Eplerenone: Will It Have a Role in the Treatment of Acute Coronary Syndromes?

*David J. Meier, MD, Bertram Pitt, MD, and Sanjay Rajagopalan, MD**

Address
*The Zena and Michael A. Wiener Cardiovascular Institute, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029-6574, USA.
E-mail: srajag@msnyuhealth.org

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Aldosterone is known to have multiple adverse cardiovascular effects that are reminiscent of but independent from angiotensin II. These effects include endothelial dysfunction, heightened thrombogenicity, inflammation, and reparative fibrosis, and have been described in experimental and human models of aldosterone excess. Recently a number of clinical investigations have demonstrated that mineralocorticoid receptor (MR) antagonism, even in conditions not traditionally associated with systemic activation of the renin-angiotensin II-aldosterone pathway, may provide additional benefits above and beyond angiotensin-converting enzyme (ACE) inhibition and angiotensin receptor blockade. The Eplerenone Neurohormonal Efficacy and Survival Study (EPHESUS) with eplerenone in patients who were post-myocardial infarction underscores the additive benefit of such a strategy in post-infarction patients that typify an at-risk population for recurrent cardiovascular events. The mechanisms operative in acute coronary syndromes (ACS), including inflammation, altered hemostasis, and endothelial dysfunction, overlap significantly with those seen in the EPHESUS patient population. One may therefore hypothesize that MR antagonism with eplerenone may be beneficial in patients with ACS. Another advantage of using eplerenone is that it offers the advantages of MR antagonism without the side effects due to blockade of other nuclear receptors such as the androgen and progesterone receptors. If MR blockade is found to be beneficial in patients with ACS, the potential reduction in morbidity, mortality, and health care costs are profound.

Introduction

Ischemic heart disease is the leading cause of death worldwide. Acute coronary syndromes (ACS), including unstable angina, non-ST elevation myocardial infarction (MI) and ST-elevation MI, account for over 2 million hospitalizations annually in the United States. Despite significant advances in pharmacotherapy (use of low molecular weight heparins, ADP receptor and glycoprotein IIb/IIIa receptor antagonists) and embracement of aggressive early invasive strategies, a substantial majority of patients suffer from recurrent events. Strategies that target the underlying pathophysiologic mechanisms in a broad multipronged fashion would theoretically be expected to be effective in dealing with this propensity to recurrent events that is beyond the scope of local therapies such as drug-eluting stents and radiation. The renin-angiotensin-aldosterone system is thought to play an important role in the development of atherosclerosis and its complications. Angiotensin II through a broad range of mechanisms that include proinflammatory, prothrombotic, and pro-oxidant effects may confer vulnerability on stable atherosclerotic plaques. Although the importance of angiotensin II as a pathologic mediator in atherosclerosis is generally accepted, there is emerging evidence that its downstream mediator aldosterone may mediate additional effects. The identification of aldosterone synthesizing enzymes and the expression of the mineralocorticoid receptors (MR) in the cardiovascular system signifies a larger role for this system beyond that of fluid and electrolyte balance. Indeed a number of investigations have implicated aldosterone in cardiovascular diseases such as hypertensive heart disease, congestive heart failure (CHF), and remodeling after an acute MI. The availability of spironolactone and more recently eplerenone (Inspra; Pfizer, New York, NY), a selective MR antagonist of similar molecular structure has made the testing of MR antagonism as a therapeutic principle in a number of diseases feasible. In this article we discuss recent laboratory and clinical findings that seem to raise the possibility that MR antagonism with eplerenone may be potentially beneficial as a therapeutic strategy in ACS.

Pathogenesis of Acute Coronary Syndromes

Culprit lesions that result in ACS are typically vulnerable plaques, characterized by a thin fibrous cap, large lipid core, and a high macrophage content [1]. The endothelium overlying such plaques is markedly dysfunctional and rather than functioning as an antithrombogenic, nitric oxide (NO)-pro-

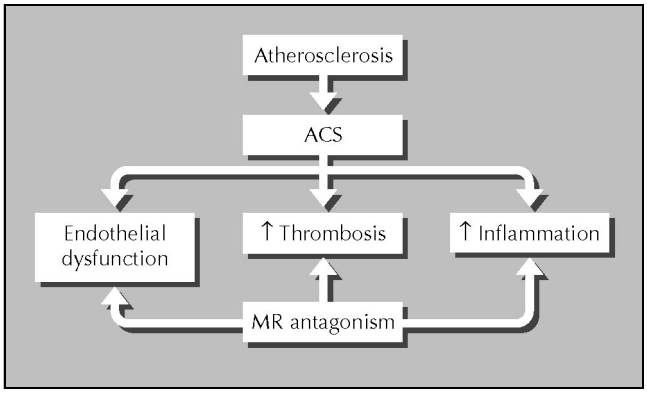

Figure 1. Broad mechanisms critical to the pathogenesis of acute coronary syndromes (ACS) that could hypothetically be influenced by mineralocorticoid receptor (MR) antagonism.

ducing anti-inflammatory layer, actively contributes to the cellular trafficking and potentiation of inflammatory and prothrombotic responses within the vessel wall. The plaque eventually undergoes intimal erosion or overt rupture, resulting in thrombus formation; a process referred to as *atherothrombosis*. Once rupture occurs, the subendothelial components are exposed to flowing blood, initiating the formation of the hemostatic aggregate responsible for the clinical manifestations of ACS. The relative balance of intrinsic plaque characteristics and extrinsic circulatory factors determines plaque vulnerability and the severity of clinical consequences. Factors such as an active inflammatory cell infiltrate and reduced collagen content in the extracellular matrix secondary to reduced synthesis or increased degradation, largely driven by matrix metalloproteinases, and a paucity of smooth muscle cells (responsible for synthesizing connective tissue matrix proteins, including collagen types I and III, elastin, proteoglycans, and glycosaminoglycans) may all contribute to vulnerability. Therefore, endothelial dysfunction, inflammation, thrombosis, and altered collagen content play a collective role in the genesis of ACS. The amelioration of these same mechanisms operative in ACS may be postulated to represent pathways through which MR blockade may favorably affect prognosis in ACS (Figs. 1 & 2).

Potential Role for Mineralocorticoid Receptor Antagonism

Endothelial dysfunction

Patients with ACS demonstrate marked transient impairment in coronary vasodilatory capacity [2]. The mechanisms of vasomotor dysfunction in ACS likely involve free radical (generated through multiple cellular sources)-mediated inactivation of NO and reductions in platelet-derived NO [3].

Aldosterone through both rapid nongenomic and genomic effects mediated by MR may modulate and impact vascular function. Both aldosterone and deoxycorticosterone acetate (DOCA) result in rapid endothelial vasodilator dysfunction in animal models and in healthy humans [4•,5••]. There is recent evidence, though, that aldosterone incubation may also stimulate NO production through activation of the phosphatidylinositol 3-kinase, pathway [6•]. Conversely, blockading MR particularly in conditions such as CHF, hypertension, and atherosclerosis is associated with an improvement in vasodilator capacity in response to endothelium-dependent agonists [7••,8•,9••]. The mechanisms through which aldosterone or conversely MR antagonism may influence endothelial function are not entirely clear, but there are some interesting links to suggest that this may either involve excess free radical generation either through its effects on potassium or through the activation of free radical-generating oxidases in the vasculature. Salt appears to markedly aggravate the ability of aldosterone to generate oxidant stress. Aldosterone infusion in conjunction with dietary salt loading markedly potentiates free radical production and widespread evidence of radical injury has been noted in such animal models [10,11••]. The increase in oxidant stress is associated with expression of redox sensitive transcription factors such as NF-κB. Treatment with spironolactone reverses these effects in a manner that is comparable to pyrrolidine dithiocarbamate (PDTC) or N-acetylcysteine, both of which are powerful antioxidants [11••]. Aldosterone-mediated free radical generation may be responsible at least in part for the increases in blood pressure seen with angiotensin II, as MR antagonism with spironolactone reduces blood pressure in concert with a decrease in superoxide generation and NADH oxidase activity [12••]. Similarly administration of eplerenone significantly decreased vascular NADH/NADPH oxidase-dependent free radical generation in diet-induced atherosclerosis in the rabbit with concomitant improvements in aortic endothelial-dependent vasodilatation [9••]. Reduction in oxidant stress and improvements in NO bioavailability in the short term may indeed translate into favorable reduction in atheroma burden. Administration of eplerenone (200 mg/kg/d) to apolipoprotein E-deficient mice for 3 months improved serum susceptibility to lipid peroxidation and reduced macrophage-derived oxidants, concomitant with a reduction in the atherosclerotic lesion area by 35% versus untreated mice [13••]. Thus, MR antagonism in ACS may be postulated to decrease oxidant stress, tip the balance in favor of more bioavailable NO, and in the long term reduce atherosclerosis progression.

Inflammation

Multiple lines of evidence point to inflammation as a key mediator in ACS. Clinically, the predictive relationship between inflammatory markers, such as C-reactive protein (CRP) and CD40, and risk in ACS has been well documented [14]. Systemic inflammation is thought to reflect vascular inflammation, in the form of a cellular infiltrate that is particularly prominent in vulnerable plaques. What is the evidence that aldosterone may play a role in influencing vascular inflammation and is there any evidence that MR antagonism may modulate this?

In studies of uninephrectomized rats fed salt, aldosterone infusion leads to increased expression of osteopontin, cyclo-

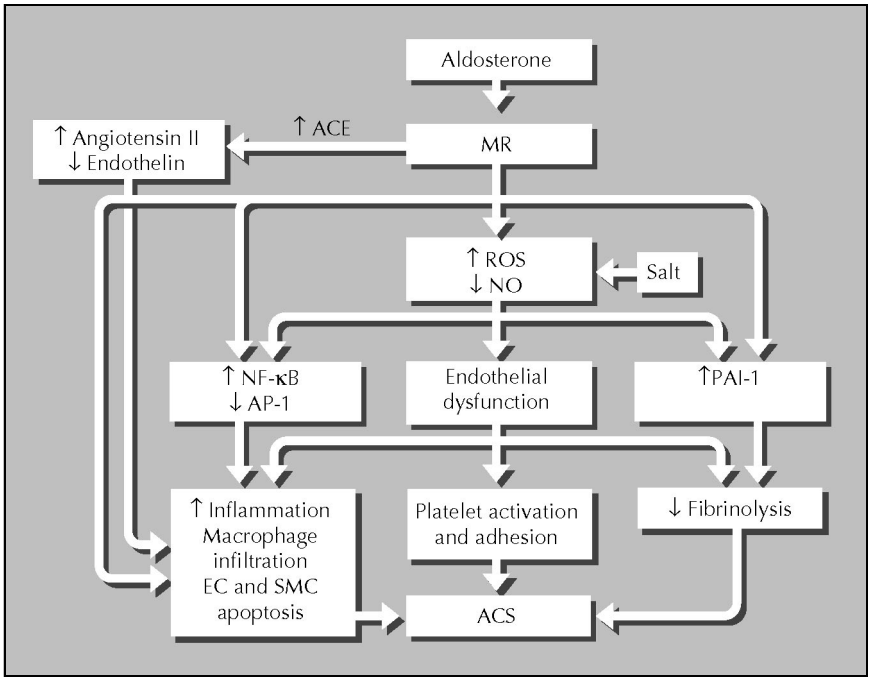

Figure 2. A role for the mineralocorticoid receptor (MR) in acute coronary syndromes (ACS). ACE—angiotensin-converting enzyme; AP-1—activator protein-1; EC—endothelial cell; NF-κB—nuclear factor kappa B; NO—nitric oxide; PAI-1—plasminogen activator inhibitor-1; ROS—reactive oxygen species; SMC—smooth muscle cells.

oxygenase-2, and TNF-α in the myocardium. Increased expression of inflammatory molecules and Th-1 cytokines in turn initiates an inflammatory cellular infiltrate in the form of invading macrophages, lymphocytes, and proliferating smooth muscle cells. Conversely, treatment with an MR antagonist in this model and in the spontaneously hypertensive stroke prone model reverses myocardial and vascular inflammation, respectively [15]. MR antagonism with spironolactone with small doses (100 ng/h for 21 days) administered in the third ventricle of the brain has been shown to decrease plasma tumor necrosis factor (TNF)-α production after postinfarction heart failure in rats, suggesting that some of the beneficial cardiovascular effects of MR blockade may be due to the reduction of proinflammatory cytokines through central MR blockade [16]. In a transgenic model of angiotensin II excess characterized by widespread inflammation, vascular injury, and myocardial injury, MR antagonism reduces collagen deposition and inflammation in the myocardium, concomitant with the down regulation NF-κB and activator protein-1 [17]. The inflammatory effects of aldosterone may be integrally related to its effects on free radical generation. Evidence to strengthen the argument that aldosterone-mediated inflammatory effects are at least in part mediated by free radicals comes from observations that the effects of aldosterone in the vasculature can be prevented by antioxidants [11••]. The inflammatory pathways activated by aldosterone may be compounded in a positive feedback manner by the effect of aldosterone on angiotensin-converting enzyme (ACE) expression [18]. Angiotensin II in turn serves as a prototypical proinflammatory mediator that may further potentiate aldosterone injury. Taken together, these findings support the notion that aldosterone results in proinflammatory effects and antagonism of MR with spironolactone or eplerenone may be anti-inflammatory.

Thrombosis

Aldosterone has been demonstrated to be an important prothrombotic determinant, and blockade of its actions may be potentially beneficial in patients with ACS who are known to have an activated coagulation cascade. Aldosterone upregulates plasminogen activator inhibitor (PAI)-1 expression in both cultured human endothelial cells and smooth muscle cells through transcriptional mechanisms [19•]. Conversely, MR blockade decreases PAI-1 levels [20•]. The effect of MR antagonists on PAI-1/tissue plasminogen activator levels has important implications not only for thrombosis and preventing the occurrence of MI, but also for renal and vascular fibrosis [21•]. MR antagonism may also have favorable effects on platelet function. Both eplerenone and trandolapril individually reduced, and the combination abolished platelet activation (evidenced by increased P-selectin expression as well as increased fibrinogen binding) in a post-MI model of CHF in the rat. The effects of eplerenone in conjunction with an ACE inhibitor were associated with normalization of platelet vasodilator-stimulated phosphoprotein, which seems to suggest the potential role of the antioxidant, NO-enhancing effects of MR antagonism in the genesis of its antiplatelet effects [22].

Altered collagen metabolism in acute coronary syndromes and postangioplasty restenosis

In experimental studies, aldosterone appears to be a key determinant of myocardial and vascular fibrosis [23]. Interestingly, the inflammatory response associated with excess aldosterone states appears to precede changes in the extracellular matrix and excessive collagen deposition [11••]. The fibrosis in response to aldosterone follows a typical perivascular pattern and is reminiscent of the pattern that follows inhibition of NO synthase [11••,24]. This suggests that the mechanisms

that are activated through aldosterone (through the MR) share common pathways with those that occur in response to NO deficiency. If aldosterone were to be profibrotic, then it would follow that MR antagonism will ameliorate myocardial remodeling and reduce fibrosis. Such an effect is indeed what has been encountered in both animal models as well as human studies that have examined this. In a post-infarction model of heart failure, the combination of eplerenone and an ACE inhibitor was better than either agent alone in preserving ventricular function and in preventing ventricular remodeling [25•]. These findings with eplerenone have been extended to a canine model of chronic heart failure as well [26]. Prevention of adverse ventricular remodeling may underlie some of the benefit seen with MR antagonism in the Randomized Aldactone Evaluation Study (RALES) study [27]. What is the evidence that MR antagonism alters remodeling of arterial vessels in atherosclerosis and restenosis (response to injury)?

Vulnerable areas in atherosclerotic blood vessels are classically associated with reductions in collagen I and III related to diminished synthesis and accelerated destruction due to activation of matrix metalloproteinases [1]. Plaque collagen content is an important determinant of plaque stability with higher levels of collagen reflecting stable plaques. Although the effects of MR antagonism in reducing collagen deposition may at first be viewed as being potentially deleterious, there has been no suggestion in vulnerable patient populations that this may be a problem [28••]. The reasons for this may be that the effects of MR antagonism in modulating collagen levels in the relatively avascular plaque may differ from its effects in the myocardium or even in the adventitia. To date there are no data on the effects of MR antagonism in arterial remodeling in native atherosclerosis and this remains an exciting area of investigation that can potentially be studied with available high-resolution means, including intravascular ultrasound and magnetic resonance imaging.

Increased collagen deposition along with vessel recoil is an important determinant of postangioplasty restenosis. Although the latter problem is significantly ameliorated with stenting, restenosis remains a significant problem in 20% to 40% of patients who undergo placement of non–drug-eluting stents. In a porcine model of angioplasty, eplerenone (1000 mg/d) significantly increased total vessel and luminal area compared with the no treatment group, without affecting neointimal volume [29•]. These effects were accompanied by a reduction in collagen density in the vascular media. Interestingly these effects were not observed in angioplastied iliac arteries suggesting a differential effect of eplerenone on vascular beds.

Conclusions

Mineralocorticoid receptor antagonism may have broad applicability as an anti-atherogenic strategy and could potentially represent an exciting new therapeutic avenue in ACS. Eplerenone is an attractive agent for this application because it is a selective MR antagonist with a reduced potential for side effects as compared with its nonselective counterpart, spironolactone. The ultimate test of the hypothesis that MR antagonism breaks the maladaptive responses inherent in ACS due to endothelial dysfunction, heightened thrombogenicity, and inflammation will, however, require further direct clinical investigation, specifically in the form of large-scale, randomized controlled trials. Should this hypothesis prove correct, the impact on public health in the treatment of cardiovascular disease, including ACS, could be very important.

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