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

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Running Title: Valsartan in heart failure

Keywords: ¹²³I-meta-iodobenzylguanidine; heart failure; angiotensin-receptor blocker

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Abstract

Objective: Cardiac autonomic function and plasma brain natriuretic peptide (BNP) concentrations have been shown to be strong prognostic indicators of overall mortality in patients with congestive heart failure (CHF). Valsartan, an angiotensin-receptor blocker, improves left ventricular function in patients with CHF, but its influence on cardiac sympathetic nerve activity and BNP concentration has not been adequately determined.

Methods: Fifty 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/mediastinum count (H/M) ratio, delayed total defect score (TDS), and washout rate (WR) were determined from $^{123}$I-meta-iodobenzylguanidine (MIBG) images and plasma BNP concentrations were measured before and after 6 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 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), WR 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, there were no significant changes in these parameters in patients receiving enalapril.

Conclusion: Plasma BNP concentration, $^{123}$I-MIBG scintigraphic, and echocardiographic parameters improved significantly after 6 months of treatment with valsartan. These findings indicate that valsartan can improve cardiac sympathetic nerve activity and left ventricular performance in patients with CHF.
INTRODUCTION
Myocardial imaging with \(^{123}\)I-meta-iodobenzylguanidine (MIBG), an analogue of norepinephrine, is a useful tool for detecting abnormalities of the myocardial adrenergic nervous system in patients with congestive heart failure (CHF).\([1][2][3]\) 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.\([2][3][4]\)

Furthermore, the level of plasma brain natriuretic peptide (BNP), secreted mainly from the ventricle,\([5]\) is also a useful prognostic indicator in patients with CHF.\([6]\)

Activation of the renin-angiotensin-aldosterone system (RAAS) promotes structural remodeling of the heart and the progression of heart failure.\([7][8]\) Several reports have suggested that inhibition of RAAS can improve cardiac sympathetic nerve activity, based on cardiac \(^{123}\)I-MIBG scintigraphic studies, in patients with CHF.\([9][10][11][12][13][14][15]\) The angiotensin-receptor blocker (ARB) valsartan, has beneficial hemodynamic and hormonal effects in patients with CHF receiving conventional therapy.\([16][17]\) Cohn et al.\([18]\) reported that the addition of valsartan significantly improved New York Heart Association (NYHA) functional class, left ventricular remodeling, 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 prior to their inclusion in the study. None of the patients had a history of heart failure. Chest radiography, standard electrocardiography, echocardiography, and $^{203}$Tl and $^{123}$I-MIBG scintigraphy were performed in all patients. Patients were in NYHA functional class II or III at the time of enrollment and had an echocardiographic LVEF < 40% (mean, 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 valvular heart disease were also excluded from the study, because cardiac function in these patients may respond differently to vasodilating therapy depending upon 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 involved were explained to all subjects, and 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 6 months of treatment.

$^{123}$I-MIBG imaging
The method used for $^{123}$I-MIBG imaging has been described previously.[9][10][11][12][13][14][19][20] $^{123}$I-MIBG was obtained from a commercial source (Daiichi Radioisotope Laboratories, Tokyo, Japan). Patients were intravenously injected $^{123}$I-MIBG (111 MBq) while in the supine position. At 15 minutes and at 4 hours after the injection, static data were acquired in the anterior view with a single-head gamma camera (Millennium MPR, GE Medical Systems, Waukesha, WI) equipped with a low-energy, general-purpose, parallel-hole collimator. Static images on a 128X128 matrix were collected for 5 minutes with a 20% window centered 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 seconds per view. Scans were acquired in a 64X64 matrix by a filtered back-projection method for reconstruction.

The heart/mediastinum count (H/M) ratio was determined from the anterior planar delayed $^{123}$I-MIBG image. The washout rate (WR) was calculated using the following formula: $\{([H] - [M])_{\text{early}} - ([H] - [M])_{\text{delayed}}\} / ([H] - [M])_{\text{early}} \times 100\%$, where [H] = mean count/pixel in the left ventricle; and [M] = 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 recommended by American Heart Association.[21] Regional tracer uptake was assessed semiquantitatively using a 5-point scoring system (0 = normal uptake; 1 = mildly reduced uptake; 2 = moderately reduced uptake; 3 = significantly reduced uptake; 4 = no uptake). The total defect score (TDS) was calculated as the sum of all defect scores.

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

**Plasma brain natriuretic peptide concentration**

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

**Echocardiography**

Echocardiographic measurements were performed using standard methods in a blinded manner before and after 6 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 using the modified Simpson method. The interobserver and intraobserver correlations for LVEDV are $r = 0.90$, $p<0.001$ and $r = 0.94$, $p<0.0001$, respectively, and for LVEF are $r = 0.90$, $p<0.001$ and $r = 0.93$, $p<0.0001$, respectively.

**Statistical analysis**

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

Clinical characteristics
In the group of patients receiving valsartan, one patient had a cerebral embolism and one patient died from an arrhythmia. In the group of patients receiving enalapril, one patient died of congestive heart failure 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 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 valvular disease (n = 8; six with mitral regurgitation and two with aortic regurgitation).

There were no significant differences in hemodynamic characteristics or cardiac medications between the two groups on entry into the study. Before treatment, the TDS, H/M ratio, WR, plasma BNP 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/d in the valsartan group versus 58(22) mg/d in the enalapril group (p=NS). The mean dose of carvedilol was 14(6) mg/d in the valsartan group versus 13(6) mg/d in the enalapril group (p=NS). The mean dose of isosorbide mononitrate was 37(8) mg/d in the valsartan group versus 36(9) mg/d in the enalapril group (p=NS). Furthermore, the dose of spironolactone was only 25 mg/d in both groups.

Comparison of cardiac ¹²³I-MIBG scintigraphic findings
The TDS, H/M ratio, and WR are summarized in Table 2 and Figure 1. In patients receiving valsartan, the TDS was significantly decreased at 6 months compared to the baseline value (p<0.01). In contrast, in patients receiving enalapril, there was no significant difference between the baseline TDS and that after 6 months of treatment. The 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 statistically significant. In patients receiving valsartan, the H/M ratio was significantly increased at 6 months compared to the baseline values (p<0.05). In contrast, in patients receiving enalapril, there were no significant differences between the values at baseline and after 6 months of treatment. In patients receiving valsartan, the WR was significantly decreased at 6 months compared to baseline values (p<0.05). In contrast, in patients receiving enalapril, there were no significant differences between the values at baseline and after 6 months of treatment.

Comparison of echocardiographic findings
The changes in LVEDV and LVEF are summarized in Table 3 and Figure 2. In patients receiving valsartan, the LVEDV was significantly decreased at 6 months compared to baseline values (p<0.05). In contrast, in patients receiving enalapril, there were no significant differences between the values at baseline and after 6 months of treatment. In patients receiving valsartan, the LVEF was significantly increased at 6 months compared to baseline values (p<0.001). In contrast, in patients receiving enalapril, there were no significant
differences between values at baseline and after 6 months of treatment.

**Comparison of plasma BNP concentration**
Plasma BNP concentrations are shown in Table 3 and Figure 2. In patients receiving valsartan, plasma BNP concentrations were significantly decreased at 6 months compared to the baseline values (p<0.05). In contrast, there was no significant difference between the BNP values at baseline and after 6 months of treatment in the patients receiving enalapril.

**Comparison of NYHA functional class**
The NYHA functional class of the patients is summarized in Table 3 and Figure 3. Patients in both groups showed improvement after 6 months of treatment compared to 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 patients receiving valsartan was significantly better than in those receiving enalapril (p<0.01).
DISCUSSION
Angiotensin-converting enzyme (ACE) inhibitors reduce angiotensin II (A-II) levels, mortality, and morbidity in patients with congestive heart failure (CHF).[23][24] ACE inhibitors are believed to act principally by blocking the formation of A-II, a potent vasoconstrictor and cardiovascular growth stimulator that may contribute to increased impedance, to left ventricular ejection, and cardiac remodeling.[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 A-II.[26][27] Therefore, a strategy of providing a greater blockade of angiotensin with valsartan compared to enalapril in the treatment of heart failure appears rational. Furthermore, it has been reported that there are subtypes of the A-II receptor.[28] One of the subtypes, the AT2 receptor, is known to have antagonistic actions against the AT1 receptor, and have favorable effects on the myocardium.[28] Therefore, because the ARB valsartan selectively inhibits the AT1 receptor, this drug may have more cardioprotective effects than ACE inhibitors.

The growth-promoting and apoptotic effects of A-II have been well documented,[29] and may contribute to the structural remodeling that promotes the progression of heart failure.[7][8] A long-term increase in LVEF has been identified as a marker of beneficial LV remodeling 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 to enalapril. Moreover, in our study, valsartan also 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,[6] since it is a ventricular hormone.[5] Patient plasma BNP concentration is reported to correlate with abnormalities of the LVEF and left ventricular end-diastolic pressure,[5] as well as with left ventricular mass.[32] Therefore, the decrease in plasma BNP levels after treatment with valsartan was probably due to a decreased left ventricular filling pressure, or an improvement in left ventricular remodeling, 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 levels may be associated with a better outcome, as was observed in the Val-HeFT 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 to enalapril.

$^{123}$I-MIBG, an analogue of norepinephrine, can be used to detect abnormalities in the myocardial adrenergic nervous system in patients with CHF.[1][2][3] Activation of the renin-angiotensin system in patients with CHF facilitates cardiac norepinephrine 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 based on cardiac $^{123}$I-MIBG scintigraphic findings in patients with CHF. However, there have been no reports comparing the effect of the two drugs (valsartan and enalapril) on
cardiac sympathetic nerve activity in patients with CHF. In this study, we examined whether valsartan improved cardiac sympathetic nerve activity in patients with CHF using $^{123}$I-MIBG scintigraphy, and found that while the TDS, H/M ratio, and WR were significantly improved in the valsartan group after 6 months of treatment, no significant changes were observed 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 nonischemic 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 to previously reported patients.\[15\] Therefore, enalapril might not recognize the improvement in $^{123}$I-MIBG scintigraphic parameters. Based on the results of our study and the previous reports, we hypothesize that angiotensin is probably more effectively blocked by valsartan treatment in patients with severe CHF.

In a clinical report, the combination of ARB and an ACE inhibitor was more beneficial for preventing left ventricular remodeling 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 to the enalapril treatment.

In general, patients with high blood pressure have impaired cardiac sympathetic nerve activity, and the use of agents has proved beneficial, as demonstrated by $^{123}$I-MIBG scintigraphy.\[38\] Moreover, patients with hypertensive heart disease have an increased plasma BNP concentration, and antihypertensive therapy decreases this parameter.\[39\] In this study, there were no significant differences in systolic and diastolic blood pressure after 6 months of treatment in either group (in patients receiving valsartan, 132(16) mmHg vs. 129(14) mmHg, and 74(8) mmHg vs. 72(10) mmHg, respectively; in patients receiving enalapril, 131(14) mmHg vs. 128(13) mmHg, and 72(8) mmHg vs. 71(9) mmHg, respectively). Therefore, we believe that valsartan therapy can improve cardiac sympathetic nerve activity and left ventricular performance in patients with CHF, and that this effect is independent of a blood pressure lowering effect.

The small number of patients included in this study was a major limitation. In addition, the doses of valsartan and enalapril in 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 therapy 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
therapy 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.

**Conclusion**

The TDS, H/M ratio, and WR determined by $^{123}$I-MIBG scintigraphy were significantly improved after 6 months of valsartan treatment. In addition, plasma BNP concentration and echocardiographic parameters improved with this treatment. In contrast, there was no significant change in these parameters with enalapril treatment. These findings indicate that valsartan treatment can improve cardiac sympathetic nerve activity and left ventricular performance in patients with CHF compared to the enalapril treatment.

**Acknowledgment**

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The authors have indicated they have no financial conflicts of interest.
References


FIGURE LEGENDS

Figure 1. Comparison of cardiac $^{123}$I-meta-iodobenzylguanidine scintigraphic findings during treatment in the 2 groups. TDS = total defect score. H/M = heart/mediastinum count. WR = washout rate. 6M = after 6 months of therapy.

Figure 2. Comparison of echocardiographic findings and plasma BNP concentrations during treatment in the 2 groups. LVEDV = left ventricular end-diastolic volume. LVEF = left ventricular ejection fraction. BNP = brain natriuretic peptide. 6M = after 6 months of therapy.

Figure 3. Changes in NYHA functional class during treatment in the 2 groups.
<table>
<thead>
<tr>
<th></th>
<th><strong>Valsartan</strong> (n=25)</th>
<th><strong>Enalapril</strong> (n=25)</th>
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<tr>
<td>Mean age (age)</td>
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<td>68 (9)</td>
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<tr>
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<td>15 / 10</td>
<td>NS</td>
</tr>
<tr>
<td>Height (cm)</td>
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<td>NS</td>
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<tr>
<td>Weight (kg)</td>
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</tr>
<tr>
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<td>NS</td>
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<tr>
<td>II / III</td>
<td>6 / 19</td>
<td>6 / 19</td>
<td>NS</td>
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<tr>
<td>Cause of CHF</td>
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<td>13 (52%)</td>
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<tr>
<td>TDS</td>
<td>43 (8)</td>
<td>43 (9)</td>
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<td>1.68 (0.36)</td>
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<tr>
<td>WR</td>
<td>46 (11)</td>
<td>47 (8)</td>
<td>NS</td>
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<tr>
<td>LVEDV (ml)</td>
<td>172 (42)</td>
<td>173 (29)</td>
<td>NS</td>
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<tr>
<td>LVEF (%)</td>
<td>31 (7)</td>
<td>32 (8)</td>
<td>NS</td>
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<tr>
<td>Plasma BNP (pg/ml)</td>
<td>237 (180)</td>
<td>235 (154)</td>
<td>NS</td>
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<td>Medical treatment</td>
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<tr>
<td>Loop diuretic</td>
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<td>Beta-blocker</td>
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<td>17 (68%)</td>
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<td>Spironolactone</td>
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<td>Nitrate</td>
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<td>Digitalis</td>
<td>2 (8%)</td>
<td>3 (12%)</td>
<td>NS</td>
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</tbody>
</table>

Values are mean (SD) or number (%).

SBP = systolic blood pressure; DBP = diastolic blood pressure; NYHA = New York Heart Association; CHF = congestive heart failure; DCM = dilated cardiomyopathy; OMI = old myocardial infarction; MIBG = meta-iodobenzylguanidine; TDS = total defect score; H/M = heart/mediastinum count; WR = washout rate; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; BNP = brain natriuretic peptide.
Table 2. Changes in total defect score, heart/mediastinum count ratio, and washout rate of patients in valsartan and enalapril groups

<table>
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<tr>
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<th>Enalapril</th>
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<td>6 months</td>
<td>Baseline</td>
<td>6 months</td>
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<td>I-123 MIBG</td>
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<tr>
<td>TDS</td>
<td>43(8)</td>
<td>39(10)*</td>
<td>43(9)</td>
<td>42(10)</td>
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<tr>
<td>H/M ratio</td>
<td>1.70(0.17)</td>
<td>1.78(0.22)†</td>
<td>1.68(0.36)</td>
<td>1.67(0.22)</td>
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</tr>
<tr>
<td>WR</td>
<td>46(11)</td>
<td>41(10)†</td>
<td>47(8)</td>
<td>46(10)</td>
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</table>

Values are mean (SD).
* p<0.01 vs. Baseline, † p<0.05 vs. Baseline.

MIBG = meta-iodobenzylguanidine; TDS = total defect score; H/M = heart/mediastinum count; WR = washout rate.
Table 3. Changes of plasma BNP concentration, left ventricular end-diastolic volume, left ventricular ejection fraction, and NYHA functional class of patients in the valsartan and enalapril groups

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

Values are mean (SD).

* p<0.05 vs. Baseline, † p<0.001 vs. Baseline, ‡ p<0.001 vs. Baseline, § p<0.01 vs. Enalapril at 6 months.

BNP = brain natriuretic peptide; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.
Comparative effects of valsartan with enalapril on cardiac sympathetic nerve activity and plasma brain natriuretic peptide in patients with congestive heart failure

Shu Kasama, Takuji Toyama, Takashi Hatori, Hiroyuki Sumino, Hisao Kumakura, Yoshiaki Takayama, Shuichi Ichikawa, Tadashi Suzuki and Masahiko Kurabayashi

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