Possible implication in the inhibition of advanced glycation end product formation. Biochem Pharmacol 1999;58:1765–73.
3. Beisswenger PJ, Howell SK, Touchette AD, Lal S, Szwergold BS. Metformin reduces systemic methylglyoxal levels in type 2 diabetes. Diabetes 1999;48:198–202.
4. Baynes JW, Thorpe SR. Role of oxidative stress in diabetic complications: a new perspective on an old paradigm. Diabetes 1999;48:1–9.
5. Giugliano D, Ceriello A, Paolisso G, Cohen RA. Diabetes mellitus, hypertension, and cardiovascular disease: which role for oxidative stress? Prog Cardiovasc Dis 1995;44:363–8.
6. Galle J, Schneider R, Winner B, et al. Glycoxidized LDL impair endothelial function more potently than oxidized LDL: role of enhanced oxidative stress. Atherosclerosis 1998;138:65–77.
7. Watts GF, Playford DA. Dyslipoproteinaemia and hyperoxidative stress in the pathogenesis of endothelial dysfunction in non-insulin-dependent diabetes mellitus: an hypothesis. Atherosclerosis 1998;141: 17–30.

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).

Paul R. Kalra, MA, MRCP
Clinical Cardiology
National Heart and Lung Institute London
Dovehouse Street
London SW3 6LY
United Kingdom
E-mail: p.kalra@ic.ac.uk

Rakesh Sharma, BSc, MRCP

PII S0735-1097(01)01619-9

REFERENCES

1. Tsutamoto T, Wada A, Maeda K, et al. Effect of spironolactone on plasma brain natriuretic peptide and left ventricular remodeling in patients with congestive heart failure. J Am Coll Cardiol 2001;37: 1228–33.
2. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study investigators. N Engl J Med 1999; 341:709–17.
3. Bellenger NG, Davies LC, Francis JM, Coats AJS, Pennell DJ. Reduction in sample size for studies of remodeling in heart failure by the use of cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2000;2:271–8.

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 Sonolayer 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

(3) reported a significant close correlation between the 2-D echocardiographic LV mass and the necropsy LV mass, and we followed the recommendation of the Committee on M-Mode Standardization of the American Society of Echocardiography (2). We believe that M-mode echocardiography with 2-D monitoring in a blinded fashion was sufficient to evaluate LV mass and LV function, especially in nonischemic CHF patients who were the subjects of this study and who had diffuse LV hypokinesis and no focal hypertrophy by 2-D echocardiography. Actually, we have reported that there was a close correlation between LV mass by echocardiography and LV mass by magnetic resonance imaging in patients with essential hypertension (4).

Takayoshi Tsutamoto, MD
First Department of Internal Medicine
Shiga University of Medical Science
Tsukinowa, Seta, Otsu 520-2192 Japan
E-mail: tutamoto@belle.shiga-med.ac.jp

Atsuyuki Wada, MD
Keiko Maeda, MD
Naoko Mabuchi, MD
Masaru Hayashi, MD
Takashi Tsutsui, MD
Masato Ohnishi, MD
Masahide Sawaki, MD
Masanori Fujii, MD
Takehiro Matsumoto, MD
Toshiki Matsui, MD
Masahiko Kinoshita, MD

PII S0735-1097(01)01646-1

REFERENCES

1. Tsutamoto T, Wada A, Maeda K, et al. Effect of spironolactone on plasma brain natriuretic peptide and left ventricular remodeling in patients with congestive heart failure. J Am Coll Cardiol 2001;37: 1228–33.
2. Sahn D, DeMaria A, Kisslo J, Weyman A. The Committee on M-Mode Standardization of the American Society of Echocardiography. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation 1978;58:1072–83.
3. Devereux RB, Casale PN, Kligfield P, et al. Performance of primary and derived M-mode echocardiographic measurements or detection of left ventricular hypertrophy in necropsied subjects and in patients with systemic hypertension, mitral regurgitation and dilated cardiomyopathy. Am J Cardiol 1986;57:1388–93.
4. Mitsunami K, Inoue S, Maeda K, et al. Three-month effects of candesartan cilexetil, an angiotensin II type 1 (AT1) receptor antagonist, on left ventricular mass and hemodynamics in patients with essential hypertension. Cardiovasc Drugs Ther 1998;12:469–74.

Increased von Willebrand Factor in the Endocardium as a Local Predisposing Factor for Thrombogenesis in Overloaded Human Atrial Appendage

We read with great interest the article by Fukuchi et al. (1), describing immunohistochemical evidence of increased expression of von Willebrand factor (vWF) in the endocardium of "overloaded" human atrial appendages, as a possible mechanism of intra-atrial thrombogenesis. They describe an increase in atrial endocardial vWF expression in patients with mitral valve disease (MVD) and heart failure, but state that the level of vWF expression is unaffected by the presence of atrial fibrillation (AF). Although we welcome the work as an advancement in our understanding of intra-atrial thrombogenesis, we respectfully suggest that Fukuchi et al. (1) may have understated the potential importance of AF and vWF expression in the endocardium of the left atrial appendage (LAA).

Fukuchi et al. (1) did not show a difference in vWF expression by direct comparison of the LAA of MVD and non-MVD (that is, heart failure) patients. In fact, only heart failure patients (n = 4) showed a significant increase in right atrial appendage (RAA) vWF expression compared with other cardiac patients, but all of the heart failure specimens were obtained postmortem, whereas all other cardiac patient specimens were obtained during cardiac surgery. Perhaps the main finding that can be truly relied upon was the detection of a significant difference between LAA and RAA levels of vWF expression in patients with MVD, with greater levels of vWF in the LAA endocardium compared to the RAA. This finding, coupled with the reported correlation between increased levels of vWF expression and the degree of observed platelet adhesion, could suggest a mechanism for left atrial (LA) thrombus development, which is associated with mitral stenosis.

Unfortunately, Fukuchi et al. (1) do not clarify the proportion of MVD patients with mitral stenosis or mitral incompetence, as mitral incompetence is believed to be associated with a reduction in risk of intra-atrial thrombogenesis. In a study using scanning electron microscopy (SEM), we recently reported evidence of more advanced endocardial changes in the LAA compared with the RAA in MVD patients, and among specimens from patients with mitral stenosis when compared to those with mitral incompetence (2). Furthermore, increasing plasma levels of vWF, an established plasma marker of endothelial damage/dysfunction, were seen to correlate with more advanced SEM endocardial changes. There was also a nonsignificant trend toward increased endocardial changes in MVD patients with AF compared to sinus rhythm. Because AF was present in 12 of the 15 MVD patients studied by Fukuchi et al. (1), the possibility arises that the presence of AF itself (or, at least, in combination with mitral stenosis) led to the increase in LAA expression of vWF in their study.

Fukuchi et al. (1) state that the presence of AF appeared not to influence the LAA expression of vWF, but this is based on only four specimens obtained from patients in sinus rhythm, of which at least one was from a postmortem specimen without MVD. In contrast, all 12 LAA specimens from the AF group were taken from live patients with MVD during a Maze procedure; thus, the comparison may be underpowered and poorly standardized. Second, although the comparison of RAA vWF levels was more appropriately powered, standardization between the two groups was again poor, with 12 out of a total of 16 AF patients studied having MVD, compared with only 3 out of 27 sinus rhythm patients. Furthermore, because the LAA is the main site of thrombogenesis in patients with AF, the lack of observed RAA changes may be of limited clinical significance.

Atrial fibrillation, with or without the additional presence of MVD, has been shown to be associated with increased levels of circulating plasma vWF, as well as other markers of thrombogenesis and platelet activation (3). We have demonstrated that peripheral levels of vWF have been shown to be similar to