Aldosterone is increasingly recognized to play an important role in the pathophysiology of heart failure due to systolic left ventricular dysfunction (SLVD) and aldosterone blockade (AB) to be effective in reducing mortality and morbidity in patients with severe chronic heart failure and heart failure due to SLVD after myocardial infarction. AB has also been shown to reduce blood pressure and target-organ damage in patients with essential hypertension. The effect of AB on mortality and morbidity will soon be investigated in patients with mild to moderate heart failure due to SLVD and in patients with heart failure with preserved left ventricular systolic function. Although AB has been shown to be effective in patients with SLVD and in those with essential hypertension without SLVD, increasing evidence suggests that it may have an even greater role in patients with atherosclerosis of the coronary and other vascular beds.

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Role of Aldosterone in Vascular Damage and Its Consequences

It is reasonable to assume that aldosterone influences vascular function because mineralocorticoid receptors are expressed in vascular endothelial and smooth muscle cells as well as in cardiac fibroblasts and cardiomyocytes. Many of the pathophysiological effects of angiotensin II on the myocardium and vascular wall may, in a large part, be due to aldosterone and can be blocked by AB as well as by an angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB); however, it appears that the combination of an AB with an ACE-I or ARB may be more effective than either alone in preventing myocardial and vascular inflammation and remodeling. Although angiotensin II is a major stimulus for the production of aldosterone, other stimuli such as potassium are also important (“aldosterone escape”), as illustrated by the ability to stimulate aldosterone production in the angiotensinogen-knockout mouse. These data suggest that AB could add to the benefits of ACE-I in reducing mortality and morbidity in patients with vascular disease without known SLVD, as shown in the Heart Outcomes Prevention Evaluation (HOPE) and European Trial on Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease (EUROPA) studies.

To date, several mechanisms have been evaluated to understand the adverse effects of aldosterone on vascular function. Aldosterone has been shown to increase NADPH oxidase activity and reactive oxygen species (ROS) generation and AB to improve endothelial function in a high-cholesterol diet rabbit model. Aldosterone has also been shown to decrease tetrahydrobiopterin, an important cofactor for endothelial nitric oxide (NO) synthase activity and NO production, and AB to improve tetrahydrobiopterin levels and restore NO synthesis. Aldosterone stimulates, and AB blocks, nuclear factor-κB and activator protein-1 signaling pathways.

Clinically, AB is additive to an ACE-I in improving endothelial function in patients with heart failure due to SLVD. Because endothelial function has been shown to be an important independent predictor of cardiovascular events in patients with coronary atherosclerosis, these results would support the hypothesis that AB will have an important role in the prevention of atherosclerosis and its consequences: myocardial infarction, stroke, and sudden cardiac death. Further evidence and support of this hypothesis come from the finding that aldosterone increases the expression of the lesion-like oxidized low-density lipoprotein receptor (LOX-1) receptor. The LOX-1 receptor has been shown to be responsible for the oxidation of LDL cholesterol and to play an important role in adhesion molecule activation.

Aldosterone also has been shown to increase tissue ACE activity and in some studies prevents angiotensin II–induced downregulation of the angiotensin II type 1 (AT1) receptor. These studies suggest a vicious cycle in which angiotensin II, through the AT1 receptor, stimulates the production of aldosterone, which in turn leads to an increase in tissue ACE activity, a further increase in angiotensin II, and therefore a further increase in aldosterone levels. Because angiotensin II and aldosterone both have been shown to increase LOX-1 receptor expression, it can be postulated that AB in addition to an ACE-I and/or an ARB might be effective in decreasing oxidized LDL cholesterol levels and ROS, with a resultant increase in NO bioavailability and a beneficial effect on the atherosclerotic process and its consequences (Figure 1). Support for this hypothesis comes from a study by Keidar et al showing that aldosterone increases macrophage oxidized LDL cholesterol concentration and atherosclerotic lesion area in the apolipoprotein E–knockout mouse. In this model, the most effective strategy to reduce atherosclerotic lesion area was the combination of AB and an ACE-I or ARB. The recent observation that aldosterone decreases the expression of the AT1 receptor in a model of hindlimb ischemia suggests yet another hypothesis and link to NO bioavailability and hence to the atherosclerotic process and its consequences (Figure 2).
These hypotheses (Figure 1 and Figure 2), although requiring further confirmation, provide a theoretical framework for the investigation of AB in the progression of atherosclerosis and its consequences. Further evidence linking aldosterone to atherosclerosis comes from studies showing that aldosterone increases and AB decreases vascular inflammation18 and metalloproteinase-2 and -9 activation.19 Vascular inflammation has been suggested to be an important pathophysiological precursor of atherosclerosis and metalloproteinase-2 and -9 activation to be important in atherosclerotic plaque destabilization. These studies suggest the need for further investigation into the proximal pathways by which aldosterone increases oxidant stress and decreases biavailable NO to influence vascular function.

The study by Garnier et al20 in this issue of Circulation provides a new model to explore the role of aldosterone in vascular damage and its consequences. In this model, transgenic mice were made to overexpress aldosterone synthase in the heart, resulting in a 1.7-fold increase in myocardial aldosterone concentration compared with wild-type animals. The increase in myocardial aldosterone was associated with endothelial-dependent and endothelial-independent vascular dysfunction without an alteration in vascular inflammation or myocardial fibrosis. These results suggest that impaired vascular function may be the first manifestation of aldosterone-induced cardiovascular damage. The cause for the vascular damage in this model has not yet been explored. It is, however, reasonable to postulate, on the basis of the concepts outlined above and evidence from the double-transgenic rat model overexpressing the human renin and human angiotensinogen gene, that the vascular damage is due to an aldosterone-mediated increase in ROS. Although an increase in NAD(P)H oxidase activity and ROS generation has been shown to lead to endothelial dysfunction8 it is likely that the selective increase in tissue aldosterone in this model and relatively high local production of ROS result in vascular smooth muscle cell damage to promote endothelial-independent vascular dysfunction. In fact, in vitro studies of vascular smooth muscle cells exposed to aldosterone demonstrate increased ROS production, transactivation of the epidermal growth factor receptor, and activation of extracellular signal-regulated kinase and c-Jun N-terminal kinase signaling, whereas AB inhibited these effects21 This model could provide an important vehicle to explore the proximate genetic and enzymatic processes involved in aldosterone-induced vascular damage as well as damage to the myocardium and other target-organ tissues. Before going further, however, it will be necessary to demonstrate that AB through genomic or

Figure 1. Aldosterone (Aldo) causes a vicious cycle by upregulating tissue ACE and preventing angiotensin II (AT$_2$)-induced downregulation of the AT$_1$ receptor (AT$_1$R). Aldo also upregulates the LOX-1 receptor (LOX-1 R), resulting in an increase in oxidized LDL cholesterol (OXLDL-C). Also, AT$_1$ and OXLDL-C increase vascular NAD(P)H oxidase activity, resulting in an increase in ROS and a destruction of NO.

Figure 2. A, Effect of angiotensin II (AT$_2$) stimulation: AT$_1$ receptor (AT$_1$R)-induced aldosterone (Aldo) decreases AT$_2$R expression during ischemia, leading to AT$_1$-induced decrease in NO availability. B, Angiotensin receptor blockade prevents AT$_1$R-induced aldosterone formation with a resultant increase in AT$_2$R expression and NO availability. C, In situations with “aldosterone escape,” AT$_1$R expression is inhibited, decreasing its effect on NO availability. D, AB in addition to an ARB results in an increase in AT$_2$R expression and an increase in NO availability.
nongenomic mechanisms can prevent the endothelial-dependent and endothelial-independent damage in this model and that it is not some other factor that is responsible for these observations. Regardless, the increasing evidence that angiotensin II and aldosterone induce common and independent ROS signaling processes,21 as well as the hypotheses outlined above, provides an impetus for further exploration of the role of AB in conjunction with an ACE-I or ARB in preventing vascular damage, the atherosclerotic process, and its consequences. It is reasonable to hope that AB will provide a further reduction in mortality and morbidity and, therefore, healthcare costs associated with atherosclerosis and its consequences when added to an ACE-I. It is not unreasonable to believe that this model20 as well as other models, such as the double human renin and human angiotensinogen rat model,21 will play an important role in our understanding of these processes and speed this application, if validated, into clinical practice.

References

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