Aldosterone inhibition and heart failure: Too good to be true?

Gary S. Francis, MD Cleveland, Ohio

The Randomized Aldactone Evaluation Study (RALES) had stunningly positive results.1 On the surface it seemed incredible that spironolactone, a drug that has been available for more than 40 years and rather underappreciated by the medical community, could reduce the mortality rate by 30% in patients with advanced heart failure. Both sudden death and death from progressive heart failure were reduced by 35% and symptoms of heart failure were also significantly reduced. These rather striking improvements occurred on background therapy with angiotensin-converting enzyme (ACE) inhibitors, digoxin, and loop diuretics. Although it has long been appreciated that aldosterone is important in the pathogenesis of heart failure, especially edema,2 more recent experimental data have supported the not-immediately-intuitive concept that excess aldosterone is related to extracellular matrix, collagen deposition, and myocardial fibrosis.3,7 Despite substantial animal data in support of the association between excessive aldosterone and myocardial fibrosis, there have been nonbelievers. Few data have been available to support such an important antifibrosis role for aldosterone in patients with heart failure. RALES certainly opened our eyes. The magnitude of the effect in RALES, which approached that of ACE inhibition in heart failure, was surprising to many. However, the trial did not seek or confirm a specific mechanism underlying the benefit of aldosterone antagonism, and some lingering doubts persisted.

In this issue of the Journal, Modena et al provide some new insight as to how aldosterone antagonism might improve the prognosis in patients with heart failure. It had previously been suggested that reduced perivascular and interstitial fibrosis would result from aldosterone antagonism, leading to a more supple, flexible myocardium.8 A less stiff heart would generally have lower filling pressure, thereby leading to less patient dyspnea and improved symptoms. Presumably less myocardial collagen would also be associated with fewer intraventricular conduction abnormalities, thereby leading to less heart block and arrhythmias. Importantly, potassium and magnesium depletion would be blunted with aldosterone antagonism, also leading to reduced vulnerability to arrhythmias. Other mechanisms, including reduced norepinephrine uptake by the myocardium, improved baroreflex function, and enhancement of parasympathetic activity, have also been postulated to be benefits of aldosterone antagonism.9

Modena et al in a carefully conducted clinical study of 46 patients with heart failure with a first episode of transmural (ST-T elevation) myocardial infarction were randomly allocated to treatment with an oral aldosterone inhibitor or placebo superimposed on background therapy of ACE inhibitor. About half the patients in each group were also receiving β-adrenergic blockers and nitrates, agents known to favorably modify post-myocardial infarction cardiac remodeling. Patients treated with the aldosterone antagonist had significantly less production of aminoterminal propeptide type II collagen (ie, less collagen synthesis) during follow-up and also had significantly smaller left ventricular volumes by echocardiography. The findings, if correct, support the original hypothesis of Brilla and Weber10 that myocardial remodeling can be efficiently blocked by small doses of aldosterone antagonist. The findings fit nicely with a large body of previous experimental animal work and with the recent outcome of the RALES trial.

Patients with advanced heart failure commonly have elevated plasma aldosterone levels, despite ACE inhibitor therapy.11 The absolute level of plasma aldosterone may not be the key element, but an inappropriately high level of aldosterone relative to the patient’s Na+ status may be what drives interstitial cardiac fibrosis.10 Secondary hyperaldosteronism is likely one of many factors, including neurohormones, cytokines, and altered loading conditions, that are important in the remodeling process. Similar left ventricular remodeling is also observed in primary aldosteronism.12 Post-myocardial infarction left ventricular remodeling can be favorably attenuated by aldosterone inhibition, according to Modena et al.

The antiremodeling effects of ACE inhibitors,13 β-
adrenergic blockers,14 and now aldosterone antagonists add further support to the broader neurohumoral hypothesis of heart failure. Prevention of myocardial remodeling is a key therapeutic goal in the treatment of patients with heart failure, and blocking multiple neurohormonal pathways may be the best form of treatment currently available. Presumably, in the study of Modena et al reduced collagen synthesis was associated with less dilation of the left ventricle after myocardial infarction, although individual patient data points are not provided. One wonders if there was any relation between the reduction in aminoterminal propeptide type II collagen and the failure to dilate the left ventricular chamber. It is also possible that the aldosterone-induced attenuation of post–myocardial infarction remodeling observed by Modena et al was due to concomitant use of β-adrenergic blockers or nitrates or to chance (the sample size is quite small). Exactly how development of fibrosis contributes to cavity dilation is not clear, but enhanced fibrosis could certainly lead to increased stiffness of the left ventricular chamber and higher filling pressures. It is of interest that endothelial receptor antagonists, also potent antiremodeling agents in the setting of experimental myocardial infarction,15-17 decrease aldosterone secretion independently of angiotensin II.18

The observations of Modena et al are consistent with the overall findings of RALES and a large body of animal work. They suggest that aldosterone antagonists reduce collagen synthesis and attenuate chamber enlargement after myocardial injury. These time-honored agents appear to be more than weak diuretics. They may be potent antiremodeling agents. Second-generation aldosterone antagonists are currently under development, and a second large randomized controlled trial is now being planned. If the second trial is also positive, it will be difficult to ignore their use for the treatment of heart failure. This author is gradually becoming a believer.

References