone levels at 17 weeks, but mean aldosterone level had returned to baseline by 43 weeks even with maximum doses of both agents. Moreover, the extent to which aldosterone escape occurs is highly variable. Among CHF patients treated with captopril for six weeks, aldosterone levels ranged from 56 pmol/L to 1,568 pmol/L.[3]

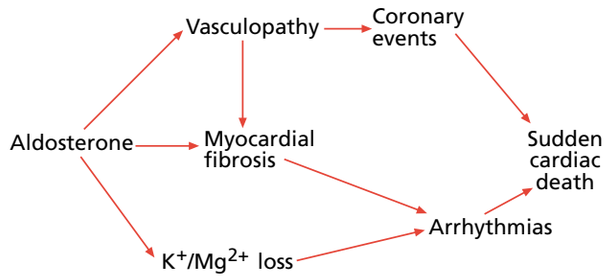
The precise mechanism by which aldosterone levels rise during ACE therapy is unclear but levels of angiotensin II (a potent stimulus for aldosterone production in the adrenal glands) are

Figure 1. Mechanisms of aldosterone escape with ACE inhibitor or angiotensin II receptor blocker therapy



Key: ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; K^+ = potassium

Figure 2. Mechanisms whereby aldosterone promotes sudden cardiac deaths



Key: K^+ = potassium; Mg^{2+} = magnesium

known to increase over time in patients receiving an ACE inhibitor.[2] Since aldosterone escape has been reported in patients without angiotensin II reactivation,[7] this cannot be the only reason. Notably, ACE inhibitors increase potassium; this is a powerful secretagogue for aldosterone and thus may be a major reason for aldosterone escape (figure 1). What this means is that it is impossible to get rid of aldosterone by blocking angiotensin II because blocking angiotensin II is inevitably accompanied by a potassium increase which then increases aldosterone. Additionally, there is evidence that aldosterone escape might even promote release of angiotensin II, via a positive feedback loop that stimulates ACE in the vasculature.[8]

It is difficult to tease out the relationship between aldosterone levels and clinical outcomes because all neurohormones tend to be elevated together. Nevertheless, in a neurohormonal substudy of the SAVE (Survival And Ventricular Enlargement) trial, mean aldosterone levels were lower among patients who remained free of cardiovascular events over two years compared to those who died, developed severe heart failure or experienced a further myocardial infarction.[9] Multivariate analysis showed that aldosterone levels were significantly correlated to risk of a cardiovascular event ($p<0.001$). It has also been reported that aldosterone escape is associated with reduced exercise capacity in patients with CHF,[10] and decreased compliance of the aorta and its major branches,[11] despite administration of ACE inhibitor therapy.

Historically, aldosterone was considered a hormone released from the adrenal cortex that exerts its effects solely through mineralocorticoid receptors to cause sodium retention and potassium loss. More recently, however, a much wider role for aldosterone has been recognised.

Traditional effects of aldosterone

In congestive heart failure, elevation of aldosterone levels does lead to excessive sodium retention with expansion of the extracellular volume, and potassium loss. By contributing to electrolyte imbalances, particularly hypokalaemia and hypomagnesaemia, aldosterone increases the sensitivity of cardiac tissue to arrhythmias with consequent increased risk of sudden death.[12,13]

Newly discovered effects of aldosterone in LVH/CHF

An intense research effort has revealed a host of new pathophysiologic mechanisms associated with aldosterone that could be expected to contribute to the progression of congestive heart failure and sudden cardiovascular death.

Endothelial dysfunction

The endothelium plays a critical role in regulation of vascular tone, platelet aggregation, adhesion of leukoctyes and the thrombotic cascade. Endothelial dysfunction is predictive of subsequent cardiovascular events (see figure 2).[14] A growing body of evidence suggests that aldosterone may contribute to endothelial dysfunction.

In normal volunteers, we showed that an infusion of aldosterone which does not alter blood pressure (BP) does, in fact, produce endothelial dysfunction.[15] This could be called a demonstration of aldosterone-induced vasculopathy.

One mechanism by which aldosterone may induce endothelial dysfunction is through reduction of nitric oxide (NO) bioavailability. Aldosterone has been shown to reduce NO bioactivity in an *in vitro* study of rat smooth muscle.[16] At the preclinical level, a study in rats with experimental CHF has demonstrated that acetylcholine-induced NO-dependent vasodilatation in aortic rings was significantly lower than in control animals.[17] Treatment with the ACE inhibitor trandolapril improved NO-mediated vasodilatation; addition of spironolactone entirely restored relaxation to the level of controls.

The main demonstration of aldosterone-induced vasculopathy in man came from our study of patients receiving ACE inhibitor therapy which showed that aldosterone blockade with spironolactone increases NO bioactivity compared to placebo.[8] In this trial, infusion of the NO synthase inhibitor L-NMMA resulted in significantly greater vasoconstriction in spironolactone-treated patients compared to those in the placebo group, indicating that

basal NO bioactivity is improved by aldosterone blockade. In the same study, spironolactone was also associated with a significant increase in forearm blood flow in response to acetylcholine, but had no effect on blood flow in response to sodium nitroprusside, an endothelium-independent vasodilator. These are exactly the findings one expects to see when a treatment (aldosterone blockade) improves endothelial function by increasing vascular NO bioactivity.

In animal models, aldosterone-induced vasculopathy has an inflammatory element i.e. more like an aldosterone-induced vasculitis. Aldosterone increases cytokine activity such as osteopontin, cyclo-oxygenase-2 and macrophage chemo-attractants.[18] There is also early evidence from a rabbit model of atherosclerosis that the selective aldosterone blocker eplerenone reduces the generation of oxygen free radicals.[19] This may be why it increases NO bioactivity, since oxygen free radicals, such as the superoxide anion, normally serve to inactivate NO. There is, as yet, no firm evidence of aldosterone being pro-inflammatory in man.

Myocardial fibrosis and cardiac remodelling

Aldosterone also contributes to the progression of heart failure by promoting perivascular and interstitial myocardial fibrosis (figure 2). This reduces the flexibility of myocardial tissue such that it increases the likelihood of diastolic dysfunction. Structural remodelling of the interstitial collagen matrix, producing patchy myocardial fibrosis, would also be expected to result in electrical inhomogeneity and be an arrhythmogenic influence. Such arrhythmogenicity may be further potentiated by the potassium and magnesium depletion induced by aldosterone. Illustrative of this is that ventricular ectopy on 24-hour ambulatory electrocardiography falls when aldosterone blockade is administered.

The pro-fibrotic effects of aldosterone have been demonstrated at a cellular level, preclinically, and in several clinical settings. *In vitro* experiments have reported that administration of aldosterone to cardiac fibroblasts significantly enhances collagen synthesis,[20] a finding that has been borne out in rat models.[21] At the preclinical level, histological examination of tissue from many rat models clearly demonstrate that aldosterone promotes cardiac and perivascular fibrosis and that this was markedly reduced in rats treated with the selective aldosterone blocker eplerenone.[22]

The first proof that aldosterone promotes myocardial fibrosis in man came when it was shown that spironolactone reduced plasma level of PIIINP in heart failure.[23] PIIINP (procollagen type III amino terminal peptide) is an indirect marker of myocardial collagen turnover in man. A similar effect of spironolactone in reducing PIIINP was seen in RALES (Randomised Aldactone Evaluation Study).[24]

The adverse effects of aldosterone on endothelial function could account partially for its pro-fibrotic action. Endothelial dysfunction could lead to microthrombi, tissue micro-infarction and injury, which repairs itself as fibrosis. Whether aldosterone produces fibrosis directly, or whether it acts via a vasculopathy-induced injury of tissues, is an intriguing and, as yet, unanswered question. Time sequence studies suggest the latter.

Decreased baroreceptor sensitivity

Another potentially harmful effect of aldosterone is its ability to blunt the baroreflex response. Perfusing the carotid sinus directly with aldosterone has been shown to reduce maximum baroreceptor discharge,[25] while, in dogs, chronic administration of aldosterone elevates the threshold for baroreflex activation and decreased peak discharge rate.[26] The first demonstration of such an effect in man came when it was shown that aldosterone inhibits baroreflex sensitivity in healthy volunteers.[27]

The clinical evidence for aldosterone blockade

In heart failure

The wealth of data indicating a pathogenic role of aldosterone in CHF has now been validated by two major prospective trials. In the RALES study, patients with severe CHF (New York Heart Association class III – IV) were randomised to receive spironolactone or placebo.[28] The trial was discontinued early because after a mean follow-up of 24 months, the relative risk (RR) of death was 0.70 (95% CI 0.6–0.82, p<0.001) among patients receiving spironolactone, i.e. a 30% reduction in risk of death with aldosterone blockade. This reduction in mortality was accounted for by both a significant fall in deaths due to progression of heart failure (RR 0.64, 95% CI 0.51–0.80, p<0.001) and to sudden cardiovascular death (RR 0.71, 95% CI 0.54–0.95, p=0.02). However, gynecomastia or breast pain occurred more often in men receiving spironolactone (10%) than placebo (1%, p<0.001) due to the drug's affinity for androgen receptors. The dose of spironolactone used in the RALES study is assumed to have no apparent diuretic effect, as judged by a substudy where the sodium retention score was measured.

The reduction in sudden cardiovascular death seen in RALES could be due to many possible mechanisms, ranging from aldosterone worsening endothelial function and so increasing acute coronary events, to it having arrhythmogenic effects by promoting myocardial fibrosis and depleting potassium and magnesium.[29]

More recently, EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) has evaluated use of the selective aldosterone blocker eplerenone in 6,632 patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure.[30] Severity of CHF was less pronounced than in RALES, with mean left ventricular ejection fraction of 33% compared to 25% in the RALES population. Pharmacotherapy also differed: most notably, 75% of patients received beta blockers versus approximately 10% of those in RALES. During a mean follow-up of 16 months, patients randomised to eplerenone had a 15% reduction in mortality compared to patients on placebo; risk of hospitalisation for heart failure also fell by 15%. Similar to the RALES study, there was a large fall (21% fall) in sudden cardiac death. This indicates that the myocardial protective effect of aldosterone blockade is maintained even in the presence of optimal therapy and in patients close to the acute phase of myocardial infarction. Incidence of gynecomastia and impotence did not differ between the eplerenone and placebo groups, due to the low affinity of eplerenone for androgen receptors.

Key messages

- Aldosterone causes a vasculopathy characterised by endothelial dysfunction
- Aldosterone also promotes myocardial fibrosis
- Two mortality trials show that aldosterone blockade reduces mortality in heart failure
- Aldosterone blockade also reduces BP in hypertension and protects target organs e.g. LVH and microalbuminuria

In hypertension

CHF is not the only disease where aldosterone blockade produces benefit. Eplerenone also has a role in essential hypertension where a useful antihypertensive effect has been seen in all types of essential hypertension, e.g. low-renin, elderly hypertensives, and high-renin hypertension. It appears to work equally irrespective of renin levels and this may be because in high-renin patients, it blocks the elevated neurohormone, aldosterone, whereas in low-renin hypertension, eplerenone has a subtle diuretic effect which reduces BP.

Interestingly, hypertensionologists seem a little divided on whether the first antihypertensive should be a thiazide or an ACE inhibitor. Intriguingly, eplerenone shares the effect of each of them in that it probably has both neurohormone blocking effects and mild diuretic effects. Nevertheless, this does not mean that eplerenone is likely to become the antihypertensive of first choice. It is likely that it will become a useful add-on antihypertensive therapy. This is especially so since it appears to have an ability to protect target organs, i.e. it reduces left ventricular hypertrophy (LVH) and it reduces microalbuminuria in diabetics. In each of the above cases, its effects on protecting target organs occur over and above ACE inhibitor therapy.

Conclusion

In addition to the traditional effects of aldosterone on fluid and sodium retention, a range of newly-recognised effects of aldosterone contribute to its detrimental effect on cardiovascular events, in particular on sudden death. Apart from the well-recognised effect of potassium and magnesium depletion, preclinical and clinical studies have shown that aldosterone promotes endothelial function and cardiac fibrosis, actions which would be expected to play an important part in promoting cardiac events.

We now have convincing clinical evidence that these effects translate to a significantly harmful effect of aldosterone in patients with CHF. Large-scale prospective studies have reported a marked and significant benefit from use of an aldosterone blocker in terms of overall mortality, cardiovascular mortality (particularly sudden death) and hospitalisation. In one trial, these improvements were seen even when patients were already taking an ACE inhibitor and a beta blocker in addition to aldosterone blockade. Optimal therapy for patients with congestive heart failure should now routinely include an aldosterone blocker since two major trials clearly documented a highly significant reduction in total mortality by doing so.

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