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EDITORIAL COMMENT

Myocardial Structural Effects of Aldosterone Receptor Antagonism in Heart Failure*

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The remarkable effectiveness of aldosterone receptor antagonists in reducing the mortality risk in patients with advanced heart failure (HF) (1) has led many to assume that the aldosterone receptor is directly involved in the process of left ventricular (LV) remodeling, which seems to be a critical mediator of the progressive syndrome of HF (2,3). This perception has been fed by preclinical evidence for aldosterone-mediated myocardial fibrosis and remodeling (4,5). But persuasive evidence has been lacking from an adequately controlled clinical trial to demonstrate that the favorable effect of this therapy could be attributed to its anti-remodeling effect rather than to another mechanism, such as an antiarrhythmic response to potassium retention. Furthermore, the interaction between aldosterone receptor blockade and the other neurohormonal inhibitors used in HF has not been explored.

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The single-site clinical trial reported in this issue of the *Journal* by investigators at the Prince of Wales Hospital in Hong Kong (6) seems to have at least in part filled this data gap. Publication of this study should also remind investigators that a single-institution study can address important questions in a modest-sized clinical trial if it is properly designed and overseen for compliance.

So is the issue now resolved? Does aldosterone receptor blockade inhibit LV remodeling? Is its effect independent of the antiremodeling effect of angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), and beta-blocker medications, which now constitute standard therapy in the management of HF? To address these questions we must examine the protocol, the results, and the interpretation.

Protocol

To provide uniform background renin-angiotensin system (RAS) inhibition, the protocol required patients to be receiving chronic ACE inhibitor therapy (dose not specified), which was discontinued at the time of randomization and replaced with a modest dose of an ARB (candesartan 8 mg). Given the mandate for RAS inhibiting therapy in HF, the design of trials such as this is always a compromise. There can be no assurance, however, of stability of RAS inhibition and certainly no assurance that the candesartan effect was similar to the prior ACE inhibitor effect. Although the population was presumably Asian and thus possibly responsive to lower doses of neurohormonal inhibitors, it is unlikely that the uncontrolled prior ACE inhibitor or the prescribed candesartan provided optimal inhibition of the RAS. Furthermore, in a trial as small as this one (48 patients), individual variability in response could weaken the significance of group comparisons. Indeed, although the group randomized to spironolactone did not differ significantly at baseline from the group randomized to placebo, modestly greater initial LV remodeling in the spironolactone arm could have influenced the subsequent response to therapy.

Results

The use of magnetic resonance imaging to quantitate LV structural changes made it possible to identify a therapeutic effect in this modest-sized trial. Most impressive was the progressive decline over the 1-year follow-up in the end-diastolic and end-systolic LV volumes. This apparent reversal of remodeling, which was accompanied by a significant reduction of LV mass, certainly suggests that spironolactone has exerted a myocardial structural effect. The fall in blood pressure in the spironolactone-treated group could have contributed to the structural benefit, but other blood pressure-lowering drugs do not necessarily cause regression of remodeling in HF (7,8).

Whether the remodeling effect of spironolactone is independent of that associated with other HF therapies is difficult to establish. Approximately 70% of the patients were said to be treated with a beta-blocker drug, but the type, dose, and duration of such therapy is not provided. Beta-blocker drugs produce reverse remodeling effects similar to that observed in this study (9), and the ARB, valsartan—albeit in a higher dose—inhibits remodeling when added to a beta-blocker drug (10). The recent A-HeFT (African-American Heart Failure Trial) study has demonstrated further regression of remodeling when a fixed-dose combination of isosorbide dinitrate and hydralazine is added to RAS blockade and beta-blocker therapy in HF (11). One-half of the patients in the current trial were being treated with a nitrate (dose not stated), and whether chronic oral nitrate therapy not accompanied by hydralazine can contribute to regression of remodeling is unknown. The Hong

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Kong trial is certainly too small to attempt stratification by background therapy to explore possible differential responses. Thus, the data are consistent with an effect independent of other inhibitor effects, but the issue cannot be fully resolved.

Interpretation

The evidence for regression of LV structural remodeling in response to spironolactone in this small trial supports the preclinical structural and clinical biomarker data suggesting a favorable effect on myocardial interstitium and collagen. These observations lend credence to the concept that the favorable effect of aldosterone inhibition on cardiovascular outcomes can at least in part be attributed to their properties to inhibit structural remodeling.

Regression of remodeling in response to an aldosterone receptor blocker drug does not necessarily lead to the conclusion that aldosterone mediates the remodeling process. Aldosterone levels are not independently predictive of survival in HF (12), and the favorable effect of aldosterone blockade does not seem to be dependent on elevated circulating levels. Furthermore, aldosterone receptors are under the influence of other steroids that might contribute to the adverse effects of receptor stimulation (13).

An important feature of this study is that it was conducted in patients with mild-to-moderate HF. The original RALES (Randomized Aldactone Evaluation Study) was carried out in advanced class (III to IV) HF. The exclusion of milder HF has led guidelines committees to limit their recommendation of spironolactone to management of such advanced HF, even though no one can seriously suggest that class III to IV HF is a different disease from class II HF. Left ventricular remodeling is a biologic process that is independent from symptoms that define clinical severity. Therefore, the data supporting a salutary remodeling effect in mild-to-moderate HF should help to convince the medical community that outcome benefit, although easier to demonstrate in patients with a higher event rate, should be applicable to all patients with the disease process.

A word of caution is required in interpreting the magnitude of effect of spironolactone observed in this study. The Hong Kong study was by its design carried out in a homogeneous population. I have long advocated for such homogeneous studies (14) not to predict the effect in any single future patient but to demonstrate therapeutic potential. Racial, ethnic, and geographic differences in disease mechanisms, frequency, severity, and therapeutic response plague efforts to apply large megatrial data to individual patient care. Whether genetic or environmental factors drive these differences, their existence should dissuade us from predicting benefits in one individual or population from a study in a different population (15,16). Few large studies have examined outcome or biologic intermediate data in Asian populations. Therefore, these data from Hong Kong should encourage us about therapeutic potential but not necessarily inform us about the magnitude of therapeutic efficacy in a different population.

Magnetic resonance imaging certainly provides accurate quantitation of LV structure. But global changes in chamber volume and wall mass, as identified in the present study, are probably only surrogates for the cellular and interstitial changes that likely are directly responsible for a favorable effect of drugs on the course of HF. Whether the unmeasured cellular effects of spironolactone differ from those of ACE inhibitor drugs, ARBs, beta-blocker drugs, and nitric oxide donors remains unknown. Knowledge of these cellular effects might allow us to use this array of drugs more rationally, perhaps on the basis of the specific cellular and interstitial abnormalities in an individual patient. Such molecular and cellular features might explain the apparent population difference identified in diverse populations. The data from this small trial emphasize how valuable it would be to demand that large trials attempt to correlate outcome effects with cardiac structural changes that could eventually serve as more precise markers for efficacy (17).

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