Potential Antiapoptotic Activity of Aldosterone Antagonists in Postinfarction Remodeling

To the Editor:

We welcome the paper from Suzuki et al.1 on the beneficial effect of eplerenone on postinfarction left ventricular remodeling in dogs. However, we believe that the authors have failed to thoroughly appraise their findings as they neglected to analyze and discuss the role of myocardial apoptosis as a major pathophysiological mechanism potentially underlying the benefits derived from aldosterone receptor antagonism.

Myocardial apoptosis plays a pivotal role in postinfarction left ventricular remodeling, as shown by several investigators, including researchers using the very same animal model as that of Suzuki et al.,1 and also including some landmark articles by the same coauthors of the Suzuki et al report.2–4 Apoptotic cardiomyocyte loss after infarction is also known to be extremely variable, and its severity and extent may be modulated by several pathophysiological mechanisms and variables, such as the renin-angiotensin system, β-adrenergic stimulation, and permanent infarct-related artery occlusion.3,4

Aldosterone has been recently shown to detrimentally affect cardiomyocyte apoptosis in normotensive rats,5 and we may thus hypothesize that aldosterone activity is another potential apoptosis-modulating mechanism in postinfarction remodeling. However, we cannot find experimental data confirming this speculation in the authors’ report, as unfortunately no assay to detect cardiomyocyte apoptosis was apparently performed. Moreover, Suzuki et al.1 failed to at least discuss the role of apoptosis in mediating progressive ventricular remodeling, myocardial fibrosis, and cardiomyocyte replacement, such as those described in their histological specimens. Nonetheless, they properly quoted the Randomized Aldactone Evaluation Study, which showed a 30% reduction in the risk of death in patients with severe heart failure on spironolactone therapy. However, established pathophysiological mechanisms underlying such a consistent clinical benefit are still lacking. The story of spironolactone is indeed strikingly reminiscent of the tales of ACE inhibitors and β-blockers. For both agents, clinical evidence of major benefit occurred quite before any plausible pathophysiological explanation could be substantiated. In fact, for ACE inhibitors as well as β-blockers, reduction of myocardial apoptosis now represents one of the principal reasons of improved clinical outlook, as shown by the outstanding studies performed by Goussev et al.3 and Sabbah et al.4

We think that the same may apply to aldosterone antagonists (and perhaps also to other investigational or established drugs known to beneficially affect left ventricular remodeling), and we believe that any experimental research regarding the effects of drugs on heart failure progression should definitively assess myocardial apoptosis, which is likely to represent a final common pathway to myocardial damage.

Giuseppe G.L. Biondi-Zoccai, MD
Antonio Abbate, MD
Alfonso Baldi, MD
Institute of Cardiology
Catholic University
Rome, Italy
gbiondizoccai@tiscali.it

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Giuseppe G.L. Biondi-Zoccai, Antonio Abbate and Alfonso Baldi

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