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Absolute, Not Relative, Changes Are Important When Interpreting Trial Data

Tsutamoto et al. (1) have recently reported on the beneficial effects of spironolactone on plasma neurohormones and echocardiographically derived left ventricular (LV) volume and mass indices in patients with nonischemic congestive heart failure. Though spironolactone is known to reduce morbidity and mortality in severe heart failure, many of the mechanisms underlying these effects have yet to be fully elucidated (2). Because aldosterone has direct myocardial actions that may play an important role in LV remodeling, it is particularly relevant to investigate the effects of spironolactone on this process.

However, several points need careful consideration when interpreting the data presented by Tsutamoto et al. (1). First, the investigators state that no significant differences existed between the placebo- and spironolactone-treated groups at baseline. However, this seems somewhat surprising considering that the mean baseline plasma-active renin concentration was 234 pg/ml in the placebo group but only 93 pg/ml in the spironolactone group. Furthermore, it appears that LV ejection fraction (LVEF) was greater and both LV end diastolic volume and mass were lower in the placebo group. Although these differences in echocardiographic parameters did not reach significance, they have an important bearing when interpreting the results after four months of active therapy. The researchers concluded that spironolactone treatment resulted in an improvement in indices of LV remodeling, which was based upon a significant difference in *changes* of echocardiographic parameters between the two groups at four months. However, when determining the clinical relevance of a novel therapy in any placebo-controlled study it is imperative to compare the absolute means between the two groups at follow-up. In our opinion, the investigators should have performed an unpaired *t* test between the groups after four months of treatment. As this has not been mentioned in the report by Tsutamoto et al. (1), should we assume that these differences did not reach statistical significance? This possibility is supported by the absolute values given in the researchers Table 2 (1). For example, although spironolactone therapy resulted in an increase in LVEF of 2.8% ($p < 0.05$), the absolute value of 35% after four months of treatment was similar to that in the placebo group (baseline, 36.6%; four months, 36.3%). This demonstrates the potential pitfalls of preenting relative changes as opposed to absolute values in assessing the clinical benefits of a therapeutic agent.

One of the reasons that Tsutamoto et al. (1) were unable to

demonstrate a significant improvement in indices of LV remodeling (in terms of absolute values) may relate to the fact that the measurements were made using echocardiography. This technique is known to have poor reproducibility when applied to subjects with impaired LV function. In contrast, cardiac magnetic resonance imaging provides highly reproducible assessments of cardiac volumes, function and mass in patients with heart failure (3). It is especially important to use a technique with high reproducibility when attempting to demonstrate significant differences using relatively small numbers of participants, as was the case in the study by Tsutamoto et al. (1).

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REPLY

We appreciate the important remarks by Kalra et al. on our article (1). We compared left ventricular (LV) volume and mass, as well as plasma levels of atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and procollagen type III aminoterminal peptide (PIIINP), before and after treatment with spironolactone or placebo. The LV volume and mass were significantly decreased in the spironolactone group, but not in the placebo group. Plasma levels of ANP, BNP and PIIINP were significantly decreased by spironolactone, but did not change in the placebo group. A significant positive correlation existed between the changes of PIIINP and changes of the LV mass index with spironolactone treatment. These findings indicate that four months of spironolactone treatment improved LV volume and mass and decreased the plasma level of BNP in nonischemic patients with congestive heart failure (CHF).

In our study (1), to the evaluation of LV mass and LV function in nonischemic CHF patients, we performed M-mode echocardiography with two-dimensional (2-D) monitoring using a Sono-layer phased-array sector scanner in a blinded fashion before and after four months of treatment with spironolactone or placebo. The LV volumes were calculated using Teichholtz's formula, and the LV ejection fraction was determined. The LV mass was calculated using a method reported previously (2). An earlier study