Aldosterone: an important mediator of cardiac remodelling in heart failure

ALLAN D STRUTHERS

Abstract

Aldosterone is intimately linked to the pathophysiology of heart failure, and high levels of aldosterone are associated with worse prognosis. Many non-renal effects of aldosterone contribute to the congestive heart failure syndrome, including endothelial dysfunction, reactive myocardial fibrosis and cardiac remodelling. The precise mechanism by which aldosterone stimulates myocardial collagen accumulation and fibrosis is not yet fully understood. It may largely occur secondary to aldosterone-related endothelial dysfunction and inflammation, since endothelial dysfunction can lead to micro-thrombus formation and tissue micro-infarction, which repairs itself by fibrosis. Other contributory effects may include a direct impact of aldosterone on the collagen synthesis pathway.

In the RALES study, spironolactone in conjunction with an angiotensin-converting enzyme (ACE) inhibitor was found to reduce mortality in chronic moderate-to-severe heart failure; the EPHESUS study more recently reported significant reductions in death and hospitalisation when eplerenone was added to ACE inhibitor and beta blocker therapy in patients with clinical evidence of heart failure following acute myocardial infarction. Clinicians should now consider routinely adding an aldosterone receptor antagonist to standard therapy of patients with left ventricular dysfunction and heart failure in order to reduce cardiac morbidity and mortality.

Key words: aldosterone, spironolactone, eplerenone, myocardial infarction, left ventricular function, endothelial function, heart failure, remodelling.

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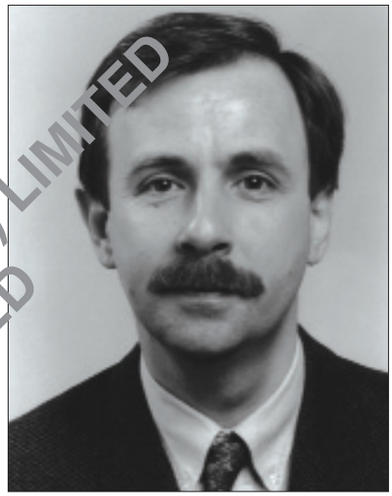

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Introduction

Aldosterone has a well-documented role in the pathophysiology of congestive heart failure (CHF), and high levels of aldosterone are associated with worse clinical outcomes[1] and reduced functional capacity[2] in patients with heart failure. Aldosterone was previously regarded solely as a hormone acting on sodium-potassium balance and widespread adoption of angiotensin-converting enzyme (ACE) inhibitor therapy was considered to obviate any detrimental effect of aldosterone. Recently it has become clear that aldosterone also exerts a myriad of other non-renal effects that may play a significant part in the pathogenesis of CHF syndrome. Several of these effects – most notably endothelial dysfunction, myocardial apoptosis and reactive myocardial fibrosis – contribute to cardiac remodelling with its associated adverse consequences. This article reviews the key preclinical and clinical evidence to date relating to these non-renal effects of aldosterone and considers possible implications for management of the heart failure patient.

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Endothelial dysfunction

Farquharson and Struthers were the first to show that aldosterone blockade improved endothelial function,[3] in a randomised, placebo-controlled crossover study in which spironolactone was administered to 10 heart failure patients receiving standard treatment with diuretics and ACE inhibitors. Endothelial function was assessed by bilateral forearm venous occlusion plethysmography, and spironolactone treatment was found to increase the forearm blood flow response to acetylcholine, by

approximately two-fold (177±29%), whereas blood flow responses with placebo were lower (95±20%, p<0.001). Subsequently, preclinical evidence confirmed this finding.[4] It is likely that aldosterone-related endothelial dysfunction is, at least in part, due to suppression of vascular nitric oxide (NO) bioavailability. An experimental model of CHF in the rat has shown that although ACE inhibitor monotherapy improved NO-mediated vasodilatation, the addition of aldosterone-blocking therapy restored vascular relaxation to control levels.[4] Clinically, the improvement in endothelial function due to aldosterone blockade has been shown to be associated with increased vascular NO bioactivity,[3] which may occur because aldosterone blockade reduces the generation of oxygen-free radicals which would normally inactivate vascular NO.[5] Recently information has accumulated to show that aldosterone causes coronary vascular dysfunction. In transgenic animals, overexpressing aldosterone synthase, the main abnormality found was coronary vascular dysfunction.[6]

There is also evidence that, at least in animals, aldosterone stimulates a vascular inflammatory response in the myocardium and other tissues, which in turn could induce endothelial dysfunction. An aldosterone-mediated increase in the activity of various inflammatory cytokines, including cyclo-oxygenase-2 and macrophage chemo-attractants, has been demonstrated in an animal model.[7]

The clinical significance of endothelial dysfunction is that it can lead to micro-thrombus formation and tissue micro-infarction, which repairs itself by fibrosis, and endothelial dysfunction-induced tissue injury is believed to play some part in the pro-fibrotic effect of aldosterone in myocardial tissue.

Apoptosis

It has been hypothesised that aldosterone may also cause cardiac injury directly, by stimulating myocyte apoptosis and thus promoting replacement fibrosis in the myocardium. A rat model of cardiac injury which resulted in hypertension, myocardial necrosis and renal damage was used to evaluate the role of aldosterone in mediating cardiovascular damage. Aldosterone blockade using eplerenone was found to reduce cardiac and renal injury markedly.[8] Further preclinical data revealed that high plasma concentrations of aldosterone (6 ng/mL) for several days could stimulate ventricular myocyte apoptosis, both *in vivo* and in primary cultures, to a similar extent to that observed with angiotensin II (AT-II) administration.[9] This apoptotic effect was inhibited by aldosterone blockade. Given these collective results, it is feasible that the acute rise in aldosterone levels following myocardial infarction (MI) may lead to aldosterone-induced cell death after infarction, and/or that the chronic aldosterone elevation seen in heart failure may lead to myocyte apoptosis. However, the extent to which this occurs and the mechanisms involved remain as yet unknown.

Myocardial fibrosis

A number of researchers have now confirmed that aldosterone stimulates myocardial fibrosis. *In vitro* experiments have demonstrated a concentration-dependent increase in collagen synthesis in adult rat cardiac fibroblasts after incubation with aldosterone administration – an effect that was blocked by spironolactone.[7] These findings have been confirmed by other preclinical data in animal models of arterial hypertension, in which aldosterone stimulated collagen accumulation within the interstitial and vascular compartments of the myocardium.[10-12] Aldosterone blockade was found to prevent myocardial fibrosis even at sub-hypotensive doses,[11,13] whereas ACE inhibition had no effect on fibrosis prevention.[11] Aldosterone infusion also induces the synthesis of several agents with known involvement in producing hypertrophy and fibrosis, including AT-1 receptor subtype-1.[12]

A rat model of MI has been used to assess the relative effect of aldosterone on reparative fibrosis, which is essential for infarct healing, versus reactive fibrosis, which is a maladaptive response.[14] Use of the aldosterone receptor antagonist eplerenone did not affect reparative collagen deposition in the infarcted myocardium, but it did have a protective effect against reactive fibrosis development in viable myocardial tissue. This protective effect was demonstrated at 28 days post-MI, when reactive fibrosis in viable myocardium was reduced in animals treated with eplerenone versus vehicle-treated animals. This suggests that aldosterone inhibition has no effect on retarding infarct healing, but that it actively prevents maladaptive response post-MI.[14]

The first clinical data to link aldosterone directly with myocardial fibrosis appeared when aldosterone blockade was found to decrease circulating levels of pro-collagen type-III amino-terminal peptide (PIIINP), a marker of ventricular collagen turnover, in a study of 31 patients with stable heart failure.[15] Serum PIIINP correlates closely with the amount of myocardial collagen type III on cardiac biopsy in heart failure patients,[16] and is higher in post-MI patients with a poor outcome.[17]

Cardiac remodelling

Aldosterone effects on myocardial fibrosis are not the only effect of aldosterone on left ventricular structure and function. Indeed, aldosterone clearly has effects on left ventricular (LV) remodelling and these are intimately linked with its effects on LV fibrosis. A reduction of PIIINP following aldosterone blockade is also associated with improvements in LV volume and mass.[18] In a group of 37 patients with non-ischaemic CHF who were randomised to aldosterone blockade versus placebo for four months, there was a significant positive correlation between the reduction in PIIINP and the reduction in both LV volume (p=0.045) and mass (p=0.0019). Spironolactone treatment significantly reduced PIIINP levels, as well as decreasing LV volume and mass, while there was no change in the placebo group.[18]

Data from the acute MI setting have supported the premise that suppression of plasma aldosterone may help to prevent left ventricular remodelling. The effect of aldosterone inhibition on post-MI collagen synthesis and left ventricular enlargement was investigated in a clinical study of 46 post-MI patients.[19] The patients were all on ACE inhibitor therapy and were randomised to receive aldosterone inhibition or placebo. After three, six and

Table 1. Summary of selected studies of aldosterone receptor antagonist therapy in patients with post-MI heart failure, chronic heart failure, or following acute MI without heart failure

Study	Population	Design	Active therapy	Standard therapy	End points	Mean follow-up	Results (active therapy group)
EPHESUS[25]	n=6,632 Post-MI LVEF ≤ 40% Symptoms of HF	Multicentre, international, randomised, double-blind, placebo-controlled	Eplerenone (25–50 mg/day) within 3–14 days of MI	ACEI 86.5% BB 75%	1° death from any cause 1° cardiac death or first hospitalisation for HF, AMI, stroke or ventricular arrhythmia	16 months	15%↓ all-cause mortality 17%↓ CV mortality 21%↓ sudden CV mortality
RALES[26]	n=1,663 NYHA class III or IV HF LVEF ≤ 35%	Multicentre, international, randomised, double-blind, placebo-controlled	Spironolactone (25 mg/day)	ACEI 94.5% BB 10.5%	1° death from any cause 2° cardiac death, cardiac hospitalisation, change in HF class	24 months	30%↓ all-cause mortality 35%↓ hospitalisation for HF Improvement in HF symptoms
Di Pasquale *et al.*, 2001[23]	n=187 AMI	Randomised, double-blind, placebo-controlled	Captopril plus canreonate (25 mg/day) *vs.* captopril plus placebo	ACEI~65% BB 35%	General monitoring of haemodynamic parameters, vital signs, laboratory measurements, coronary angiogram	90 days	Improved diastolic and systolic LV parameters Due to decreased collagen production?
Cicoira *et al.*, 2002[24]	n=106 Stable CHF diagnosed LVEF ≤ 45%	Randomised, double-blind, placebo-controlled	Spironolactone (12.5–50 mg/day)	ACEI 62% BB 69%	Echocardiography parameters Cardiopulmonary exercise testing	12 months	Improved diastolic and systolic LV parameters Improved exercise tolerance (50 mg/day)

Key: ACEI = angiotensin-converting enzyme inhibitor; AMI = acute myocardial infarction; BB = beta blocker; CV = cardiovascular; HF = heart failure; LVEF = left ventricular ejection fraction; LV = left ventricular; NYHA = New York Heart Association; EPHESUS = Eplerenone Heart Failure Efficacy and Survival Study; RALES = Randomized Aldactone Evaluation Study

12 months of treatment, PIIINP serum levels were significantly higher in the placebo group compared to the aldosterone inhibitor group (p<0.05 at three and six months; p<0.01 at 12 months), and the cohort receiving aldosterone inhibitor therapy had a significant reduction in LV volume at six and 12 months. In a separate study[20] of patients who had experienced a first acute MI, addition of an aldosterone antagonist to ACE inhibitor therapy was again found to reduce PIIINP levels significantly.

The reasons why aldosterone promotes adverse LV remodelling are not fully understood but they are probably multiple. It has certainly been clearly demonstrated that aldosterone blockade leads to marked improvements in LV function. In dogs with moderate heart failure, three months of treatment with the selective aldosterone receptor antagonist eplerenone prevented progressive LV systolic and diastolic dysfunction.[21] Moreover, eplerenone was found to reduce cardiomyocyte cross-sectional area by 28% compared with untreated animals, indicating attenuation of left ventricular remodelling. Administration of eplerenone over a period of nine weeks to rats with severe LV dysfunction after extensive MI has also been found to improve LV remodelling.[22] The rise in left ventricular end-diastolic pressure and end-diastolic volume was attenuated compared to placebo. Interestingly, combined administration of eplerenone and ACE inhibitor therapy significantly improved left ventricular ejection fraction (LVEF) versus placebo, which was not the case with either eplerenone or ACE inhibitor therapy alone.[22]

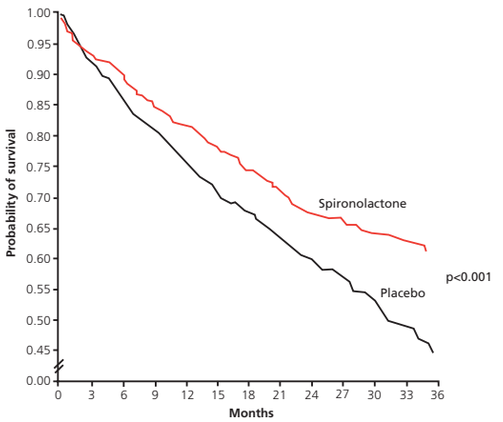
Clinically, addition of canreonate (active metabolite of spironolactone) to ACE inhibitor therapy improved left ventricular systolic and diastolic parameters in post-MI patients;[23] similarly, aldosterone blockade enhanced LV volume (p=0.03) and function (p=0.02) in a dose-dependent manner in patients with chronic heart failure (table 1).[24]

B-type natriuretic peptide (BNP)

Aldosterone blockade is also associated with decreased levels of B-type natriuretic peptide (BNP), which is a well-established marker of LV modelling.[27] Importantly, BNP is also a good indicator of prognosis in heart failure.[28] Mean BNP level fell from 200 pg/mL at baseline to 90 pg/mL in a cohort of 37 heart failure patients after four months' treatment with spironolactone (p<0.01). There was no significant fall among patients randomised to placebo.[18] A significant fall in BNP levels with an associated improvement in LVEF as demonstrated by transthoracic echocardiography has been reported in patients with heart failure (New York Heart Association [NYHA] class I-III) in the presence of aldosterone blockade.[29]

One recent clinical study has undertaken a comprehensive assessment of the effects of aldosterone blockade in mild heart failure patients who are already taking optimum therapy of both an ACE inhibitor and a beta blocker.[30] These patients with mild or asymptomatic heart failure were enrolled in a double-blind crossover study comparing three months' therapy with spirono-

Figure 1. Kaplan-Meier analysis of the probability of survival among patients with moderate-to-severe chronic heart failure randomised to spironolactone or placebo



Number at risk:

Placebo	841	775	723	678	628	592	565	483	379	280	179	92	36
Spironolactone	822	766	739	698	669	639	608	526	419	316	193	122	43

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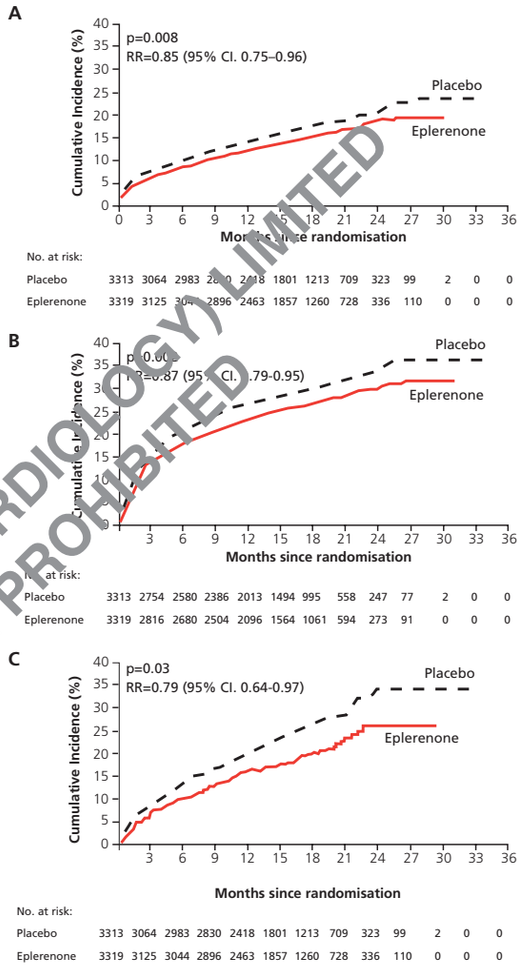
Figure 2. Kaplan-Meier estimates among patients with clinical evidence of heart failure following myocardial infarction for: **A**) rate of death from any cause; **B**) rate of death from cardiovascular causes or hospitalisation for cardiovascular events, and **C**) rate of sudden cardiac death stratified according to treatment with eplerenone or placebo



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lactone versus placebo. Aldosterone blockade improved endothelial function (as measured by acetylcholine-induced vasodilation), reduced the collagen marker PIIINP, reduced BNP and reduced both LV internal diameter and LV mass index.

The RALES and EPHESUS megatrials

Two large trials have evaluated the use of an aldosterone receptor antagonist in patients with heart failure in addition to an ACE inhibitor: the Randomized Aldactone Evaluation Study (RALES) study and the Eplerenone Heart Failure Efficacy and Survival Study (EPHESUS) (table 1). In the RALES study, there was a 30% reduction in mortality among patients with chronic moderate-to-severe heart failure randomised to spironolactone (NYHA class III-IV) (figure 1), together with a reduction in frequency of hospitalisation for worsening heart failure (table 1).[26] A sample of 260 patients taking part in the RALES study was analysed for serological markers of cardiac collagen synthesis, including PIIINP, to monitor cardiac tissue repair and fibrosis.[31] Over a six-month period, markers of collagen synthesis significantly decreased in the cohort receiving the aldosterone blocker but were unchanged in the placebo cohort: the change in PIIINP with aldosterone blockade versus baseline was -0.87 (p=0.003), versus +0.11 in the placebo group (p=n.s.). Similarly, there was a significant reduction in plasma levels of BNP following three and six months' spironolactone therapy (-23% at both time-points, p=0.004 and p=0.05, respectively), which may have been due to changes in left ventricular diastolic filling pressure or compliance.[32]

In the EPHESUS study, the selective aldosterone receptor antagonist eplerenone was administered within 3–14 days of MI (i.e. during the acute phase) to patients with LVEF <40%, most of whom had symptoms of heart failure (NYHA class II-IV).[25] At mean follow-up of 16 months, there were significant reductions in all-cause mortality, cardiovascular disease and hospitalisation with eplerenone (figure 2). Progression of heart failure was also improved, as indicated by a significant reduction in the number of patients requiring hospitalisation for heart failure. In contrast to the RALES study, where only approximately 10% of patients were given a beta blocker, in the EPHESUS study 75% of patients received a beta blocker. In both studies, approximately 90% of patients received an ACE inhibitor. A subgroup analysis

Key messages

- Aldosterone stimulates adverse cardiac remodelling, perhaps largely as a result of aldosterone-induced endothelial dysfunction and inflammation, myocyte apoptosis and myocardial fibrosis
- Aldosterone antagonism significantly reduces cardiac fibrosis in patients with either acute or chronic heart failure and improves left ventricular (LV) function
- The addition of an aldosterone receptor antagonist to standard care, namely angiotensin-converting enzyme inhibitor and beta blocker therapy, significantly improves morbidity and mortality among patients with heart failure post-myocardial infarction (MI), and among patients with moderate-to-severe chronic heart failure
- Inclusion of an aldosterone antagonist in the routine care of patients with moderate-to-severe heart failure and/or post-MI with LV dysfunction now appears to be indicated

showed that eplerenone significantly reduced PIIINP levels and that changes were significant as early as week four; by month nine, eplerenone had reduced PIIINP levels from baseline by -11.5% versus -2.3% for patients receiving placebo (p=0.002).[33] Elevations in PIIINP levels were associated with increased risk of total mortality and cardiovascular mortality/ hospitalisation.

The agents available to block the aldosterone receptor are spironolactone and eplerenone. The main difference between them is that the former can produce sexual side effects such as gynaecomastia, impotence and menstrual irregularities which do not occur with the latter. Both drugs can cause hyperkalaemia and renal dysfunction, which means that it is essential to monitor renal function intermittently, especially in the first week of therapy. Obviously a certain number of patients will not be able to take these drugs, especially those with an elevated creatinine (e.g. > 200 µmol/L) either initially or during therapy as well as those in whom plasma potassium increases to ≥ 6 mmol/L during therapy.

Conclusions

Aldosterone exerts several effects that contribute significantly to adverse LV remodelling, most notably endothelial dysfunction, which is thought to lead to tissue injury and reparative myocardial fibrosis. Other contributors are myocyte apoptosis and direct stimulation of collagen synthesis. The improvement in survival seen with aldosterone blockade in patients with chronic heart failure[26] and in LV dysfunction following acute MI[25] is likely to be at least partly accounted for by reduced remodelling. The mortality benefit of aldosterone blockade is apparent even in patients receiving both ACE inhibitor and beta blocker therapy,[25] indicating that routine use of an aldosterone receptor antagonist in patients with heart failure should be considered in addition to standard therapy.

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Conflict of interest

ADS has received honoraria and research funding from Pfizer.

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