Aldosterone-induced vasculopathy: a new reversible cause of cardiac death

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The traditional view is that angiotensin II (Ang II) is the principal culprit in the renin-angiotensin-aldosterone system (RAAS). However, it is now appreciated that aldosterone is a second culprit and that the harmful effects of aldosterone are additional to those of Ang II. The relative importance of Ang II and aldosterone can be illustrated by the fact that during chronic angiotensin-converting enzyme inhibitor (ACE-I) therapy, there is more escape of aldosterone than there is of Ang II. Indeed, we recently showed that both aldosterone and plasma Ang II are elevated in many CHF patients who are being treated with chronic ACE-I therapy, but in our patients, 38% had an elevated aldosterone while only 15% had an elevated plasma Ang II level. The important clinical point is that there is plenty of residual aldosterone around for this to be a potential problem, even in the presence of an ACE-I. Indeed, one could now say that in ACE-I-treated CHF patients, aldosterone escape increases mortality while Ang II escape does not. This is based on the fact that the RALES study with aldosterone blockade was positive, while the effect of valsartan in ValHeFT was neutral, as far as mortality was concerned.

Initially, the idea that aldosterone ‘escaped’ in the presence of an ACE-I came as a surprise, but it should not really be surprising, since aldosterone is under the control not only of Ang II, but also of potassium. Therefore, although ACE-I-induced reductions in Ang II should suppress aldosterone, this is counterbalanced by the stimulation of aldosterone by ACE-I-induced K⁺ increases.

What, therefore, are the harmful effects of aldosterone in CHF? Interestingly, it is now recognised that aldosterone exerts major effects on all the principal mechanisms which produce cardiac death. It is therefore worth first discussing the more general idea of what these principal mechanisms are, irrespective of aldosterone.

Coronary artery disease is obviously a key factor leading to cardiac death. As well as coronary disease, another main factor which independently promotes cardiac death is left ventricular dysfunction, which is usually accompanied by left ventricular fibrosis. Indeed, the feature of LV dysfunction which is particularly arrhythmogenic is the accompanying LV fibrosis. Patchy LV fibrosis means that the electrical currents have to take detours around the fibrotic areas, which promotes arrhythmias.

The third main factor influencing cardiac death are those which are extrinsic to the heart, but which are pro-arrhythmic in themselves. Of these, the most important factor is autonomic (sympathovagal) imbalance. Here, it is the balance between the sympathetic and the parasympathetic nervous system which counts. The sympathetic nervous system (SNS) is pro-arrhythmic while the parasympathetic is antiarrhythmic. This is exemplified by animal studies which show that vagal stimulation not only improves survival, but also reduces arrhythmias in animals undergoing coronary artery ligation, which inevitably activates the SNS. In patients, cardiac autonomic balance is best measured by heart rate variability and baroreflex testing. Innumerable studies have shown that abnormalities in both heart rate variability and baroreflex testing are independently and significantly linked with cardiac death. It is clear that, at any given LVEF, a poor heart rate variability and/or poor baroreceptor function are strongly linked with impending cardiac death.

As mentioned above, aldosterone has adverse effects on all aspects of this: coronary endothelial dysfunction, LV fibrosis and autonomic imbalance. However, the adverse effect of aldosterone on all three of these factors may well stem from its ability to produce its own vasculopathy.

Aldosterone-induced vasculopathy
Aldosterone is now known to be synthesised by human vascular cells. Furthermore, aldosterone is recognised to exert a number of different adverse effects on the vasculature. The most important of these is that aldosterone reduces, and spironolactone increases, endothelial nitric oxide (NO) bioactivity. What is particularly striking about this effect is that aldosterone blockade increased endothelial NO activity by 94%, whereas ACE-I and statins usually only improve endothelial dysfunction by approximately 25–35%. Improving endothelial dysfunction is important, since it is likely to be associated with a reduced incidence of cardiovascular events. This idea is based on several observations. First, four studies now show clearly that endothelial dysfunction at baseline is associated with future cardiovascular events. Secondly, there are now three treatments (statins and ACE-I in HOPE and spironolactone in RALES) which in parallel improve brachial artery endothelial dysfunction and reduce cardiovascular events and mortality in large trials. (The data for Vitamin E’s effects on endothelial dysfunction and on cardiovascular events are equally mixed for both)
endpoints, which could be said to make Vit E a fourth therapy where treatment-induced changes in endothelial dysfunction correspond with treatment-induced changes in cardiovascular events.) How, therefore, does aldosterone produce endothelial dysfunction? One distinct possibility is that aldosterone might be increasing superoxide radicals, which deplete endogenous NO. This possibility arises because Ang II is known to generate superoxide anions and generation of oxygen free radicals is a key process in Ang II-induced endothelial dysfunction. The importance of this mechanism was proven by the fact that Vitamin C virtually negates Ang II-induced endothelial dysfunction. Furthermore, since Ang II and aldosterone both reduce NO bioactivity, it would be surprising if the mechanism of such an effect on NO activity were to be different between Ang II and aldosterone. Therefore, there is a strong possibility that aldosterone-induced impairment of vascular NO arises because aldosterone induces oxidative stress in the endothelium. If so, the implications would be enormous, since oxidative stress is now regarded as a universal mechanism contributing to tissue injury in many different diseases and in many different organs.

There is even more to aldosterone-induced vasculopathy than endothelial dysfunction, although the latter is probably the main influence. In addition, however, aldosterone appears to also reduce vessel compliance by reducing distensibility of the vascular smooth muscle layer. It is unknown whether this is a primary effect of aldosterone or whether it is secondary to reduced endothelial NO activity.

As well as inducing vasculopathy, aldosterone has potentially harmful effects within the blood vessel lumen, where it promotes blood clotting by inhibiting fibrinolysis, by means of increasing plasminogen activator inhibitor-1 (PAI-1). Thus, aldosterone has harmful effects on all three layers on the blood vessel, the lumen, the endothelium and the smooth muscle (Figure 1). Clearly, the combination of these three harmful vascular effects of aldosterone would be expected to lead to microthrombi and tissue infarction and injury, and this has now been clearly demonstrated. Indeed, in the animal model of spontaneous hypertensive rats, spironolactone reduced tissue injury in the brain and kidney by 60–70% at a dose which did not alter blood pressure (BP). Similarly, in the L-NAME model of rat hypertension, aldosterone blockade and adrenalectomy both completely blocked myocardial necrosis at doses which did not alter BP at all. Therefore, in both of these animal models, endogenous aldosterone mediates severe tissue infarction/injury, which is likely to be caused, at least in part, by aldosterone-induced vasculopathy.

Another completely separate vascular effect of aldosterone has come to light. It now appears that aldosterone can activate vascular angiotensin responses. Aldosterone can enhance the binding of Ang II to its receptors and amplify Ang II responses. Aldosterone significantly increased the binding density of both ACE and Ang II receptors in animal experiments. In fact, in tissue culture, aldosterone increases ACE mRNA 23-fold. In order to explore this phenomenon in man, Farquharson and Struthers showed that spironolactone reduced vascular tissue ACE activity, since spironolactone reduced the vascular response to exogenous angiotensin I (Ang I), but had no effect on the response to Ang II. In this experimental model, infused Ang I does not have any vascular effects until it is converted into Ang II, which is why the differential infusion of Ang I and Ang II can be used to assess vascular ACE activity. This raises a new possibility, which is that aldosterone may exert a positive feedback loop on vascular ACE (Figure 2). In that sense, aldosterone blockade may exert ‘extra ACE inhibition’, over and above the coincidental ACE inhibitor drug.

### Aldosterone-induced myocardial fibrosis

Another prime adverse effect of aldosterone, which was first described by Karl Weber, is its ability to stimulate fibrosis in the myocardium. This is one of the adverse effects of aldosterone which appears to be attributable not only to aldosterone but also to Ang II. Brilla et al. showed that aldosterone induces biventricular fibrosis in the rat and that myocardial fibrosis could be prevented by spironolactone at a dose which was too low to alter BP.
Studying myocardial fibrosis in man is difficult, but the idea has recently been proposed that plasma levels of procollagen type III amino terminal peptide (PIIINP) may be a useful index of myocardial collagen turnover. Interestingly, we recently found that spironolactone reduced PIIINP levels in CHF patients, which is the first clinical evidence that aldosterone promotes myocardial collagen formation. Zannad and colleagues have shown that spironolactone had its main effect in the RALES trial in those patients who had high initial levels of PIIINP which were reduced by spironolactone.

From the above, it is very likely that aldosterone causes patchy myocardial fibrosis, which could lower the threshold for malignant ventricular arrhythmias in CHF, and that this was a likely reason for the reduction in mortality by spironolactone in the RALES trial. What we do not know is how much of this fibrosis is a direct effect of aldosterone and how much is a result of aldosterone-induced vasculopathy causing tissue ischaemia and injury.

**Aldosterone-induced sympathovagal imbalance**

Spironolactone has now been shown to have important autonomic effects on sympathovagal activity. For example, spironolactone reduces cardiac adrenergic activity, but perhaps more importantly, it increases parasympathetic activity. The importance of a parasympathomimetic effect can be illustrated by animal studies of coronary artery ligation, where coincidental vagal stimulation dramatically improved survival and reduced the incidence of reperfusion arrhythmias. Such an effect of aldosterone blockade boosting parasympathetic activity is particularly prominent in the 6 a.m.–10 a.m. period of the day, when endogenous aldosterone is high. Indeed, the early morning surge of aldosterone may acutely produce an autonomic imbalance, which promotes the well-known early morning peak in cardiac deaths.

The link between aldosterone and the autonomic nervous system can be demonstrated in yet another way. Baroreflex sensitivity is a further way of assessing autonomic balance (or imbalance). Animal and human studies have clearly shown that aldosterone per se inhibits baroreflex activity. The importance of a blunting of baroreflex activity has been clearly demonstrated in numerous studies showing that baroreflex insensitivity is an independent predictor of mortality, as too is poor heart rate variability, which are two standard techniques for assessing autonomic balance. Thus, the fact that aldosterone has adverse effects on autonomic balance could well be pivotal in aldosterone promoting cardiac death.

However, there is a whole new twist to this concept. Recently it has become apparent that NO is a key regulator of autonomic function in man. Thus, the probability arises that vascular NO is a key determinant of autonomic balance and therefore therapies which increase vascular NO will produce the knock-on effect of also improving autonomic imbalance. Obviously, what this could mean is that aldosterone-induced vasculopathy, with its attendant decrease in vascular NO, could be a prime cause of autonomic imbalance in CHF.

**Summary**

The idea arising is that the key culprit mechanism with regard to aldosterone may well be its ability to produce a vasculopathy characterised by NO deficit, and that aldosterone-induced fibrosis and aldosterone-induced autonomic imbalance could be a consequence of aldosterone vasculopathy (Figure 3).

Aldosterone thus exerts harmful effects on the key processes which promote cardiac death; on endothelial dysfunction, on myocardial fibrosis and on sympathovagal imbalance. It is possible that they are all attributable, to some extent, to a novel aldosterone-induced vasculopathy, which produces a relative deficit of vascular NO. The future should now explore whether aldosterone-induced vasculopathy is a phenomenon only occurring in chronic heart failure, or whether this also occurs in other diseases.

**References**

1. MacFadyen RJ, Lee AFC, Morton JJ, Pringle SD, Struthers AD. How often are AII and aldosterone concentrations raised during chronic ACE treatment in CCF? Heart 1999;82:57-61.


