Plasma aldosterone levels in patients with coronary artery disease without heart failure or myocardial infarction: implications for pathophysiology, prognosis, and therapy

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This editorial refers to ‘Aldosterone, mortality, and acute ischaemic events in coronary artery disease patients outside the setting of acute myocardial infarction or heart failure’1, by F. Ivanes et al., on page 191

Increased plasma levels of aldosterone and cortisol have been associated with an increased risk of mortality and hospitalization for heart failure (HF) in patients with a reduced left ventricular ejection fraction (REF). Mineralocorticoid receptor antagonists (MRAs), which block the effects of both cortisol and aldosterone on the MR,2 are effective in reducing total mortality as well as hospitalizations for HF in patients with chronic HFREF and in patients with HFREF early post-myocardial infarction (MI). Increased levels of aldosterone in patients with HF and a preserved left ventricular ejection fraction (PEF) as well as in patients early post-MI without clinical evidence of HF have also been associated with an increase in cardiovascular risk. MRAs are therefore currently being investigated in patients with HFPEF and in patients with both ST-elevation and non-ST-elevation MI without clinical evidence of HF.

Ivanes et al. have reported on the measurement of plasma aldosterone in 799 consecutive patients with coronary artery disease (CAD) referred for elective coronary angioplasty.2 Patients with an acute MI or an acute coronary syndrome requiring urgent revascularization and those with clinical evidence of HF were not included. Over a mean follow-up of 14.9 months, multivariant Cox model analysis showed that plasma aldosterone levels were independently associated with an increase in cardiovascular events. They also found that plasma aldosterone levels provided complementary and incremental prognostic information above and beyond that provided by measurement of brain natriuretic peptide (BNP) and high sensitivity C-reactive protein, and positively correlated with the presence of obesity and hypertension, suggesting a potentially important role for aldosterone in patients with the metabolic syndrome. Also of interest is their finding that the use of angiotensin-converting enzyme (ACE) inhibitors was not associated with a reduction in plasma aldosterone levels, suggesting ‘aldosterone escape’ and therefore an increased risk of cardiovascular events related to aldosterone despite the use of an ACE inhibitor. They also noted an increase in plasma aldosterone levels in patients with hypertension and those treated with diuretics, which in part might explain the increased risk of atherosclerosis and its cardiovascular consequences: MI, stroke, and sudden cardiac death in patients with hypertension.

While activation of the angiotensin type 1 receptor (AT1-R) is an important stimulus for the production of aldosterone from the adrenal gland, neither ACE inhibitors nor angiotensin receptor-blocking agents (ARBs) are sufficient to block the production of aldosterone,3 due to the presence of other stimuli such as potassium. Furthermore, an increase in aldosterone and or activation of the MR results in an upregulation of ACE activity and AT1-R expression, i.e. a vicious cycle with increasing activation of the renin–angiotensin–aldosterone system (RAAS). To block this vicious cycle and to obtain maximal benefits it is necessary to block both the MR and the AT1-R.

The observations by Ivanes et al.2 as well as the association of an increase in plasma aldosterone levels with an increase in cardiovascular events in patients with CAD in the LOURIC study4 have important mechanistic, prognostic, and therapeutic implications for patients with CAD. While lipid-lowering therapy has been associated with a significant reduction in cardiovascular risk in patients with CAD, there remains a relatively high risk of cardiovascular events despite their use. Aldosterone increases the expression of the lecithin-like, oxidized, LDL receptor (Lox-1),5 predisposing to the oxidation of LDL-cholesterol (LDL-C), thus possibly negating some of the potential benefits of lipid-lowering therapy. Similarly, while ACE inhibitors are associated with a reduction in
cardiovascular events in patients with CAD without evidence of HF, there remains a relatively high incidence of cardiovascular events even when an ACE inhibitor is combined with effective lipid-lowering therapy. In part this residual cardiovascular risk in patients with CAD despite current treatment with lipid-lowering therapy and or an ACE inhibitor can be explained by their failure to suppress aldosterone production from the adrenal gland, especially in patients with obesity in whom the adipocyte plays an important role in the production of aldosterone. However, while an increase in plasma aldosterone levels $\geq 35$ pg/mL appears to predict an increase in cardiovascular events in the study by Ivanes et al., it will require a far larger number of patients over a wide range of ages, renal function, and cardiovascular medications before we can be confident as to the exact level of plasma aldosterone that is associated with an increase in cardiovascular risk.

The association between an increase in plasma aldosterone levels and or activation of the MR and an increase in cardiovascular events in patients with CAD independent of the presence of MI or HF as suggested by the study of Ivanes et al. is supported by preclinical studies as outlined in Figure 1. For example, MR expression in the vascular wall is increased with age through an angiotensin II-dependent mechanism contributing to vascular inflammation; aldosterone decreases endothelial glucose-6-phosphate dehydrogenase (G6PD) activity with a resultant decrease in glutathione, antioxidant reserves, and nitric oxide (NO) availability with its known consequences on endothelial function and the atherosclerotic process. Rajagopalan et al. were the first to show that an MRA improved endothelial function and atherosclerosis in a lipid-fed animal model independent of MI, HF, or hypertension. Subsequent pre-clinical studies in primates have also suggested a beneficial effect of MRAs on endothelial function and the atherosclerotic process beyond that provided by ACE inhibitors. MR activation is associated with an increase in the proinflammatory transcriptional factors nuclear factor-κB (NF-κB) and activator protein 1 (AP-1) with an increase in inflammatory cytokines and apoptosis. Of interest is the role of macrophages in the atherosclerotic process: the finding that MRs are expressed in macrophages; that aldosterone increases NAD(P)H vascular oxidase activity and oxidized LDL-C concentration in macrophages; that macrophages release matrix metaloproteases and tissue factor that could affect plaque stability; and that knockout of the MRs on macrophages prevents many of the consequences of aldosterone in the myocardium and vascular wall. The role of the macrophage MR on atherosclerotic plaque stability will therefore be an important area of future investigation. Aldosterone, by inhibiting the formation of bone marrow-derived progenitor endothelial cells, may have an important role limiting endothelial repair after injury and, by stimulating the production of plasminogen activator inhibitor (PAI-1), may adversely affect fibrinolysis after plaque rupture.

**Figure 1** Potential role of MR activation in the development of atherosclerosis, coronary artery disease, and its clinical consequences.
Although large-scale randomized studies of MRAs in patients with CAD without MI, HF, or hypertension are not currently available, the study by Ivanes et al.² combined with our increased understanding of the role of MR activation and its effects on oxidative stress, inflammation, NO availability, apoptosis, macrophage function, endothelial repair, and fibrinolysis suggests an important role for plasma aldosterone levels to predict future cardiovascular events and for MRAs in the prevention and therapy of CAD above and beyond that provided by current lipid-lowering therapy, ACE inhibitors, or ARBs. However, the potential benefits of MRAs, especially in elderly patients with CAD many of whom have concomitant chronic kidney disease (CKD), might in part be limited by their potential risk of hyperkalaemia (serum potassium $\geq 5.5$ mEq/L). In view of the continued ageing of the population, the epidemic of visceral obesity, diabetes mellitus, and CKD, in conjunction with the use of ACE inhibitors or ARBs in many of these patients, all potential risk factors for the development of hyperkalaemia, it will be necessary to select patients carefully and to serially monitor serum potassium with adjustment of the dose of the MRA accordingly. Further efforts to prevent the development of hyperkalaemia, such as the use of new potassium-binding polymers¹⁴ and the exploration of new non-steroidal MRAs,¹⁵ that at least in preclinical studies appear to block the MR with a more favourable sodium/potassium ratio than spironolactone or eplerenone, take on new urgency if the promise of a further reduction in cardiovascular risk and cardiovascular hypertrophy and remodeling in mice. J Clin Invest 2010; 120:3350–3364.

Conflict of interest: none declared.

References

14. Pitt B, Anker SD, Bushinsky DA, Kitzman DW, Zannad F, Huang I-Z, on behalf of the PEARL-HF investigators. Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with CAD without MI or heart failure as suggested by the study of Ivanes et al.² is to be fulfilled.