Value of Non-antiarrythmic Drugs in Preventing Sudden Cardiac Death: Aldosterone Antagonists

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Introduction

Sudden cardiac death remains as an important public health problem, even in industrialised countries, despite the considerable improvement in emergency medical services and the introduction of new therapeutic strategies. Sudden cardiac death (SCD) is responsible for 50% of the mortality from cardiovascular disease [1]. In many cases, SCD may be the first manifestation of coronary artery disease. It is the most common cause of death due to ischaemic heart disease among the adult population under 65 years of age, and survival rates after out-of-hospital cardiac arrest remain low. It has been shown in clinical trials that, compared to the administration of antiarrhythmic drugs, implantable cardioverter defibrillators (ICD) significantly reduce mortality due to SCD. This treatment option has added a new dimension to the prevention and management of SCD. Besides antiarrhythmic drugs and ICDs, there are other drugs that have an indirect but nonetheless important role in preventing SCD. Although these medications do not have a direct electrophysiologic action, they prevent SCD by affecting basic neurohumoral, ischaemic, biochemical, and fibrotic mechanisms that may cause ventricular tachyarrhythmias. Aldosterone antagonists are an example of non-antiarrhythmic drugs that have been shown to reduce the incidence of SCD in clinical trials.

Cardiovascular Effects of Aldosterone

Following its discovery in the early 1950s, the endocrine actions of aldosterone have been extensively studied and documented [2–5]. Aldosterone's

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main endocrine function is the regulation of sodium and potassium, and volume homeostasis. The activity of the hormone is mediated through sodium reabsorption and potassium excretion in the distal renal tubules and collecting ducts. Its release from the adrenal cortex is stimulated by increased levels of serum potassium, angiotensin II, adrenocorticotropic hormone (ACTH), and by sodium depletion [6–8]. Aldosterone regulates extracellular volume and electrolyte balance via mineralocorticoid receptors on renal tubular epithelial cells.

In addition to renal tubular epithelial cells, mineralocorticoid (MR) receptors are present in various non-renal locations [9], mainly, heart [10, 11], brain tissue [12], and the vasculature [13]. This finding suggests that aldosterone has local effects at different tissue levels. In animal studies, aldosterone biosynthesis was also shown in myocardium [11], brain [12] and vascular smooth muscle cells [14]. Aldosterone synthesis at extra-adrenal sites seems to be regulated by the same factors that regulate adrenal synthesis, and many of the negative effects of aldosterone are mediated by MR receptors in these non-renal sites. For example, increased local production of aldosterone and angiotensin converting enzyme (ACE) have been detected in the ventricles of patients with heart failure. It has been shown that aldosterone contributes to cardiovascular toxicity in humans independent of the effects of angiotensin II, and a correlation exists between aldosterone concentration and cardiovascular morbidity and mortality. In the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS), significantly greater mortality at 6 months was shown in patients who had baseline aldosterone concentration above the median values [15].

In patients with heart failure, overproduction of aldosterone leads to an inappropriate increase in sodium and water retention. This fluid and sodium retention produces a volume overload that further impairs the ability of the heart to pump adequate amount of blood to peripheral tissues. With the reduction of forward blood flow, a generalised systemic vasoconstriction occurs that impairs renal blood flow. Eventually, a vicious circle is formed in which the release of angiotensin II from the kidneys leads to a further rise in aldosterone and volume overload.

Aldosterone increases the risk of ventricular arrhythmias by increasing renal potassium and magnesium excretion [16]. Because of the negative effect of this electrolyte imbalance, aldosterone increases the risk of SCD in patients with heart failure and in post-myocardial-infarction (MI) patients. In patients with congestive heart failure, the kaliuretic and magnesiuretic effects of aldosterone can be reverted by aldosterone receptor antagonists, which may explain the preventive effects of these drugs on SCD. Aldosterone has also been demonstrated to have proarrhythmogenic effects on rabbit cardiomyocytes by increasing sodium influx and Na/K pump activity [17].

An animal study showed that aldosterone exposure increased calcium current in adult rat cardiomyocytes, an effect that was inhibited following aldosterone blockade by spironolactone [18].

It has been shown in various animal models and clinical studies that aldosterone causes cardiovascular injury, independent of its effects on blood pressure – the so-called mechanical effects of aldosterone. Aldosterone causes vascular inflammation and fibrosis in animal models. The mechanisms through which aldosterone causes cardiac and vascular fibrosis have been investigated in many studies. Aldosterone increases vascular angiotensin (AT)1 receptor binding [19]. It also increases AT1 receptor density and mRNA accumulation in rat heart [20]. Thus, aldosterone may, at least in part, exert its adverse effects on cardiac remodelling by potentiating the effects of angiotensin II. Moreover, aldosterone has been shown to have a direct profibrotic action by increasing collagen production by cardiac fibroblasts [21, 22]. It also increases plasminogen activator inhibitor-1 (PAI-1) expression, which promotes fibrosis [23, 24]. In an animal study in normotensive rats, aldosterone infusion for 24 h led to increased cardiomyocyte apoptosis [25]. Since necrotic myocytes serve as stimuli for fibrosis in myocardium [26], increased apoptosis and myocardial necrosis may be another mechanism to explain aldosterone-mediated cardiac fibrosis.

Propeptide of type III collagen (PIIINP) is a serum marker of collagen synthesis. In the Randomised Aldactone Evaluation Study (RALES), serum PIIINP levels were significantly reduced in a group of patients treated with spironolactone [27]. In a study by Modena, 46 post-MI patients were randomised to spironolactone or to placebo. After a 1-year follow-up, serum PIIINP levels were found to be lower in the treatment arm [28]. These data suggest that aldosterone exerts an adverse remodelling effect on myocardium and promotes cardiac fibrosis. Increased myocardial fibrosis may act as a substrate for the genesis of life-threatening ventricular arrhythmias.

Aldosterone has also been shown to have proatherogenic actions and it promotes endothelial dysfunction [29]. Possible mechanisms that may be involved in aldosterone's effect on endothelial function include aldosterone-induced reduction of NO levels and a reduction in the generation of oxygen free radicals [30, 31]. Patients with heart failure who were treated with spironolactone for 1 month had an increased endothelium-dependent forearm blood-flow response to acetylcholine [32]. Aldosterone induces vascular inflammation and fibrinoid necrosis of the small arteries and arterioles, leading to a reperative fibrotic process. An inverse relation between aldosterone and large-artery compliance in late-stage heart failure patients has also been suggested [33]. Together with its hypertensive effects, aldosterone increases the occurrence of ischaemic events by promoting endothelial dysfunction, perivascular fibrosis, and a decrease in arterial compliance. This

constitutes a suitable background for the progression of heart failure and the occurrence of arrhythmic SCD.

Experimental studies suggest that aldosterone has autonomic effects, independent of the actions of angiotensin II. Aldosterone blunts the baroreceptor heart-rate response to noradrenaline infusion and increases sympathetic nervous system activity [34]. It modulates parasympathetic tone and results in reduced heart rate variability (HRV) parameters. Reduced HRV is associated with increased mortality and a higher incidence of SCD in heart failure [35]. Aldosterone has also been shown to block extraneuronal noradrenaline uptake [36]. All of these actions of aldosterone can predispose to arrhythmias and SCD.

In a study conducted in rats, aldosterone blockade by canrenone (active metabolite of spironolactone) was found to attenuate left ventricular (LV) remodelling, improve LV systolic and diastolic function, reduce interstitial and perivascular fibrosis, decrease myocardial norepinephrine content, and increase the ventricular fibrillation threshold [37]. A study by Ramires et al. showed that addition of spironolactone to standard therapy in patients with congestive heart failure due to idiopathic or ischaemic dilated cardiomyopathy reduces the frequency of ventricular premature complexes and episodes of non-sustained ventricular tachycardia [38]. Aldosterone blockade has also been shown to reduce vascular collagen turnover, improve HRV, and reduce heart rate, especially in the early morning hours [35]. The latter finding is particularly noteworthy as it suggests that blocking the action of aldosterone reduces the incidence of ischaemia in the early-morning, when sudden death is 2.5 times more common in patients with heart failure. Addition of spirondactone to conventional treatment decreases QT dispersion [39] and has positive effects on HRV [40].

The 'Aldosterone Escape' Phenomenon

Despite the lowering of angiotensin II activity, ACE inhibitors completely block aldosterone production. In fact, a progressive rise in aldosterone levels under ACE inhibitor therapy has been demonstrated in clinical studies. This finding, termed 'aldosterone escape,' may be explained by ATII production independent of ACE activity (so-called angiotensin escape), ACE production that is not inhibited by ACE inhibitors, and ATII-independent aldosterone production. MacFadyen and colleagues reported that in patients with symptomatic heart failure who were on ACE inhibitor therapy aldosterone suppression failed in 38% of cases [41]. In the Randomised Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) pilot study, aldosterone levels were significantly lower after 17 weeks in both treatment arms

(candesartan and enalapril); however, levels returned almost to baseline in all three groups by the 43rd week [42]. In another study, conducted in a smaller sample of heart failure patients, 11 of 34 patients had elevated serum aldosterone levels in spite of complete ACE inhibition [43]. These data, together with knowledge of the correlation between serum aldosterone levels and mortality in heart failure patients, constitute the rationale for more specific blockade of aldosterone action in addition to ACE inhibition in patients with heart failure.

Sudden Cardiac Death and Aldosterone Receptor Antagonists: What We Have Learned from Recent Trials

Two important landmark studies have shown the clinical benefits of aldosterone receptor antagonists, RALES [44] (Randomised Aldactone Evaluation Study) and EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) [45].

RALES was a randomised double-blind study that enrolled 1663 patients with severe heart failure, a LV ejection fraction below 35%, and who were being treated with ACE inhibitor, digitalis, and diuretics. Patients were randomly assigned to receive 25 mg spironolactone or placebo to assess the primary end-point of death from all causes. The trial was stopped early, after a mean follow-up of 24 months, because of the significant beneficial effect of spironolactone. There was a 30% reduction in the risk of death among patients in the spironolactone group. Importantly, spironolactone reduced the risk of death from progressive heart failure and SCD. The authors suggested that the preventive effect of spironolactone on SCD was related to decreased potassium loss and increased myocardial uptake of norepinephrine in response to the drug. The potential of spironolactone in preventing myocardial fibrosis was also suggested to have a role in reducing the risk of SCD, as myocardial fibrosis is well-known to predispose patients to reentry ventricular arrhythmias. One of the criticisms of the RALES study was that only 11% of the patients were on beta-blocker therapy. Since some of the beneficial effects of beta-blockers and spironolactone are produced by similar mechanisms, it is unclear whether spironolactone would still have a beneficial effect if the majority of patients were also on beta-blocker therapy. A substudy of RALES, published later, implicated a potential link between the antifibrotic effects of spironolactone and decreased mortality [27]. In this study, serum levels of PIIINP, which is a marker of collagen turnover, were significantly reduced by spironolactone and this predicted decreased mortality.

Eplerenone is a new, competitive antagonist of aldosterone that has a

higher degree of selectivity for the mineralocorticoid receptor. EPHESUS was conducted as a double-blind, placebo-controlled study to evaluate the effect of eplerenone on mortality and morbidity among post-MI patients with additional complications of LV dysfunction and heart failure. The 6632 patients participating in the study were randomly distributed to eplerenone and placebo arms in addition to optimal medical therapy. After 16 months of follow-up, eplerenone was found to reduce risk of death from any cause by 15%. It also reduced cardiovascular deaths and hospitalisations due to cardiovascular events. Interestingly, eplerenone decreased the rate of SCD by 21%. In contrast to RALES, 75% of the patients in EPHESUS were on beta-blocker therapy.

In EPHESUS, a large part of the reduction in cardiovascular mortality was due to a 21% reduction in the rate of SCD. The authors postulated that this important beneficial effect was due, in part, to a positive effect of aldosterone on electrolyte (especially potassium and magnesium) balance. Other proposed mechanisms were reduction of coronary vascular inflammation and interstitial fibrosis, reduction of oxidative stress, improvement in endothelial function, attenuation of platelet aggregation, improvement in ventricular remodelling, reduction of sympathetic tonus, and improvement in HRV and norepinephrine uptake.

Conclusions

Based on these data, we can conclude that although aldosterone antagonists are non-antiarrhythmic drugs, they have a significant preventive effect on SCD. The available data have focused particularly on the patients with low ejection fraction and congestive heart failure. New studies are needed to expand the indications to use aldosterone antagonists to prevent SCD. Potential mechanisms by which these drugs prevent SCD include prevention of aldosterone-induced cardiac and arterial fibrosis, improvement in arterial compliance, reduction of the adverse effects of aldosterone on cardiac remodelling, improvement of endothelial function and NO activity, improvement in the autonomic nervous system function via a reduction in sympathetic nervous system tonus, improvement in HRV and baroreflex sensitivity, and an increase in myocardial norepinephrine uptake By decreasing urinary excretion of potassium and magnesium, aldosterone antagonists also aid in protecting against life-threatening ventricular arryhthmias.

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