Large clinical trials have demonstrated profound benefits of aldosterone inhibition by spironolactone in patients with heart failure (impairment of left ventricle function <40%) and with eplerenone in patients with myocardial infarction. The key enzyme in aldosterone production is aldosterone synthase (CYP11B2). CYP11B2 is predominantly expressed in the adrenal gland but is also expressed in the cardiovascular system. Angiotensin (Ang) II is the major stimulus for CYP11B2-related aldosterone synthesis. Preclinical and clinical studies have shown that Ang II inhibition is pivotal to the treatment of heart failure and ischemic heart disease. The previous belief was that inhibition of Ang II should be sufficient to block aldosterone production; however, aldosterone levels can be elevated although Ang II production is inhibited or its action is blocked. This state of affairs is called the aldosterone breakthrough phenomenon; its mechanisms are unclear. Indeed, additional inhibition of the mineralocorticoid receptor (MR) reduces proteinuria in Ang-converting enzyme inhibitor–treated patients with early diabetic nephropathy.

The strong effect of aldosterone on inflammation in the cardiovascular system has been reviewed recently. MR antagonism prevents vascular injury and cardiac fibrosis, activation of activator protein-1 and nuclear factor kappa B, and upregulation of the basic fibroblast growth factor in hearts of rats doubly transgenic for the human renin and angiotensinogen genes. MR antagonism decreases aortic inflammation, fibrosis, and hypertrophy in hypertensive rats. Like Ang II, aldosterone activates reduced nicotinamide-adenine dinucleotide phosphate oxidases in the rat and increases expression of the reduced nicotinamide-adenine dinucleotide phosphate oxidase subunit p22phox in human monocytes.

The present study by Michea et al now demonstrates the impressive effect of the MR antagonist spironolactone on left ventricular hypertrophy (LVH) induced by chronic renal failure. Renal failure is associated with one of the highest risks for cardiovascular morbidity and mortality. Impaired renal function is independently associated with heightened risk for death, cardiovascular death, and hospitalization for heart failure in patients with chronic heart failure with both preserved and reduced left ventricular ejection fraction.

Michea et al demonstrated in uremic rats that intervention with spironolactone reduced ultrasone and cellular parameters of LVH; significantly reduced markers of cardiac over-load, ANP and BNP gene expression; and reduced MR-dependent cardiac SGK1 expression, an indicator for cardiac MR activation. The dramatic reduction in LVH under treatment was accompanied by a clear reduction of parameters for oxidative stress, myocardial NOX-2, NOX-4, p47phox, and dihydroethidium staining. Increased oxidative stress activates the redox-sensitive nuclear factor kappa B, triggering inflammation. Aldosterone-stimulated activation of nuclear factor kappa B in the heart was prevented recently in NOX-2–deficient mice. These mechanisms lead to cardiac inflammation, interstitial fibrosis, and cardiac hypertrophy, as well as increased cardiac morbidity (Figure).

Importantly, the authors also investigated cardiac aldosterone levels and expression of CYP11B2 to address potentially local effects of aldosterone synthesis. There were no differences in the expression levels for these 2 parameters in all of the groups. This in accordance with experimental evidence from Chai et al and other groups who found that adrenal aldosterone is the relevant source for MR activation in the cardiovascular system under experimental conditions.

The present report by Michea et al strongly supports the evidence of MR activation as an important pathophysio logical factor in patients with renal failure and cardiac disease. In the clinical setting, a number of smaller trials in patients with renal failure were evaluated and favored the concept of spironolactone therapy to slow both progression of renal disease and cardiovascular disease. However, adverse effects have to be considered. The most deleterious is hyperkalemia, particularly in patients with reduced renal function, heart failure, or diabetes, but careful titration and the use of low doses of MR antagonists minimizes this risk. The current findings support the obvious need for a larger interventional trial targeting MR activation in patients with chronic renal disease, as well as end-stage renal failure.
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None.

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