Effect of Beta-Blocker on Left Ventricular Function and Natriuretic Peptides in Patients With Chronic Heart Failure Treated With Angiotensin-Converting Enzyme Inhibitor

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To evaluate whether or not β-blockers can improve the condition of patients with heart failure treated with a combination of diuretics, digitalis and angiotensin-converting enzyme inhibitor (ACEI), 52 patients with chronic heart failure who have been treated with ACEI for more than 6 months were enrolled. They were divided into 2 groups: 26 patients continued the same therapy another 6 months or more (group A), and 26 patients were given oral metoprolol for 6 months or more, in addition to the ACEI (group B). Echocardiographic parameters and atrial and brain natriuretic peptides (ANP, BNP) were measured. The left ventricular dimensions at end-diastole and end-systole were significantly decreased and fractional shortening was significantly increased in group B after 6 months' treatment with the β-blocker, but these parameters remained unchanged in group A. Plasma levels of both ANP and BNP were significantly decreased in group B, but remained unchanged in group A. These results indicate that concomitant β-blocker therapy can improve left ventricular function and attenuate plasma ANP and BNP levels in patients with chronic heart failure treated with ACEI. (Jpn Circ J 2000; 64: 365–369)

Key Words: Angiotensin-converting enzyme inhibitor; Beta-blocker; Heart failure; Natriuretic peptides

Dilated cardiomyopathy (DCM) is an important cause of morbidity and mortality among patients with congestive heart failure. The prognosis in patients with chronic heart failure (CHF) has been improved by the use of angiotensin-converting-enzyme inhibitors (ACEI) or β-blockers.1-4 In addition, the American College of Cardiology/American Heart Association (ACC/AHA) task force reported that ACEI therapy was appropriate for all patients with a significantly reduced left ventricular ejection fraction (LVEF).6 However, we often encounter patients with recurrent heart failure, despite ACEI treatment, so it is likely that ACEI therapy alone is not necessarily sufficient for patients with CHF. Two meta-analyses showed that treatment of CHF with β-blockers also improves prognosis.5-7 Conventionally used prognostic parameters such as functional status, LVEF, left ventricular dimension, transmural flow velocity profiles and left ventricular end-systolic wall stress are important predictors of the mortality in patients with DCM.8-11 In addition, recent studies indicate that there is a good relationship between the plasma levels of natriuretic peptides (atrial natriuretic peptide, ANP; brain natriuretic peptide, BNP) and the severity of CHF.12-15 It has also been reported that the plasma level of ANP in patients with CHF was attenuated by ACEI or β-blocker treatment.16-18 Thus, the purpose of the present study was to elucidate whether β-blockers can improve the clinical symptoms, left ventricular fractional shortening and plasma levels of natriuretic peptides in patients with CHF who have been treated with a combination of diuretics, digitalis and ACEI.

Methods

Study Population

Patients were considered eligible for the study when they had had symptomatic CHF for more than 3 months and left ventricular fractional shortening less than 25%. In addition, the study patients had to be clinically stable under the conventional therapy (diuretics and digitalis) for more than 4 weeks prior to the study. The final study population consisted of 52 patients (mean age, 52±11 years; 43 men, 9 women): 47 had heart failure caused by idiopathic DCM, 2 had hypertensive heart failure, 2 had viral myocarditis and 1 had ischemic cardiomyopathy. Patients were excluded if they had unstable angina, obstructive lung disease or asthma, or symptomatic peripheral vascular disease. All patients participated in the present study after giving informed consent.

Study Protocol

ACEI (enalapril [mean dose, 7.5±2.3 mg] or captopril [mean dose, 42±14 mg]) was given for 6 months to all patients (Table I). After the 6 months’ treatment, 14 patients were classified as New York Heart Association (NYHA) functional class grade III, 31 as class II and 7 as class I. The cardiothoracic ratio on chest X-ray was 51.7±4.9%. Eleven patients were in atrial fibrillation. Subsequently, 26 patients continued to receive the same therapy for another 6 months (group A), while the other 26
patients were given oral metoprolol in addition to the ACEI for a further 6 months (group B). Patients received titrated doses of metoprolol, beginning with a low value of 2.5 or 5 mg that was increased gradually up to the maximal dose tolerated, as determined by end-points of either a decrease in systolic blood pressure to less than 90 mmHg, a decrease in heart rate at rest to less than 50 beats/min or clinical deterioration. The mean maintenance dose of metoprolol was 39.8±16.9 mg (from 15 to 80 mg).

**Echocardiographic Study**

M-mode and two-dimensional echocardiography was performed in all patients using an Aloka SSD 870 or SSD 9000 imaging system (Tokyo, Japan) with a 2.5- or 3.5-MHz transducer. The M-mode echocardiogram was recorded on a strip-chart recorder at a paper speed of 50 mm/s and 100 mm/s. From the M-mode echocardiographic study, the following conventional variables were measured according to the criteria of the American Society of Echocardiography:19 left atrial dimension (LAD), left ventricular dimension at end-diastole (LVDd) and at end-systole (LVDs), and percent fractional shortening (%FS). At the time of the echocardiographic study, arterial blood pressure was determined in duplicate using a cuff sphygmomanometer.

**Measurement of Plasma Levels of ANP and BNP**

Plasma ANP and BNP levels were determined following the method reported previously.20 A blood sample was drawn from the antecubital vein in the morning after 30 min of supine rest and immediately transferred into chilled glass tubes, containing disodium ethylenediaminetetraacetic

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### Table 1 Clinical Characteristics of the 2 Treatment Groups

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=26)</th>
<th>Group B (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>51±10</td>
<td>52±15</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>26/6</td>
<td>23/3</td>
</tr>
<tr>
<td>NYHA functional class (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>II</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>III</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Etiology of heart failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic dilated cardiomyopathy</td>
<td>24 (92%)</td>
<td>23 (88%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Ischemia</td>
<td>0 (0%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Concomitant medications (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Furosemide</td>
<td>22 (85%)</td>
<td>20 (77%)</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>10 (38%)</td>
<td>13 (50%)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Enalapril</td>
<td>11 (42%)</td>
<td>11 (42%)</td>
</tr>
<tr>
<td>Captopril</td>
<td>15 (58%)</td>
<td>15 (58%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>6 (23%)</td>
<td>5 (19%)</td>
</tr>
</tbody>
</table>

There were no statistically significant differences between the 2 groups at baseline. NYHA, New York Heart Association.

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### Table 2 Changes in Hemodynamic and Echocardiographic Data in the 2 Groups During 6 Months of Follow-up

<table>
<thead>
<tr>
<th></th>
<th>HR (beats/min)</th>
<th>SBP (mmHg)</th>
<th>LAD (mm)</th>
<th>LVDd (mm)</th>
<th>LVDs (mm)</th>
<th>FS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>70.2±11.3</td>
<td>114±12</td>
<td>40.3±5.8</td>
<td>64.12±6.1</td>
<td>50.5±7.4</td>
<td>21.6±5.6</td>
</tr>
<tr>
<td>After</td>
<td>72.2±12.2</td>
<td>112±12</td>
<td>40.6±6.6</td>
<td>63.62±6.9</td>
<td>50.3±8.0</td>
<td>21.3±5.9</td>
</tr>
<tr>
<td>Group B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>71.7±12.4</td>
<td>116±17</td>
<td>45.1±9.9</td>
<td>65.82±8.1</td>
<td>53.6±10.4</td>
<td>19.1±6.9</td>
</tr>
<tr>
<td>After</td>
<td>65.5±8.2*</td>
<td>122±13*</td>
<td>42.3±7.3</td>
<td>62.23±7.9</td>
<td>47.8±4.9</td>
<td>23.6±6.8</td>
</tr>
</tbody>
</table>

Values are the mean ± standard deviation. *p<0.05 compared with before, †p<0.01 compared with before; ‡p<0.001 compared with before. There were no statistically significant differences at baseline measures between the 2 groups. HR, heart rate; SBP: systolic blood pressure; LAD, left atrial dimension; LVDd, left ventricular dimension at end-diastole; LVDs, left ventricular dimension at end-systole; FS, fractional shortening.

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**Fig.1** Changes in New York Heart Association (NYHA) functional class I-IV before and after treatment for group A and group B.
acid (1 mg/ml) and aprotinin (500 U/ml), and centrifuged at 4°C. The plasma was frozen and stored at −80°C for radioimmunoassay (RIA; Shiono RIA assay kit, Shionogi Co., Ltd, Osaka, Japan). The normal values for plasma ANP and BNP in our institution were less than 43.0 pg/ml and less than 17.0 pg/ml, respectively.

Statistical Analysis

Data are presented as the mean value±SD. Baseline characteristics were compared by unpaired t test or chi-square test (for nonparametrically distributed values). Changes in measures were compared by two-way (group effect and time effect) repeated measures analysis of variance. Differences within groups were tested by Student’s paired t test only if the repeated measures analysis demonstrated an intragroup time effect. Difference of the NYHA functional class, ANP and BNP within groups was tested by Wilcoxon signed rank test. All calculations were performed on a personal computer using the statistical package StatView 1994 (Abacus Concepts, Inc, Berkeley, CA, USA). A value of p<0.05 was considered significant.

Results

Comparison of Baseline Clinical Characteristics Between the Two Groups

The baseline characteristics of the 2 groups are given in Table 1. There were no significant differences in age, gender, the NYHA functional class, concomitant medications or the number of patients in atrial fibrillation, nor were there significant differences between the 2 groups in the mean dose of concomitant medications. As shown in Table 2, there were no significant differences in heart rate, systolic blood pressure, LAD, LVDD, LVDs or %FS at the start of the study between group A and group B.

Effects of β-blocker Therapy

Fig 1 shows that the NYHA functional class remained unchanged in group A, but significantly decreased in group B. Table 2 shows the changes in the echocardiographically determined parameters. In group A, there were no significant changes in heart rate, systolic blood pressure, LAD, LVDD, LVDs or %FS, but in group B, after the 6 months’ treatment, heart rate decreased and systolic blood pressure increased. In addition, LAD, LVDD and LVDs significantly decreased and %FS increased significantly.

Comparison of the Plasma Levels of ANP and BNP

Fig 2 shows that the plasma levels of both ANP and BNP were not significantly changed in group A (from 43±43 to 41±46 pg/ml and from 77±103 to 89±143 pg/ml, respectively). However, in group B the plasma levels of both ANP and BNP significantly decreased (from 42±45 to 25±26 pg/ml, p=0.0080 and from 133±221 to 64±63 pg/ml, p=0.0022, respectively).

Discussion

The present study indicates that β-blocker therapy with metoprolol can improve not only clinical symptoms but also left ventricular function even in patients with CHF being treated with ACEI. In addition, the plasma levels of ANP and BNP in patients treated with β-blocker significantly decreased.

The beneficial effect of β-blockers on left ventricular function in patients with CHF is acknowledged. The increase in EF associated with metoprolol treatment is known to be between 4 and 11%. In addition, Olsen et al reported that FS associated with the treatment with carvedilol increased by 5%. In the present study, the mean increase of FS in patients treated with metoprolol was 4%, a similar effect to that reported previously. In addition, our results indicate that β-blockers can improve the clinical symptoms and left ventricular function even in patients treated with ACEI, which means that ACEI treatment may be insufficient for most patients with CHF, although the.
reasons for this remain to be determined. However, there are two hypotheses. First, it is known that the plasma concentration of aldosterone increases during long-term treatment with ACEIs and aldosterone is one of the key hormones in the pathophysiology of heart failure. In fact, therapy with spironolactone, an aldosterone receptor antagonist, can attenuate recurrent heart failure. On the other hand, it is known that the β-blocker, carvedilol, decreases the plasma level of aldosterone. The second theory is the formation of angiotensin II. Recent studies have elucidated that the human heart contains a dual pathway of angiotensin II formation and confirmed that the major enzymatic pathway for angiotensin II formation in the heart is not blocked by ACEIs. Thus, it seems likely that cardiac angiotensin II formation is not abolished during chronic therapy with ACEI. It may be that both these mechanisms are closely related to the recurrence of heart failure in patients treated with ACEI.

Previous studies have shown that the plasma levels of ANP and BNP are a sensitive marker of the severity of congestive heart failure and both peptides are closely related to left ventricular function. In addition, the plasma levels of BNP provide prognostic information in patients with heart failure. In the present study, both ANP and BNP levels significantly decreased in the group receiving β-blocker therapy, which confirmed previous reports that the plasma level of ANP significantly decreased with β-blocker therapy. Marked improvement of the clinical symptoms, left ventricular function and levels of natriuretic peptides strongly suggests that β-blocker therapy should be given even in patients being treated with a combination of diuretics, digoxin and ACEI.

**Study Limitation**

A recognized limitation of the present study is that the study protocol was not randomized. There were no significant differences in baseline clinical characteristics and left ventricular dysfunction between 2 groups, but the left atrial dimension and BNP before β-blocker treatment were larger, but nonsignificantly, in group B than in group A. Thus, the lack of randomization may somewhat influence the results. Another limitation is the relatively small number of study patients. Although we are aware that a large number of subjects could have improved the power of our results, nevertheless the size of our study population did not alter the effect of the β-blocker in these patients with CHF.

**References**


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