CARDIOVASCULAR MEDICINE

Comparative effects of valsartan and enalapril on cardiac sympathetic nerve activity and plasma brain natriuretic peptide in patients with congestive heart failure

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Objective: To evaluate the effects of valsartan on cardiac sympathetic nerve activity, plasma brain natriuretic peptide (BNP) concentration, cardiac function, and symptoms in patients with congestive heart failure (CHF) by comparison with those of enalapril.

Methods: 50 patients with CHF (left ventricular ejection fraction (LVEF) < 40%) were randomly assigned to valsartan (80 mg/day; n = 25) or enalapril (5 mg/day; n = 25). All patients were also treated with a loop diuretic. The delayed heart to mediastinum count (H/M) ratio, delayed total defect score (TDS), and washout rate were determined from ^{123}I-meta-iodobenzylguanidine (MIBG) images. Plasma BNP concentrations were measured before and after six months of treatment. The left ventricular end diastolic volume (LVEDV) and LVEF were also determined by echocardiography.

Results: In patients receiving valsartan, TDS decreased from a mean (SD) of 43 (8) to 39 (10) (p < 0.01), H/M ratio increased from 1.70 (0.17) to 1.78 (0.22) (p < 0.05), washout rate decreased from 46 (11)% to 41 (10)% (p < 0.05), and plasma BNP concentration decreased from 237 (180) pg/ml to 143 (93) pg/ml (p < 0.05). In addition, LVEDV decreased from 172 (42) ml to 151 (45) ml (p < 0.05) and LVEF increased from 31 (7)% to 39 (10)% (p < 0.001). However, these parameters did not change significantly in patients receiving enalapril.

Conclusion: Plasma BNP concentration and ^{123}I-MIBG scintigraphic and echocardiographic parameters improved significantly after six months of treatment with valsartan. These findings indicate that valsartan can improve cardiac sympathetic nerve activity and left ventricular performance in patients with CHF.

M yocardial imaging with ^{123}I-meta-iodobenzylguanidine (^{123}I-MIBG), an analogue of noradrenaline, is a useful tool for detecting abnormalities of the myocardial adrenergic nervous system in patients with congestive heart failure (CHF).[1–3] Moreover, cardiac ^{123}I-MIBG scintigraphic findings and left ventricular function are correlated,[3] and ^{123}I-MIBG scintigraphy has a useful prognostic value in patients with CHF.[2–4] Furthermore, the concentration of plasma brain natriuretic peptide (BNP), secreted mainly from the ventricle,[5] is a useful prognostic indicator in patients with CHF.[6]

Activation of the renin–angiotensin–aldosterone system (RAAS) promotes structural remodelling of the heart and the progression of heart failure.[7 8] Several reports have suggested, based on cardiac ^{123}I-MIBG scintigraphic studies, that inhibition of RAAS can improve cardiac sympathetic nerve activity in patients with CHF.[9–15] The angiotensin receptor blocker (ARB) valsartan has beneficial haemodynamic and hormonal effects in patients with CHF treated conventionally.[16 17] Cohn *et al*[18] reported that the addition of valsartan significantly improved New York Heart Association (NYHA) functional class, left ventricular remodelling, left ventricular ejection fraction (LVEF), and signs and symptoms of heart failure. However, its influence on cardiac sympathetic nerve activity and BNP concentration has not been sufficiently determined.

In the present study, we evaluated the effects of valsartan on cardiac sympathetic nerve activity, plasma BNP concentration, cardiac function, and symptoms in patients with CHF by comparison with those of enalapril.

METHODS
Study patients

From December 2001 through March 2003, 54 patients were admitted to our institution with a first episode of CHF. A detailed history and physical examination were obtained before their inclusion in the study. None of the patients had a history of heart failure. All patients underwent chest radiography, standard ECG, echocardiography, and thallium-201 and ^{123}I-MIBG scintigraphy. Patients were in NYHA functional class II or III at the time of enrolment and had an echocardiographic LVEF < 40% (mean (SD) 32 (8)%).

Patients were excluded from the study if they had congenital heart disease, unstable angina, recent acute myocardial infarction, primary hepatic failure, or active cancer. Patients with stenotic valvar heart disease were also excluded from the study because cardiac function in these patients may respond differently to vasodilating treatment depending on intravascular volume, cardiac sympathetic nerve system, and RAAS activity.

This study was approved by the ethics review board of our institution. The nature and purpose of the study and risks

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; CHF, congestive heart failure; H/M, heart to mediastinum count; ^{123}I-MIBG, iodine-123 labelled meta-iodobenzylguanidine; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RAAS, renin-angiotensin-aldosterone system; SPECT, single photon emission computed tomographic; TDS, total defect score; Val-HeFT, valsartan heart failure trial; WR, washout rate

involved were explained to all patients. Written informed consent to participate in the study was obtained.

Study protocol

Twenty seven patients were randomly assigned to valsartan (80 mg/day) and the remaining 27 patients were assigned to enalapril (5 mg/day). All patients were also treated with a loop diuretic. Treatment with digitalis and vasodilators was allowed. We performed a series of examinations before and after six months of treatment.

^{123}I-MIBG imaging

The method used for ^{123}I-MIBG imaging has been described.[9–14 19 20] ^{123}I-MIBG was obtained from a commercial source (Daiichi Radioisotope Laboratories, Tokyo, Japan). Patients were intravenously injected with ^{123}I-MIBG (111 MBq) while in the supine position. At 15 minutes and at four hours after the injection, static data were acquired in the anterior view with a single head gamma camera (Millennium MPR, GE Medical Systems, Waukesha, Wisconsin, USA) equipped with a low energy, general purpose, parallel hole collimator. Static images on a 128×128 matrix were collected for five minutes with a 20% window centred on 159 keV, corresponding to the ^{123}I photopeak. After the static planar images were acquired, single photon emission computed tomographic (SPECT) images were obtained. The camera was rotated over 180° from the 45° right anterior oblique position to the 45° left posterior oblique position in 32 views with an acquisition time of 40 s/view. Scans were acquired in a 64×64 matrix by a filtered back projection method for reconstruction.

The heart to mediastinum count (H/M) ratio was determined from the anterior planar delayed ^{123}I-MIBG image. The washout rate (WR) was calculated from the formula: $[(H - M)$ early $- (H - M)$ delayed$]/(H - M)$ early $\times 100$ (%), where H is mean count/pixel in the left ventricle and M is mean count/pixel in the upper mediastinum. In this study, time decay was not corrected for the calculation of WR.

The delayed myocardial SPECT images of each patient were divided into 17 segments as recommended by the American Heart Association.[21] Regional tracer uptake was assessed semiquantitatively by a five point scoring system (0, normal uptake; 1, mildly reduced uptake; 2, moderately reduced uptake; 3, significantly reduced uptake; and 4, no uptake). The total defect score (TDS) was calculated as the sum of all defect scores.

Two independent observers with no knowledge of patient clinical status or medical treatment determined interobserver variability in a blinded fashion. The interobserver correlation was highly significant ($r = 0.90$, $p < 0.001$).

Plasma BNP concentration

Blood samples were collected into test tubes containing EDTA after the patient had rested in the supine position for at least 30 minutes. Plasma was separated by centrifugation and was frozen at −84℃. Then the plasma concentration of BNP was measured with a specific immunoradiometric assay for human BNP with a commercially available kit (Shionogi, Osaka, Japan) as previously reported.[13 14 22]

Echocardiography

Echocardiographic measurements were taken by standard methods in a blinded manner before and after six months of treatment. Two independent and experienced echocardiographers who had no knowledge of the study performed all measurements. Left ventricular end diastolic volume (LVEDV) and LVEF were calculated with the modified Simpson's method. The interobserver and intraobserver correlations for LVEDV were $r = 0.90$, $p < 0.001$ and

$r = 0.94$, $p < 0.0001$, respectively, and for LVEF were $r = 0.90$, $p < 0.001$ and $r = 0.93$, $p < 0.0001$, respectively.

Statistical analysis

Data were statistically analysed with Statview (Abacus Concepts, Berkeley, California, USA) for Macintosh (Apple Computer, Inc, Cupertino, California, USA). Numerical results are expressed as the mean (SD). Baseline categorical data of the two groups were compared by the χ^2 test. The differences between continuous variables were evaluated with an unpaired t test. Changes in NYHA functional class were assessed with the Wilcoxon matched pairs signed ranks test. For patients who underwent repeated assessments, changes from baseline were evaluated within each treatment group with a paired t test and between the valsartan and enalapril groups, with two way analysis of variance. A value of $p < 0.05$ was considered significant.

RESULTS
Clinical characteristics

In the group of patients receiving valsartan, one patient had a cerebral embolism and one patient died of an arrhythmia. In the group of patients receiving enalapril, one patient died of CHF during the follow up period and one was excluded because of the onset of unstable angina. Therefore, 50 of the 54 patients (31 men and 19 women, mean (SD) age 68 (9) years, range 42 to 80 years) enrolled in the trial completed the entire protocol. The causes of heart failure were idiopathic dilated cardiomyopathy (n = 25), old myocardial infarction (n = 17), or valve disease (n = 8; six with mitral regurgitation and two with aortic regurgitation).

The two groups did not differ significantly in haemodynamic characteristics or cardiac medications on entry into the study. Before treatment, TDS, H/M ratio, WR, plasma BNP

Table 1 Baseline patient characteristics

	Valsartan (n = 25)	Enalapril (n = 25)	p Value
Age (years)	67 (10)	68 (9)	NS
Men/women	16/9	15/10	NS
Height (cm)	160 (9)	162 (10)	NS
Weight (kg)	58 (8)	59 (9)	NS
SBP (mm Hg)	132 (16)	131 (14)	NS
DBP (mm Hg)	74 (8)	72 (8)	NS
NYHA functional class			
II/III	6/19	6/19	NS
Cause of CHF			
DCM	12 (48%)	13 (52%)	NS
OMI	8 (32%)	9 (36%)	NS
Valve disease	5 (20%)	3 (12%)	NS
^{123}I-MIBG			
TDS	43 (8)	43 (9)	NS
H/M ratio	1.70 (0.17)	1.68 (0.36)	NS
WR	46 (11)	47 (8)	NS
Echocardiography			
LVEDV (ml)	172 (42)	173 (29)	NS
LVEF(%)	31 (7)	32 (8)	NS
Plasma BNP (pg/ml)	237 (180)	235 (154)	NS
Medical treatment			
Loop diuretic	25 (100%)	25 (100%)	NS
β Blocker	15 (60%)	17 (68%)	NS
Spironolactone	8 (32%)	7 (28%)	NS
Nitrate	6 (24%)	5 (20%)	NS
Calcium antagonist	6 (24%)	9 (36%)	NS
Digitalis	2 (8%)	3 (12%)	NS

Values are mean (SD) or number (%).
BNP, brain natriuretic peptide; CHF, congestive heart failure; DBP, diastolic blood pressure; DCM, dilated cardiomyopathy; H/M, heart to mediastinum count; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; ^{123}I-MIBG, iodine-123 labelled meta-iodobenzylguanidine; NS, not significant; NYHA, New York Heart Association; OMI, old myocardial infarction; SBP, systolic blood pressure; TDS, total defect score; WR, washout rate.

Table 2 Changes in TDS, H/M ratio, and WR of patients in valsartan and enalapril groups

	Valsartan		Enalapril	
	Baseline	6 months	Baseline	6 months
^{123}I-MIBG				
TDS	43 (8)	39 (10)*	43 (9)	42 (10)
H/M ratio	1.70 (0.17)	1.78 (0.22)**	1.68 (0.36)	1.67 (0.22)
WR	46 (11)	41 (10)**	47 (8)	46 (10)

Values are mean (SD).
*p<0.01 v baseline; **p<0.05 v baseline.

concentration, LVEDV, LVEF, and NYHA functional class in both groups were similar (table 1). In this study, baseline cardiac medication was not changed for any of the patients during the follow up period. The mean dose of furosemide was 56 (23) mg/day in the valsartan group versus 58 (22) mg/day in the enalapril group (not significant). The mean dose of carvedilol was 14 (6) mg/day in the valsartan group versus 13 (6) mg/day in the enalapril group (not significant). The mean dose of isosorbide mononitrate was 37 (8) mg/day in the valsartan group versus 36 (9) mg/day in the enalapril group (not significant). Furthermore, the dose of spironolactone was only 25 mg/day in both groups.

Comparison of cardiac ^{123}I-MIBG scintigraphic findings
Table 2 and fig 1 summarise TDS, H/M ratio, and WR. In patients receiving valsartan, TDS was significantly decreased at six months compared with the baseline value ($p < 0.01$). In contrast, in patients receiving enalapril, TDS at baseline and after six months of treatment did not differ significantly. Segmental analysis of TDS showed that this tended to improve due to uptake of the inferior wall in both groups, although the improvement was not significant. In patients receiving valsartan, the H/M ratio was significantly increased at six months compared with the baseline values ($p < 0.05$). In contrast, in patients receiving enalapril, H/M ratio at baseline and after six months of treatment did not differ significantly. In patients receiving valsartan, the WR was significantly decreased at six months compared with the baseline values ($p < 0.05$). In contrast, in patients receiving enalapril, WR at baseline and after six months of treatment did not differ significantly.

Comparison of echocardiographic findings
Table 3 and fig 2 summarise the changes in LVEDV and LVEF. In patients receiving valsartan, LVEDV was significantly decreased at six months compared with baseline values ($p < 0.05$). In contrast, in patients receiving enalapril, LVEDV at baseline and after six months of treatment did not differ significantly. In patients receiving valsartan, LVEF was significantly increased at six months compared with baseline values ($p < 0.001$). In contrast, in patients receiving enalapril, LVEF at baseline and after six months of treatment did not differ significantly.

Comparison of plasma BNP concentration
Table 3 and fig 2 show plasma BNP concentrations. In patients receiving valsartan, plasma BNP concentrations were significantly decreased at six months compared with the baseline values ($p < 0.05$). In contrast, BNP concentration at baseline and after six months of treatment did not differ significantly in the patients receiving enalapril.

Comparison of NYHA functional class
Table 3 and fig 3 summarise the NYHA functional class of the patients. Patients in both groups improved after six months
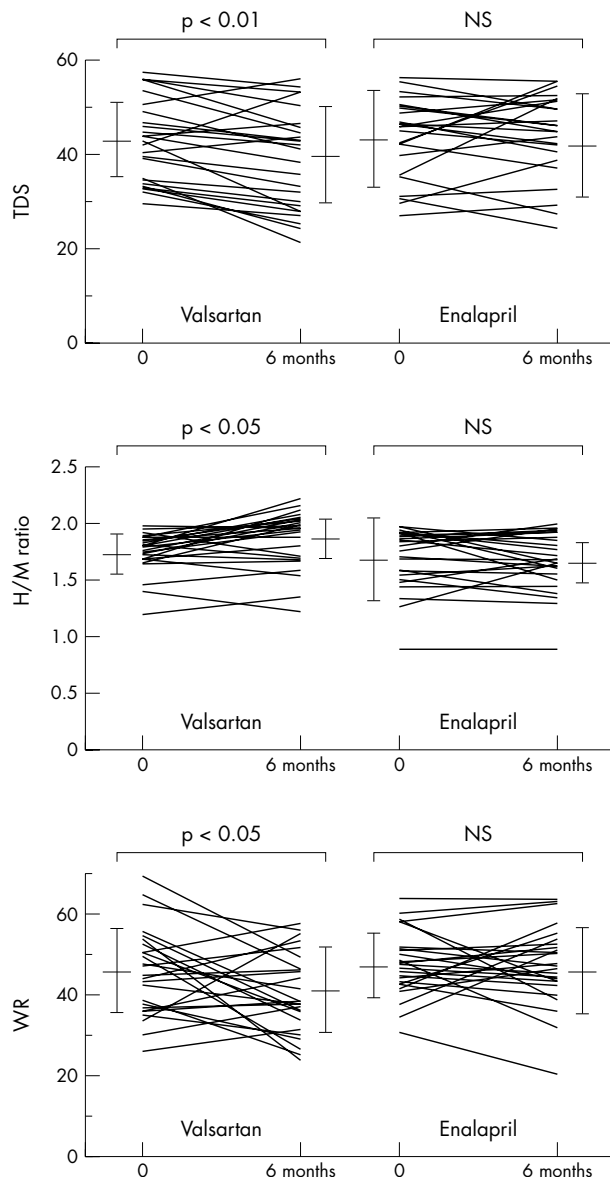

Figure 1 Comparison of cardiac iodine-123 labelled meta-iodobenzylguanidine scintigraphic findings during treatment in the two groups. H/M, heart to mediastinum count; NS, not significant; TDS, total defect score; WR, washout rate.

Table 3 Changes of plasma BNP concentration, LVEDV, LVEF, and NYHA functional class of patients in the valsartan and enalapril groups

	Valsartan		Enalapril	
	Baseline	6 months	Baseline	6 months
Plasma BNP (pg/ml)	237 (180)	143 (93)*	235 (154)	200 (95)
LVEDV (ml)	172 (42)	151 (45)*	173 (29)	172 (33)
LVEF (%)	31 (7)	39 (10)**	32 (8)	35 (10)
NYHA class				
I/II/III	0/6/19	8/15/2*** †	0/6/19	2/14/9*

Values are mean (SD).
*p<0.05 v baseline; **p<0.001 v baseline; ***p<0.001 v baseline;
†p<0.01 v enalapril at 6 months.

of treatment compared with the baseline values (in patients receiving valsartan, $p < 0.001$; in patients receiving enalapril, $p < 0.05$). After treatment, the NYHA functional class of the
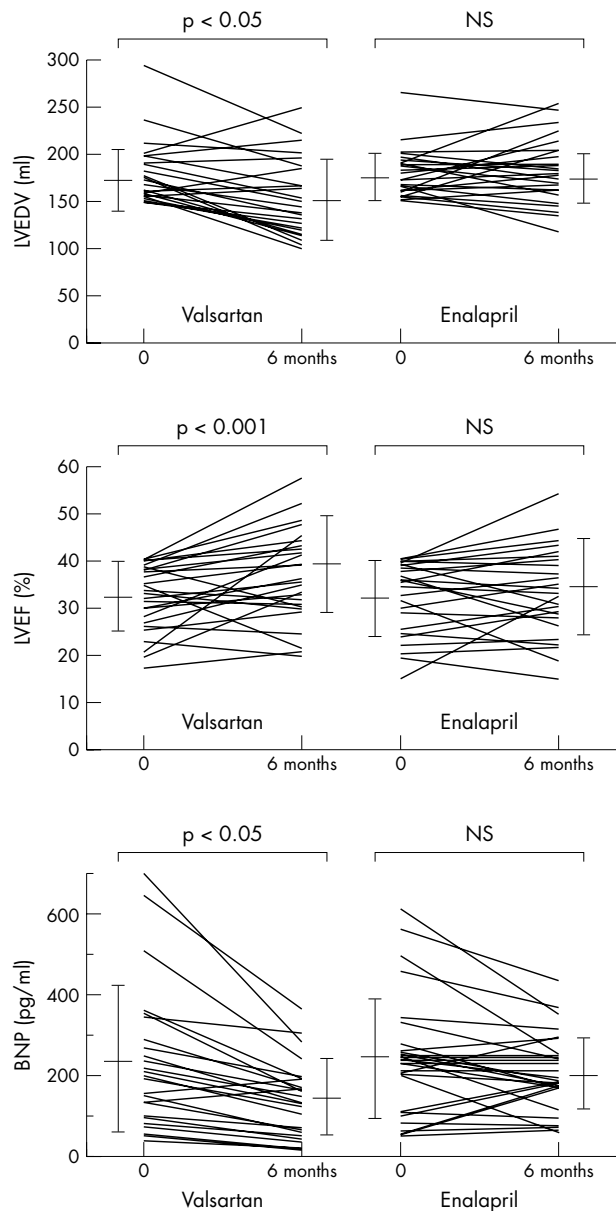
Figure 2 Comparison of echocardiographic findings and plasma brain natriuretic peptide (BNP) concentrations during treatment in the two groups. LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction.

patients receiving valsartan was significantly better than in those receiving enalapril ($p < 0.01$).

DISCUSSION

Angiotensin converting enzyme (ACE) inhibitors reduce angiotensin II concentrations, mortality, and morbidity in patients with CHF.[23][24] ACE inhibitors are believed to act principally by blocking the formation of angiotensin II, a potent vasoconstrictor and cardiovascular growth stimulator that may contribute to increased impedance, left ventricular ejection, and cardiac remodelling.[25] However, growing evidence supports an important role for non-ACE mediated enzymatic pathways (for example, chymase pathway) in the conversion of angiotensin I to angiotensin II.[26][27] Therefore, a strategy of providing greater blockade of angiotensin with valsartan than with enalapril in the treatment of heart failure appears rational. Furthermore, subtypes of the angiotensin II

receptor have been reported.[28] One of the subtypes, the type 2 receptor, is known to have antagonistic actions against the type 1 receptor and to have favourable effects on the myocardium.[28] Therefore, because the ARB valsartan selectively inhibits the angiotensin II type 1 receptor, this drug may have more cardioprotective effects than ACE inhibitors.

The growth promoting and apoptotic effects of angiotensin II have been well documented and may contribute to the structural remodelling that promotes the progression of heart failure.[7][8][29] A long term increase in LVEF has been identified as a marker of beneficial left ventricular remodelling that is manifested as a reduced chamber volume.[30] This structural effect is associated with an improvement in survival.[31] Cohn et al[18] reported that the addition of valsartan significantly improved cardiac function and reduced mortality and morbidity in patients with heart failure. In our study, left ventricular volume and cardiac function were significantly improved by valsartan compared with enalapril. Moreover, in our study, valsartan improved the symptoms of heart failure as measured by changes in the NYHA functional class.

Plasma BNP concentration is a useful prognostic indicator in patients with CHF, since it is a ventricular hormone.[5][6] Patient plasma BNP concentration is reported to correlate with abnormalities of LVEF and left ventricular end diastolic pressure, as well as with left ventricular mass.[5][32] Therefore, the decrease in plasma BNP concentrations after treatment with valsartan was probably due to decreased left ventricular filling pressure, an improvement in left ventricular remodelling, or both factors.[32] Moreover, treatment of CHF guided by plasma BNP concentration has been reported to reduce cardiovascular events[33]; thus, a decrease in BNP concentrations may be associated with a better outcome, as was observed in the Val-HeFT (valsartan heart failure trial) study.[18] Furthermore, Latini et al[34] found that plasma BNP concentration was the most powerful indicator after valsartan treatment in patients with CHF. In our study, plasma BNP concentrations were significantly decreased by valsartan compared with enalapril.

^{123}I-MIBG, an analogue of noradrenaline, can be used to detect abnormalities in the myocardial adrenergic nervous system in patients with CHF.[1-3] Activation of the renin–angiotensin system in patients with CHF facilitates cardiac noradrenaline release; therefore, treatment with ACE inhibitors may affect cardiac sympathetic activity.[35][36] Somsen et al[15] reported that ACE inhibitors can improve cardiac sympathetic nerve activity on the basis of cardiac ^{123}I-MIBG scintigraphic findings in patients with CHF. However, no reports have compared the effect of the two drugs (valsartan and enalapril) on cardiac sympathetic nerve activity in patients with CHF. In the present study, we examined whether valsartan improved cardiac sympathetic nerve activity in patients with CHF by using ^{123}I-MIBG scintigraphy. Whereas TDS, H/M ratio, and WR were significantly improved in the valsartan group after six months of treatment, we observed no significant changes in the enalapril group.

On the basis of cardiac ^{123}I-MIBG scintigraphy, our study showed that treatment with the ACE inhibitor enalapril did not improve cardiac sympathetic nerve activity, although a previous report had indicated that this treatment did result in an improvement.[15] However, that study included patients with almost non-ischaemic cardiomyopathy. In contrast, 36% of the patients in the enalapril group in our study had CHF due to old myocardial infarction. Moreover, in the patients included in our study, cardiac function was relatively low and left ventricular volume was relatively high compared with previously reported patients.[15] Therefore, enalapril did not cause improvement in ^{123}I-MIBG scintigraphic parameters. On the basis of the results of our study and previous reports,
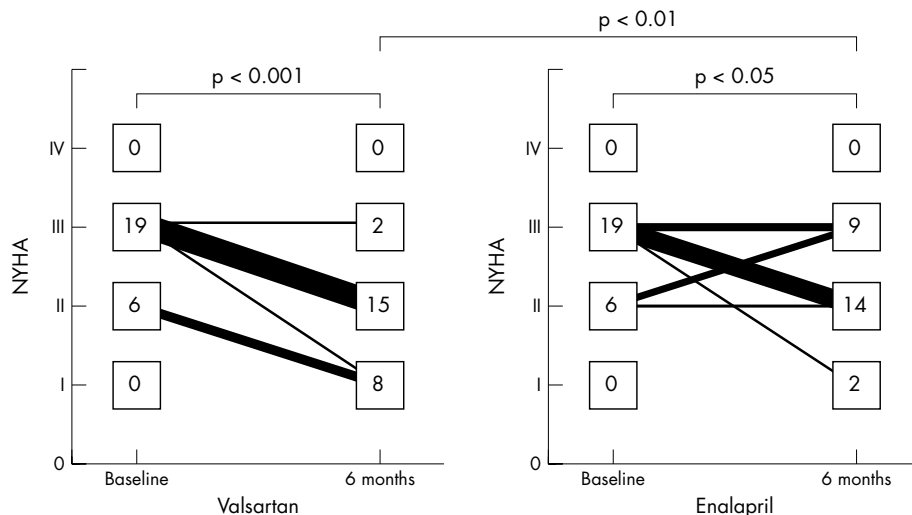
Figure 3 Changes in New York Heart Association (NYHA) functional class during treatment in the two groups.

Conclusion

TDS, H/M ratio, and WR determined by ^{123}I-MIBG scintigraphy were significantly improved after six months of valsartan treatment. In addition, plasma BNP concentration and echocardiographic parameters improved with this treatment. In contrast, these parameters did not change significantly with enalapril treatment. These findings indicate that valsartan treatment can improve cardiac sympathetic nerve activity and left ventricular performance in patients with CHF compared with enalapril treatment.

we hypothesise that valsartan treatment probably blocks angiotensin more effectively in patients with severe CHF.

In a clinical report, the combination of ARB and an ACE inhibitor was more beneficial for preventing left ventricular remodelling and suppressing neurohormonal activation than either ARB or an ACE inhibitor alone.[37] However, in that report, ARB alone was more effective in patients with CHF than the ACE inhibitor alone.[37] Therefore, valsartan ARB treatment may improve cardiac sympathetic nerve activity and left ventricular performance in patients with CHF compared with enalapril treatment.

In general, patients with high blood pressure have impaired cardiac sympathetic nerve activity, and the use of agents has proved beneficial as shown by ^{123}I-MIBG scintigraphy.[38] Moreover, patients with hypertensive heart disease have an increased plasma BNP concentration, and antihypertensive treatment decreases this parameter.[39] In the present study, systolic and diastolic blood pressure did not differ significantly after six months of treatment in either group (in patients receiving valsartan, 132 (16) mm Hg v 129 (14) mm Hg and 74 (8) mm Hg v 72 (10) mm Hg, respectively; in patients receiving enalapril, 131 (14) mm Hg v 128 (13) mm Hg and 72 (8) mm Hg v 71 (9) mm Hg, respectively). Therefore, we believe that valsartan can improve cardiac sympathetic nerve activity and left ventricular performance in patients with CHF and that this effect is independent of a blood pressure lowing effect.

The small number of patients included in this study was a major limitation. In addition, the doses of valsartan and enalapril given to our patients were lower than those used in previously reported trials.[18 23 24] However, the doses of these agents used in Japan are generally lower than those used in other countries. Valsartan at a dose of 80 mg once daily and enalapril of 5 mg are considered to be effective and safe for the treatment of Japanese patients with heart failure.[11 14] Therefore, the doses in this study were not too low for Japanese patients with heart failure. Moreover, Shimizu et al[40] reported that combination treatment with enalapril and valsartan had an additive effect at lower doses compared with enalapril alone in hamsters with heart failure. On the other hand, our study design did not include a combination treatment group. In the future, we need to study the effects of valsartan alone, enalapril alone, and their combination at half the dose of each agent on cardiac sympathetic nerve activity and left ventricular parameters in a larger number of patients.

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