Aldosterone: clinical implications in essential hypertension

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Abstract
The blockade of renin-angiotensin-aldosterone system with ACE inhibitors or angiotensin receptor antagonists has resulted in beneficial effects in essential hypertensive patients. However, occurrence of cardiovascular events has not been appropriately controlled beyond a certain percentage. One reason could be the pathophysiological effects of aldosterone, the final component of the system. The aldosterone escape phenomenon could explain undesirable outcomes observed in hypertensive patients even under treatment with ACE inhibitors or angiotensin antagonists. Aldosterone has direct effects on the vasculature, the heart and the kidney. Aldosterone has been associated with vascular smooth muscle cell hypertrophy, endothelial dysfunction, cardiac fibrosis, proteinuria and renal vascular injury. Animal models and clinical trials have proven the benefit of aldosterone receptor antagonism. Even in small doses, spironolactone was able to attenuate proteinuria and reduce death and morbidity among heart failure patients. The potential advantage of eplerenone, the first drug of a new class – selective aldosterone receptor antagonists – lies on a very low incidence of side effects, although clinical studies are still necessary to confirm efficacy, tolerability and safety. In conclusion, aldosterone antagonism must be considered in hypertensive patients presenting heart failure or proteinuria and in those with resistant hypertension. With the increased recognition of hyperaldosteronism in “essential” hypertension, the use of such drugs may become more widespread.

Keywords: Mineralocorticoid; Spironolactone; Angiotensin; Blood vessels; Endothelium; Collagen; Kidney; Heart failure.

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Introduction
Although the number of hypertensive patients under treatment increased in the last decade in many countries, the prevalence of heart failure and renal dysfunction is still increasing. Considering that hypertension is a primary cause for heart and renal disease, this indicates that factors related to end-organ damage are not being controlled adequately, independently of blood pressure reduction. The beneficial effects of angiotensin converting enzyme (ACE) inhibitors in patients with heart failure have been clearly demonstrated. Nevertheless, the evidence of benefit with respect to cardiovascular mortality

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in essential hypertension with ACE inhibitors or angiotensin antagonist treatment remains weak, although results of STOP-Hypertension-2\textsuperscript{2}, CAPPS\textsuperscript{3} and in diabetics UKPDS\textsuperscript{4} show favorable outcomes. These data may be strengthened shortly with the results of clinical trials such as VALUE (Valsartan Antihypertensive Long-term Use Evaluation), LIFE (Losartan Intervention For Endpoint Reduction In Hypertension Study)\textsuperscript{5} and ALLHAT (Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial).\textsuperscript{6}

It has been widely believed that an increase in the survival rate among hypertensive patients could be obtained with a better blockade of the renin-angiotensin-aldosterone system. Elevated aldosterone levels may be observed in some patients chronically treated with ACE inhibitor or angiotensin receptor antagonist.\textsuperscript{7} This phenomenon called “aldosterone escape” suggests alternative mechanisms, besides angiotensin II, regulating aldosterone synthesis.\textsuperscript{8,10} Adrenocorticotrophic hormone and potassium-dependent aldosterone secretion could also partially explain this phenomenon.\textsuperscript{11} Interestingly, endothelin-1 and its receptor subtypes A and B are expressed in the adrenal cortex and endothelin directly stimulates aldosterone secretion in humans via both receptor subtypes.\textsuperscript{12} An interaction between the endothelin system and the renin-angiotensin system could favor an increase in aldosterone production.\textsuperscript{13} An additional potential explanation could be a certain degree of autonomy of aldosterone secretion in subsets of essential hypertensive patients.\textsuperscript{14}

Experimental studies have shown that the heart, kidneys and vessels can be damaged directly by aldosterone. Aldosterone antagonism may reduce myocardial, renal and vascular injury. Indeed, in the Randomized Aldactone Evaluation Study (RALES), the aldosterone antagonist spironolactone reduced mortality in patients with heart failure.\textsuperscript{15} Thus, there is growing evidence that aldosterone may be a new risk factor for cardiovascular disease. Recently, Schlaich et al.\textsuperscript{16} studied aldosterone response in normotensive young men with positive and negative family history of arterial hypertension. These authors observed an inadequate suppression of aldosterone synthesis in response to salt loading and an exaggerated aldosterone production in response to angiotensin II. These findings are consistent with the increased risk for essential hypertension among relatives of hypertensive patients, which may in part be attributed to aldosterone. It is also consistent with the increasing appreciation that hyperaldosteronism may be much more prevalent than previously acknowledged among “essential” hypertensive patients. Prevalence rates around 15% have been reported by recent studies using more reliable methods to detect primary aldosteronism such as aldosterone/plasma renin activity ratio and the fludrocortisone suppression test.\textsuperscript{17}

This review will focus on the relatively recent discovery of non-classic actions of aldosterone in target tissues and their importance in the pathophysiology and complications of essential hypertension.

**Vascular changes**

Thirty years ago, Brunner et al. showed normal or high plasma-renin activity and aldosterone secretion in patients with myocardial infarction or stroke.\textsuperscript{18} This finding seems to be the first description of aldosterone as a risk factor for cardiovascular complications not uncommon in hypertensive patients. Vascular tone and remodeling are regulated by all the components of the renin-angiotensin system, which are all present in the vascular wall. Hatakeyama\textsuperscript{19} et al. detected biosynthesis of aldosterone in vascular smooth muscle and in endothelial cells. The mineralocorticoid receptor was also described in the vascular wall, mainly in smooth muscle cells. The authors identified a link between vascular aldosterone and angiotensin II-induced hypertrophy of vascular smooth muscle cells. Other studies have also detected biosynthesis of aldosterone in the vascular wall.\textsuperscript{20,21} This may indicate a paracrine action of aldosterone.\textsuperscript{22} Local production of aldosterone and binding to its receptor in smooth muscle cells could contribute to regulate vascular tone and vascular remodeling in hypertension.

An interaction between aldosterone and angiotensin II in the vascular wall has also been described recently. We initially demonstrated a role for mineralocorticoids in the regulation of vascular angiotensin binding sites in vivo.\textsuperscript{23} Later we demonstrated that infusion of aldosterone produced an increase in the density of binding sites for angiotensin in mesenteric arteries in vivo.\textsuperscript{24} As well, aldosterone was able to upregulate angiotensin receptors in vascular smooth muscle cells in vitro,\textsuperscript{24} finding that was later reproduced by others.\textsuperscript{25} Thus, elevated plasma aldosterone may result in upregulation of vascular angiotensin II receptors. Likewise, the endothelin system has also been implicated in vascular structural changes induced by aldosterone. Recently, we reported that endothelin receptor antagonism may prevent vascular remodeling in aldosterone-infused rats.\textsuperscript{26} In this study, after 6-week administration, aldosterone resulted in hypertrophic remodeling of small mesenteric arteries. Blockade of the endothelin system with an ET\textsubscript{A} receptor antagonist prevented blood pressure elevation and vascular hypertrophy. In addition, this study demonstrated, for the first time, that aldosterone is
able in vivo to increase vascular endothelin-1 tissue concentrations. Interestingly, ET<sub>A</sub> receptor antagonist also prevented hypokalemia in aldosterone-infused rats.

The vascular actions of aldosterone do not seem to be restricted to small vessels. Duprez et al. evaluated compliance of the aorta and its major branches in chronic heart failure patients treated with ACE inhibitors and diuretics. These authors concluded that heart failure patients presented the aldosterone escape phenomenon that was inversely correlated with the compliance of large arteries in both supine and standing positions. Similarly, Blacher et al. have investigated arterial compliance in 56 patients with sustained essential hypertension in comparison with 36 normotensive subjects. Systemic arterial compliance was strongly and negatively correlated with plasma aldosterone in hypertensive patients, but not in normotensive controls. Even after adjustment for age and blood pressure, the negative correlation between plasma aldosterone and arterial compliance remained significant.

Besides structural and mechanical changes, aldosterone can provoke vascular functional alterations. Farquharson and Struthers observed improvement in endothelial dysfunction after use of spironolactone in 10 patients with chronic heart failure. This effect was related to increased nitric oxide bioactivity. Indeed, according to the authors, it is difficult to know whether spironolactone has effects on other vasodilating substances, such as prostacyclin and endothelium-derived hyperpolarizing factor (EDHF) or only on nitric oxide bioactivity. Another factor that may contribute to endothelial dysfunction caused by aldosterone is a relative increase in sympathetic tone. Aldosterone may potentiate effects of catecholamines by blocking noradrenaline uptake in the heart. Finally, baroreflex dysfunction associated with elevated aldosterone levels has also been described.

**Cardiac effects**

Several studies have shown the presence of mineralocorticoid receptors in cardiac myocytes and endothelial cells. There is accumulating evidence that aldosterone has direct effects on the heart. Infusion of aldosterone during 8 weeks was able to produce marked accumulation of interstitial and perivascular collagen in the heart of uninephrectomized rats drinking 1% NaCl solution. On the other hand, this result raised the question whether the direct effects of aldosterone on extracellular matrix in this aldosterone-salt model are dependent on blood pressure. However, several studies demonstrated that the increased collagen deposition occurs in both left and right ventricles. Moreover, even at low doses that do not change blood pressure, spironolactone is able to prevent cardiac fibrosis induced by aldosterone. This seems to indicate that aldosterone may induce cardiac fibrosis directly by collagen deposition independent of blood pressure levels.

Multiple mechanisms seem to be involved in aldosterone-induced cardiac fibrosis. It is well known that angiotensin II stimulates adrenal cortex to produce aldosterone. The reciprocal may also occur to some degree. Robert et al. identified the angiotensin AT<sub>1</sub> receptor as a target of aldosterone. These authors reported that spironolactone decreased elevated AT<sub>1</sub> receptor levels. AT<sub>1</sub> receptors may be upregulated by aldosterone, possibly leading to increased responsiveness of cardiac cells to angiotensin II. The endothelin system may also play a role in this process. Endothelin receptor antagonism decreased aldosterone-induced cardiac fibrosis.

Clinical studies have confirmed direct actions of aldosterone on the heart. Schlaich et al. studied the effects of aldosterone on left ventricle structure and function before and after suppression of aldosterone by salt loading. Urinary aldosterone concentration after an oral salt load decreased in normotensives but not in hypertensive subjects. There was no relationship between aldosterone levels at baseline and left ventricle structure or function. However, after salt loading urinary aldosterone concentration correlated with left ventricular mass and impaired fractional fiber shortening, independent of 24-hour ambulatory blood pressure. Interestingly, this was significant only in hypertensive patients. Moreover, serum aldosterone levels after salt loading correlated with left ventricular mass in hypertensive subjects. In summary, inadequate suppression of aldosterone in response to an increase in oral salt intake is related to left ventricle structural and functional changes in hypertensive patients, independent of blood pressure levels. Previous studies had already noted this relationship between plasma aldosterone levels and left ventricular hypertrophy, all of them independent of blood pressure.

The beneficial effect of aldosterone blockade has been extensively studied in heart failure patients. Spironolactone has already been related to reduction in markers of myocardial collagen turnover. This beneficial action is associated with parasympathomimetic effects, with reduction in heart rate, particularly during the dawn hours. These two mechanisms may result from indirect effects of spironolactone in heart failure patients, preventing arrhythmia and cardiac death.

Aldosterone excess is associated with other deleterious actions.
Elevated urinary magnesium excretion results in magnesium loss. Circulating catecholamines increase as a result of blockade of norepinephrine uptake by the myocardial nerve endings. Together with other mechanisms previously described, these are possible causes of arrhythmia and sudden death in patients with elevated plasma aldosterone levels (Table 1).

In the Randomized Aldactone Evaluation Study (RALES), use of low dose spironolactone in heart failure patients receiving standard therapy, including ACE inhibitors and diuretics, determined an important reduction in morbidity and mortality. There was a 30 percent reduction in the risk of death among patients treated with spironolactone. In the same group, the frequency of hospitalization for worsening heart failure was 35 percent lower. The beneficial effect of spironolactone was so clear that blockade of mineralocorticoid receptors has become standard therapy for patients with heart failure on top of ACE inhibitors or angiotensin receptor antagonists.

Renal effects

Arterial hypertension and diabetes mellitus are the principal causes of end-stage renal disease (ESRD) and elevated blood pressure is considered an important risk factor for the deterioration of renal function in other clinical settings, including diabetic nephropathy. The renin-angiotensin-aldosterone system plays an important role in this process. Several clinical trials have proven that inhibition of the renin-angiotensin system attenuates the progression of renal disease.

Elevated plasma aldosterone levels in patients with renal insufficiency may be attributed to stimulus by angiotensin II and potassium. However, Hene et al. have reported aldosterone excess in 28 patients with renal failure and normal serum potassium levels and plasma renin activity. More importantly, aldosterone levels were highest in the subgroup of patients with more severe impairment in renal function.

Another important mechanism that is implicated in the worsening of renal function is proteinuria. Excessive protein load in direct contact with glomerular, mesangial and tubulointerstitial cells contributes to progressive impairment in renal function. Microalbuminuria, resulting from intraglomerular hypertension, has been demonstrated to be a risk factor for cardiovascular morbidity. Patients with primary aldosteronism present greater incidence and intensity of proteinuria when compared to patients with essential hypertension. Some experimental and clinical trials have shown that spironolactone may reduce proteinuria, indicating an alternative mechanism for the benefits derived from aldosterone antagonists in patients with renal failure.

The renal alterations caused by aldosterone may be the result of direct action, independently of blood pressure elevation. In the experimental situation, using stroke-prone spontaneous hypertensive rats (SHRSP), which is a model of malignant hypertension, Rocha et al. evaluated whether aldosterone infusion was able to reverse the renal-protective effects of captopril. Initially, they showed that captopril treatment reduced aldosterone levels and prevented the development of proteinuria and renal vascular lesions. After aldosterone infusion, captopril-treated rats presented proteinuria, associated with glomerular and vascular lesions in the kidney. Systolic blood pressure was not significantly different between the two groups. These findings differentiate the role of aldosterone from that of angiotensin II in the progression of hypertensive renal disease.

Clinical use of aldosterone antagonists

Spironolactone has been used as an aldosterone receptor antagonist for many years. Only recently, animal models and clinical studies have proven its beneficial effect on cardiac and renal disease, common complications among hypertensive patients. The significant reduction in the morbidity and death with spironolactone in heart failure patients demonstrated in RALES has brought new perspectives to this class of drug. Aldosterone antagonism may be necessary in clinical situations that require more complete inhibition of renin-angiotensin system. However, some side-effects may limit this approach. Spironolactone may provoke hyperkalemia, particularly in renal failure patients, and when associated with an ACE inhibitor. Thus, serum potassium levels must be periodically measured, and the drug has to be discontinued in case of moderate to severe hyperkalemia. Curiously, the incidence of serious hyperkalemia with spironolactone was only 2% in RALES. Spironolactone may also have antagonist actions on androgen and progesterone receptors, resulting...

Table 1 – Potential causes of aldosterone-induced arrhythmias in heart failure and hypertensive patients

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<thead>
<tr>
<th>Potential causes of aldosterone-induced arrhythmias</th>
<th>Heart failure and hypertensive patients</th>
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<tr>
<td>Hypokalemia</td>
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<td>Magnesium loss</td>
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<td>Blockade of myocardial norepinephrine uptake</td>
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<td>Baroreceptor dysfunction</td>
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in breast pain, gynaecomastia and impotence. These side effects can limit its use among men, particularly younger individuals.

The sexual side-effects are less frequent with the new selective aldosterone receptor antagonist (SARA), eplerenone. The affinity for androgen and progesterone receptors is lower for eplerenone than for spironolactone. Experimental studies have confirmed the beneficial effects of eplerenone, with improvement of vascular injury, mainly in the kidney, and prevention of proteinuria, independently of its effect on blood pressure. Eplerenone has already demonstrated safety and good tolerability in patients with heart failure, and good 24-h control of blood pressure with once or twice daily dosing. We now need to wait for the results of some soon to be finished clinical trials such as the EPHESUS trial, which evaluates the efficacy of eplerenone in systolic dysfunction after acute myocardial infarction.

Conclusions

We have described many favorable effects of aldosterone receptor antagonist in several clinical settings. The concept of aldosterone escape is an important one to consider when we block the renin-angiotensin system with ACE inhibitors or with angiotensin receptor antagonists. We can no longer consider aldosterone as a hormone with classical renal actions of water and sodium retention and potassium excretion. The direct pathophysiological actions of aldosterone on cardiovascular tissues are now well known. In fact, many angiotensin II actions might be mediated by aldosterone, although further studies are necessary to prove this hypothesis. At this point in time, we can conclude that hypertensive patients presenting with heart failure or proteinuria, particularly when blood pressure control is difficult in spite of the use of ACE inhibitors or angiotensin receptor blockers, may also require small doses of an aldosterone receptor antagonist, with attention to side effects, specifically a close follow-up of serum potassium levels.

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