Beneficial Effect of Perindopril on Cardiac Sympathetic Nerve Activity and Brain Natriuretic Peptide in Patients With Chronic Heart Failure

— Comparison With Enalapril —

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Background In patients with chronic heart failure (CHF), it remains unclear whether perindopril is more cardioprotective than enalapril.

Methods and Results Forty-five stable CHF outpatients undergoing conventional therapy including enalapril therapy were randomized to 2 groups [group I (n=24): continuous enalapril treatment; group II (n=21): enalapril was changed to perindopril]. Cardiac sympathetic nerve activity was evaluated using cardiac ^{123}I -metaiodobenzylguanidine (MIBG) scintigraphy, hemodynamic parameters and neurohumoral factors before and 6 months after treatment. There was no difference in baseline characteristics between the 2 groups. In group I, there were no changes in MIBG parameters, left ventricular ejection fraction (LVEF) or plasma level of brain natriuretic peptide (BNP). In contrast, in group II the delayed heart/mediastinum count ratio was significantly increased (2.0 ± 0.07 vs 2.15 ± 0.07 , $p=0.013$) and the washout rate was significantly decreased (33.0 ± 1.4 vs 30.5 ± 1.2 , $p=0.030$) after 6 months compared with the baseline value. In addition, LVEF was significantly increased and the plasma BNP level was significantly decreased.

Conclusion These findings suggest that for the treatment of CHF, perindopril is superior to enalapril with respect of cardiac sympathetic nerve activity and BNP. (Circ J 2008; 72: 740–746)

Key Words: Brain natriuretic peptide; Enalapril; Heart failure; Metaiodobenzylguanidine; Perindopril

Angiotensin-converting enzyme inhibitors (ACEI) have been widely used and shown to reduce morbidity and mortality in patients with chronic heart failure (CHF).^{1–3} Enalapril is an ACEI widely used for the treatment for CHF.^{1,2,4} Qualitative differences may exist among ACEI, and tissue ACEI (such as ramipril and perindopril) are highly lipophilic and have strong enzyme-binding capabilities; such ACEI probably provide greater penetration into the target organ than other ACEI such as enalapril.^{4–6} In a rat CHF model with dilated cardiomyopathy, perindopril treatment showed more favorable effects on myocardial mRNA expression of TGF- β 1 and collagen III than enalapril.⁷ In patients after acute myocardial infarction, perindopril treatment was associated with lower mortality than enalapril, suggesting that perindopril is superior to enalapril for the management of CHF patients.^{8,9}

Activation of the sympathetic nervous system is one of the important prognostic predictors of CHF patients.^{10,11} Cardiac imaging with ^{123}I -metaiodobenzylguanidine (MIBG),

an analogue of norepinephrine, is a useful tool for detecting abnormalities of the myocardial sympathetic nerve activity and predicting the mortality of patients with CHF.^{12–16} In addition, plasma levels of cardiac natriuretic peptides such as atrial natriuretic peptide and brain natriuretic peptide (BNP) are well-established powerful risk markers in CHF.^{11,17–21} The present study was to evaluate the comparative effects of perindopril with enalapril on cardiac sympathetic nerve activity (CSNA) evaluated using MIBG parameters and plasma BNP in CHF patients who have already received standard therapy, including carvedilol and spironolactone.

Methods

Patients

The subjects were 45 stable CHF outpatients receiving conventional therapy, including enalapril, carvedilol and spironolactone, for more than 6 months (mean follow-up period = 2.2 ± 0.15 years). The left ventricular ejection fraction (LVEF) was measured using 2-dimensional echocardiography or ventriculography using contrast medium or radioisotopes. LVEF was less than 45% at the initial diagnosis in all subjects. The etiology of systolic CHF was ischemic cardiomyopathy or dilated cardiomyopathy. Patients with acute myocardial infarction, valvular heart disease, malignancy or renal failure (serum creatinine >2.0 mg/dl) were excluded. In addition, patients receiving angiotensin receptor blockers, other ACEI or β -blockers other than carvedilol were excluded. Informed consent was obtained from all patients for

(Received October 17, 2007; revised manuscript received November 26, 2007; accepted December 11, 2007)

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Table 1 Comparisons of Baseline Characteristics Between Chronic Heart Failure Patients Treated With Enalapril and Perindopril

	Group I enalapril (n=24)	Group II perindopril (n=21)	p value
Age (years)	59.0±2.9	55.4±2.9	0.400
Gender (M/F)	22/2	17/4	0.395
DCM/ICM (n)	20/4	16/5	0.712
NYHA functional class			0.812
I/II/III (n)	3/19/2	4/15/2	
LVEF (%)	44.1±2.5	42.6±2.3	0.672
LVDd (mm)	62.6±2.3	64.4±2.1	0.557
LVDs (mm)	49.8±2.9	50.7±2.4	0.806
Atrial fibrillation, n, (%)	8 (33)	4 (19)	0.329
HR (beats/min)	65±1.9	71±4.3	0.18
SBP (mmHg)	112±2.6	111±3.1	0.701
DBP (mmHg)	68±1.7	68±1.3	0.986
BNP (pg/ml)	149±26	127±32	0.611
Norepinephrine (pg/ml)	414±30	417±39	0.944
Aldosterone (pg/ml)	103±17	83±12	0.355
Endothelin-1 (pg/ml)	2.54±0.4	2.4±0.2	0.754
¹²³ I-MIBG			
H/M ratio	2.1±0.07	2.0±0.07	0.398
WR	31±1.4	32.6±1.4	0.439
Treatments			
Duration of treatments (month)	29±2.4	25.0±2.9	0.265
Dose of enalapril at baseline (mg/day)	8.6±0.6	9.0±0.6	NS
Dose of ACEI (mg/day)	8.6±0.6	4.9±0.5	—
Digitalis, n, (%)	10 (41)	10 (47)	0.765
Loop diuretics, n, (%)	12 (75)	15 (71)	0.99
Spiroglactone, n, (%)	24 (100)	21 (100)	NS
Carvedilol, n, (%)	24 (100)	21 (100)	NS
Dose of carvedilol (mg/day)	17.8±0.9	16.7±1.0	0.40

DCM, dilated cardiomyopathy; ICM, ischemic cardiomyopathy; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; LVDd, left ventricular diastolic diameter; LVDs, left ventricular systolic diameter; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; BNP, brain natriuretic peptide; MIBG, metaiodobenzylguanidine; H/M, heart/mediastinum count; WR, washout rate; ACEI, angiotensin-converting enzyme inhibitor.

participation in the present study, according to the protocol approved by the Committee on Human Investigation at our institution.

Study Protocol

Forty-five stable CHF outpatients undergoing conventional therapy including enalapril therapy were randomized to 2 groups [group I (n=24): continuous enalapril treatment at a stable dose; group II (n=21): enalapril changed to perindopril at a dose of 4 mg/day instead of enalapril (10 mg/day), which is a comparable antihypertensive dose]. The dose of perindopril was practically adjusted to maintain the clinical systolic blood pressure target.

Within a week after entry, cardiac MIBG scintigraphy and echocardiography were performed. At the same time, blood samples were collected for the measurement of the plasma levels of BNP, norepinephrine, aldosterone and endothelin-1 after at least 30 min of supine bed rest. Six months later, the same measurements were obtained. None of the patients had a cardiovascular event during the follow-up periods. Physicians were blind to the values of MIBG parameters and echocardiographic parameters and plasma levels of neurohumoral factors until the completion of the present study.

MIBG Imaging

All patients were injected intravenously with 3 mCi of ¹²³I-MIBG images were obtained using a single-head gamma camera with a low-energy collimator (Toshiba GCA-901A, Toshiba, Tokyo, Japan). Energy discrimination

was provided by a 20% window centered on the 159 KeV photopeak. A 5-min static acquisition was performed at 15 min (early) and 180 min (delayed) after radioisotope injection as previously reported.¹⁶ On the anterior planar image, a region of interest (ROI) was manually placed over the heart and another ROI was placed over the upper mediastinal area. Using early and delayed images, the heart to mediastinum (H/M) ratio and the washout rate (WR) were calculated from the average counts in each ROI by 2 independent observers. The WR was defined as the percentage change in cardiac activity (H) from early to delayed images within the left ventricular area as follows: [(H)–(M)] early–[(H)–(M)] delayed/[(H)–(M)] early×100 (%). Decay correction was not applied.

Assessment was done in a blinded fashion by 2 independent observers with no knowledge of the clinical status or medical therapy of the patients. The interobserver differences in the H/M ratio (delayed) and WR were not significant. In our laboratory, the normal values of the H/M ratio (delayed) and WR were 2.60±0.24 and 28.0±3.1%, respectively.¹⁶

Measurement of Plasma Neurohumoral Factors

Samples for the assay of plasma BNP concentration were transferred to chilled disposable tubes containing aprotinin (500 kallikrein inactivator unit/ml). The blood samples were immediately placed on ice and centrifuged at 4°C. Then the plasma BNP concentration was measured with a specific immunoradiometric assay using a commercial kit (Shionogi, Osaka, Japan) as reported previously.¹⁷ The plasma norepi-

NYHA

EF (%)

Fig 1. Changes in New York Heart Association (NYHA) functional class and left ventricular ejection fraction (EF) during enalapril treatment.

NYHA

EF (%)

Fig 2. Changes in New York Heart Association (NYHA) functional class and left ventricular ejection fraction (EF) during perindopril treatment. * $p < 0.05$ vs the baseline value.

nephrine concentration was measured using high-performance liquid chromatography as reported previously.¹⁷ The plasma levels of endothelin-1 and aldosterone were measured using radioimmunoassay as previously reported.^{22,23} Physicians were blind to the values of MIBG parameters and plasma levels of neurohumoral factors until completion of the present study.

Statistical Analysis

All results are expressed as the mean $\pm$ SEM. Univariate analysis was performed using a Student's *t*-test. Categorical data were compared against a chi-square distribution. Changes in New York Heart Association (NYHA) functional class were assessed using Wilcoxon matched pairs signed rank test. Effects of chronic treatment were assessed within a group using paired *t*-test and analysis of variance to compare between-group changes. A *p* value < 0.05 was regarded as significant.

Results

Patient Characteristics (Table 1)

At the initial diagnosis of CHF (systolic heart failure), LVEF was $31.7 \pm 1.5\%$ and increased to $43.4 \pm 1.7\%$ after 2.3 ± 0.15 years of conventional therapy including enalapril, carvedilol and spironolactone. There was no difference in baseline characteristics and follow-up periods after the initial diagnosis and treatment between the 2 groups. At entry

to the present study, there was no difference in the dose of enalapril between the 2 groups. All patients have already received carvedilol (17.3 ± 0.7 mg/day) and spironolactone (25 mg/day) at baseline in both groups. Before randomization to continued enalapril or the change to perindopril, there was no significant difference in LVEF (44.1 ± 2.5 vs $42.6 \pm 2.3\%$). At baseline, there was no difference in plasma levels of BNP, norepinephrine, aldosterone or endothelin-1 between the 2 groups and there was no difference in H/M ratio or WR between the 2 groups.

After randomization, in group I, enalapril treatment was continued at the same dose (8.6 ± 0.6 mg/day) and in group II, enalapril was changed to perindopril (4.9 ± 0.5 mg/day). Medications other than ACEI did not change and none of the patients had cardiovascular events during the present study period.

Comparison of NYHA Functional Class and Hemodynamics Before and After Randomization of the Treatment

In patients receiving enalapril (group I), NYHA functional class and LVEF did not change (41.1 ± 2.5 vs $44.9 \pm 2.8\%$, $p = 0.29$) after 6 months compared with the baseline value (Fig 1). In patients receiving perindopril (group II), blood pressure did not change ($111 \pm 3.1/68 \pm 1.3$ vs $112 \pm 2.8/68 \pm 1.0$ mmHg) but NYHA functional class improved and LVEF significantly increased after 6 months of perindopril treatment (42.6 ± 2.3 vs $44.9 \pm 2.3\%$, $p = 0.013$) (Fig 2).

Fig 3. Comparisons of biomarkers before and after 6-month treatment with enalapril. BNP, brain natriuretic peptide; ET-1, endothelin-1.

Fig 4. Comparisons of biomarkers before and after 6-month treatment with perindopril. BNP, brain natriuretic peptide; ET-1, endothelin-1. * $p < 0.05$ vs the baseline value.

Fig 5. Comparisons of cardiac ^{123}I -metaiodobenzylguanidine scintigraphic parameters before and after 6-month treatment with enalapril. H/M, heart to mediastinum ratio; WR, washout rate.

Fig 6. Comparisons of cardiac ^{123}I -metaiodobenzylguanidine scintigraphic parameters before and after 6-month treatment with perindopril. H/M, heart to mediastinum ratio; WR, washout rate.

Comparison of Neurohumoral Factors Before and After Randomization of the Treatment

In patients receiving enalapril (group I), plasma levels of BNP (148.9 ± 26 vs 169.3 ± 33 pg/ml, $p=0.36$), norepinephrine (414 ± 30 vs 361 ± 35 pg/ml, $p=0.19$), aldosterone (103.8 ± 17 vs 92.8 ± 12 pg/ml, $p=0.53$) and endothelin-1 (2.5 ± 0.4 vs 2.2 ± 0.9 pg/ml, $p=0.39$) did not change after 6 months compared with the baseline value (Fig 3). In patients receiving perindopril (group II), plasma levels of norepinephrine (417 ± 39 vs 386 ± 42 pg/ml, $p=0.55$), aldosterone (83 ± 12 vs 82.6 ± 6.8 pg/ml, $p=0.96$) and endothelin-1 (2.4 ± 0.2 vs 2.2 ± 0.1 pg/ml, $p=0.47$) did not change, but plasma BNP significantly decreased (127.4 ± 32 vs 83 ± 18 pg/ml, $p=0.042$) after 6 months of perindopril treatment (Fig 4).

Comparison of ^{123}I -MIBG Findings Before and After Randomization of the Treatment

In patients receiving enalapril (group I), both H/M ratio (2.09 ± 0.07 vs 2.12 ± 0.07 , $p=0.450$) and WR (31.1 ± 1.4 vs 32.1 ± 0.07 , $p=0.395$) did not change after 6 months compared with the baseline value (Fig 5). In contrast, in patients receiving perindopril (group II), the H/M ratio was significantly increased (2.0 ± 0.07 vs 2.15 ± 0.07 , $p=0.013$) and WR was significantly decreased (33.0 ± 1.4 vs 30.5 ± 1.2 , $p=0.030$) after 6 months compared with the baseline value (Fig 6).

Discussion

The prognoses of CHF patients remain poor despite conventional medical therapy such as ACEI, β -blockers and spironolactone.²⁴ In the present study, we demonstrated that, compared to treatment containing enalapril, treatment switching from enalapril to perindopril improves the NYHA functional class, CSNA, LVEF and plasma BNP level in out-patients with stable CHF who are already receiving carvedilol and spironolactone. This suggests that perindopril has a more potent and prolonged angiotensin-converting enzyme blockade in the failing heart than enalapril.⁶

Previous studies have suggested that ACEI, angiotensin receptor blocker, β -blockers and spironolactone can improve the parameters of cardiac ^{123}I -MIBG scintigraphy and decrease plasma levels of BNP in patients with CHF.^{16,23,25-36} Both parameters of cardiac ^{123}I -MIBG scintigraphy and plasma BNP levels are useful surrogate markers for the management of CHF patients. We have reported that repeated measurements of cardiac ^{123}I -MIBG imaging parameters before and after 6-month optimized treatments are useful for predicting the prognoses of patients with moderate to severe CHF.¹⁶ In our previous study, the H/M ratio (delayed) was significantly increased after 6 months of optimal treatment in survivors but was significantly decreased in non-survivors, and that the changes in cardiac ^{123}I -MIBG imaging

parameters after 6 months were independent prognostic predictors of long-term outcome.

Recently, Kasama et al reported that the initiation of ACEI treatments improves symptoms and cardiac ^{123}I -MIBG scintigraphic parameters, and that the improvements were greater after perindopril treatment compared to those after enalapril treatment.³⁷ The differences of the present study from their study are the baseline treatment of CHF and doses of ACEI, but their observations and our findings were similar and consistent with the report by Masuelli et al.⁹ Kasama et al compared the initial effects of enalapril (5 mg/day) and perindopril (2 mg/day) in CHF patients who had been admitted to hospital due to heart failure and one-half of patients had already taken β -blockers and none of the patients had been taking spironolactone.³⁷ They found that CSNA was improved after 6 month in the perindopril treatment group but not in the enalapril group. In the present study, we compared the effects of switching from enalapril to perindopril on stable outpatients with CHF who were all already taking carvedilol and spironolactone. We found that CSNA was improved after 6 months for those in whom the treatment was switched from enalapril to perindopril but not in those for whom enalapril treatment was continued. More recently, Kasama et al has reported that long-term carvedilol treatment could improve both CSNA and left ventricular remodeling in patients with DCM.³⁸ Although in the present study left ventricular volume was not changed after 6 months in the perindopril treatment group (data not shown), long-term follow-up may be needed to evaluate left ventricular remodeling.

Although the small number of patients with CHF included in the present study and a relatively short-term follow-up period were limitations, the present findings support the hypothesis that the administration of different ACEI may result in different cardiac and hemodynamic effects. As the abnormality of CSNA and plasma levels of BNP are thought to be more useful surrogate markers of the prognosis of CHF patients than plasma levels of norepinephrine and endothelin-1, the present study may provide a rationale for a multicenter, double-blind study designed to investigate whether these positive effects of perindopril treatment have any impact on prognosis.^{16,19,21}

Acknowledgements

We wish to thank Aoi Murata for excellent technical assistance. We also express thanks to Mr. Daniel Mrozek for assistance in preparing the manuscript. The present study was supported by a Grant-in-Aid for Scientific Research in Japan.

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