Comparative Effects of Amlodipine Monotherapy and Combination Therapy With Betaxolol on Cardiac Autonomic Nervous Activity and Health-Related Quality of Life in Patients With Poorly Controlled Hypertension

Bonpei Takase, MD1; Yasuchika Takeishi, MD2; Tadakazu Hirai, MD3; Jong-Dae Lee, MD4; Hiroyasu Uzui, MD4; Shoichi Senda, MD5; Kunihisa Miwa, MD6; Yuji Hiraoka, MD7; Toru Kinugawa, MD8; Ryohei Hosokawa, MD9; Masatoshi Fujita, MD10

**Background**  The aim of the study was to evaluate whether the combined treatment of calcium channel blocker, amlodipine and ß-blocker, betaxolol, favors affecting cardiac autonomic nervous activity (CANA) and health-related quality of life (HRQL).

**Methods and Results**  A total of 65 patients with a poor blood pressure (BP) control with a low dose amlodipine therapy were randomly assigned to the amlodipine dose-up group (n=21) and betaxolol adding group (n=44). Before and after a 6-month treatment, BP, heart rate variability (HRV), HRQL and blood chemistries were evaluated. Low frequency (LF) spectra/high frequency (HF) spectra and HF/total power spectra (TP) were calculated as indexes of CANA, and HRQL was assessed by the questionnaire sheets. BP was well controlled in all patients of the present study. In the betaxolol adding group, LF/HF decreased (2.1±1.9 to 1.3±0.9, p<0.05) and HF/TP reciprocally increased (0.41±0.17 to 0.52±0.18, p<0.05), whereas the amlodipine dose-up group showed no significant changes in the HRV. HRQL was significantly improved in the betaxolol adding group, whereas it remained unchanged in the amlodipine dose-up group. Blood chemistries remained unchanged except for the slightly increased plasma brain natriuretic peptide concentrations in the betaxolol adding group (36±47 to 62±62 pg/ml, p<0.05).

**Conclusions**  Combined treatment of amlodipine and betaxolol appears to be more useful than amlodipine dose-up therapy, because combined treatment improves CANA and HRQL. (Circ J 2008; 72: 764–769)

**Key Words:** Amlodipine; Anti-hypertensive therapy; Betaxolol; Cardiac autonomic nervous function
referred to each hospital as a result of poor BP control, despite the treatment with amlodipine of 2.5 mg to 5.0 mg daily for at least 8 weeks. All of the study patients had systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg. In addition, resting heart rate showed ≥50 beats/min. Exclusion criteria were as follows: (1) the presence of atrial fibrillation; (2) allergic reaction to anti-hypertensive agents; (3) diabetic acidosis; (4) advanced heart blocks; (5) cardiogenic shock; (6) congestive heart failure; (7) pregnancy; or (8) any other acute disorders. Informed consent was obtained from each patient. The study protocol was approved by each institutional review board of participating hospitals.

Study Protocol
This was a multicenter prospective open-labeled blinded endpoints study. Each eligible patient was randomly assigned to 1 of 2 treatment arms of 6 months in a 1:2 ratio, to focus on the combination treatment with betaxolol. Each treatment arm consisted of the amlodipine dose-up group and the betaxolol adding group. The study protocol is summarized in Fig 1. Before the dose-up of amlodipine or adding betaxolol, BP was measured with use of a sphygmomanometer in a sitting position, and 12-lead electrocardiogram (ECG), venous blood sampling for measuring blood chemistries and ambulatory ECG monitoring in a supine position were carried out. From the blood samples, brain natriuretic peptide (BNP, pg/ml), hemoglobin A1c (%), fasting insulin (IU/ml) and fasting blood sugar (mg/dl) were measured by the standard method. HRQL was evaluated using the questionnaire sheets of the SF-8 Japanese version. All of these measurements were repeated before and after each treatment. In the amlodipine dose-up group, amlodipine was gradually titrated by 2.5 mg dose until the patient’s BP met an optimal level; systolic BP <130 mmHg and diastolic BP <85 mmHg. In the betaxolol adding group, betaxolol was started at the dose of 2.5 mg and was gradually titrated by 2.5 mg until the above optimal BP levels were achieved. All patients were followed-up for 6 months.

Measurement of HRV
Ambulatory ECG monitoring in a supine position was performed in a dim-lighted, quiet and temperature controlled room by using a Fukuda Denshi Holter system (CardiWalk, SM-60, Tokyo, Japan) and was analyzed by a Fukuda Denshi Holter analyzer (SCM 6000, Dual Holter Workstation system, Fukuda Denshi). Ambulatory ECG monitoring was performed at the almost same time of the day for 30 min before and after the 6-month treatment. All

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**Fig 1.** The scheme of the study protocol. BP, blood pressure; ECG, electrocardiogram; HRV, heart rate variability; HRQL, health-related quality of life; SF-8, short form 8-item health survey.

**Table 1 Patients Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Amlodipine dose-up group (n=21)</th>
<th>Betaxolol adding group (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65±10</td>
<td>67±9</td>
</tr>
<tr>
<td>M/F</td>
<td>8/13</td>
<td>28/16</td>
</tr>
<tr>
<td>SV1+RV5 in ECG (mV)</td>
<td>3.2±0.8</td>
<td>3.3±1.1</td>
</tr>
<tr>
<td>Amlodipine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dosage (mg)</td>
<td>3.6±1.3</td>
<td>3.8±1.3</td>
</tr>
<tr>
<td>Combination treatment (%)</td>
<td>18 (86%)</td>
<td>35 (80%)</td>
</tr>
<tr>
<td>Angiotensin II receptor blocker (%)</td>
<td>3 (14%)</td>
<td>9 (20%)</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor (%)</td>
<td>2 (10%)</td>
<td>6 (14%)</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>1 (5%)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>1 (5%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>3 (14%)</td>
<td>5 (11%)</td>
</tr>
</tbody>
</table>

Data are mean±SD.  
ECG, electrocardiogram.  
Diabetes mellitus, fasting blood sugar (FBS) >126 mg/dl; hypercholesterolemia, total cholesterol >220 mg/dl.
30 min recording segments were divided into 6 segments of contiguous 5 min intervals. For each 5 min interval, all RR intervals were transferred to a personal computer for the frequency domain analysis of HRV. All RR intervals of 5 min segments were then transformed using a fast Fourier transform to obtain power spectra. The segments that contained any arrhythmias were excluded from the subsequent analysis. The direct current component was excluded in the calculation of the power spectrum to remove the non-harmonic components in the very low-frequency region (<0.04 Hz)\textsuperscript{12}

Total frequency (TF) spectra (0.04–0.40 Hz), low frequency (LF) spectra (0.04–0.15 Hz) and high frequency (HF) spectra (0.15–0.40 Hz) were obtained. The ratio of LF to HF as well as the ratio of HF to TF were expressed as LF/HF and HF/TF, respectively.\textsuperscript{12–14} Among all segments, maximum and minimum values of LF/HF and HF/TF were discarded and the remaining 3 values were averaged.

HRQL Assessment
All patients answered the self-administered HRQL ques-

\begin{table}[h]
\centering
\caption{Effects of Each Treatment on Hemodynamics and HR Variability}
\begin{tabular}{|l|l|l|l|}
\hline
 & \textbf{Amlodipine dose-up group} & & \textbf{Betaxolol adding group} \\
 & \textbf{Pre} & \textbf{Post} & \textbf{Pre} & \textbf{Post} \\
\hline
SBP (mmHg) & 149±8 & 125±10* & 151±9 & 128±9* \\
DBP (mmHg) & 86±7 & 75±6* & 87±7 & 77±8* \\
HR (beats/min) & 74±10 & 70±8* & 73±9 & 60±7* \\
TF (ms\textsuperscript{2}/Hz) & 1,813±5,108 & 811±962 & 576±1,589 & 708±1,332 \\
LF (ms\textsuperscript{2}/Hz) & 892±1,949 & 492±653 & 246±414 & 310±286 \\
HF (ms\textsuperscript{2}/Hz) & 921±2,284 & 320±344 & 330±1,188 & 398±786 \\
LF/HF & 2.3±2.1 & 1.8±1.3 & 2.1±1.9 & 1.3±0.9* \\
HF/TF & 0.40±0.19 & 0.43±0.18 & 0.41±0.17 & 0.52±0.18* \\
\hline
\end{tabular}
\end{table}

Data are mean±SD.

HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; TF, total frequency spectra; LF, low frequency spectra; HF, high frequency spectra.

\textsuperscript{*}p<0.05 vs pre in the amlodipine dose-up group; \textsuperscript{#}p<0.05 vs pre in the betaxolol adding group.

Fig 2. Effect of each treatment on low frequency spectra to high frequency spectra ratio (LF/HF). Pre AML, before the amlodipine dose-up treatment; Post AML, 6 months after the amlodipine dose-up treatment; Pre BTXL, before the betaxolol adding treatment; Post BTXL, 6 months after the betaxolol adding treatment. \textsuperscript{*}p<0.05 vs pre BTXL.

Fig 3. Effect of each treatment on high frequency spectra to total frequency spectra ratio (HF/TF). Format is the same as in Fig 2. \textsuperscript{*}p<0.05 vs pre BTXL.
uestionnaires at randomization and after the 6-month treatment to assess both general well-being and specific subjective symptoms. They answered the questionnaires during the clinic visit before any other measurements or examinations were made. To promote quality and avoid missing values, the questionnaires were checked for completeness before the patient left the clinic.

**Statistical Analysis**

Data are expressed as the mean±SD. The paired Student’s t-test was used to compare data before and after the amlodipine dose-up and the betaxolol adding treatment. The unpaired Student’s t-test was also applied to compare data between the 2 groups. Differences were considered significant at p<0.05.

**Results**

**Patient Profile**

The present study consisted of 21 patients in the amlodipine dose-up group and 44 patients in the betaxolol adding group as shown in Table 1. Average values of SV1+RV5 in the 12-lead ECG were similar in both groups. Baseline average amlodipine dosage was comparable between the amlodipine dose-up and the betaxolol adding groups that was 3.6 mg (2.5 mg in 12 patients, 5 mg in 9 patients) and 3.8 mg (2.5 mg in 21 patients, 5 mg in 23 patients), respectively. Most of the patients were in the amlodipine monotherapy. The remaining patients were in a combination treatment with angiotensin II receptor blocker or angiotensin converting enzyme inhibitor. For each group patient,
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Changes in Hemodynamics, HRV and HRQL

The effects of each treatment on hemodynamics and HRV are summarized in Table 2. Both the amlodipine dose-up and betaxolol adding groups showed significantly and similarly decreased systolic and diastolic BP. In the betaxolol adding group, the heart rate more profoundly decreased than the amlodipine dose-up group. As shown in Table 2 and Figs 2 and 3, the betaxolol adding group showed the significant decrease of LF/HF and reciprocal increase of HF/TP, whereas no significant changes were observed in the amlodipine dose-up group. In addition, the betaxolol adding group showed the more profound salutary effect on the HRQL than the amlodipine dose-up group. These findings are compatible with decreased HF/TP shown by the previous study. Moreover, in 15 of 44 patients of the betaxolol adding group, the echocardiographically determined left ventricular dimensions and contraction did not change significantly (data not shown). The metabolism of carbohydrates and lipid profiles was not affected by the betaxolol adding treatment. Because no side-effects were observed in patients with poorly controlled hypertension, despite taking a low dose of amlodipine.

In the betaxolol adding group, LF/HF decreased and HF/TP increased with a statistical significance, whereas these parameters were not changed in the amlodipine dose-up group. These findings are compatible with decreased cardiac sympathetic nervous activity along with a concomitant increase in cardiac vagal nervous activity. Because sympathetic nervous hyperactivity is one of the well known mechanisms of primary (essential) hypertension, the attenuation in cardiac sympathetic activity is necessary for the treatment of poorly controlled hypertensive patients. In addition, the improvement of HRV indexes secondary to the autonomic nervous regulation might specifically maintain the HRQL in the hypertensive patients. Such a favorable finding agrees with a previous report. There were no significant side-effects in both treatment groups. However, BNP significantly increased in the betaxolol adding group after 6 months of treatment. The average BNP value of 62 pg/ml is reported to be not significant in the clinical settings. In addition, the mild increase of BNP by the -blocker treatment was previously reported. However, our results of BNP increase by betaxolol are in agreement with the previous study. Moreover, in 15 of 44 patients of the betaxolol adding group, the echocardiographically determined left ventricular dimensions and contraction did not change significantly (data not shown). The metabolism of carbohydrates and lipids was not affected by the betaxolol adding treatment. Because no side-effects were observed in both the amlodipine dose-up and betaxolol adding groups, these treatments appear to be clinically relevant in patients with poorly controlled hypertension, despite taking a low dose amlodipine.

The present study showed that the combined treatment of calcium channel blocker and -blocker (the betaxolol adding group) had more beneficial effects on CANA assessed by HRV and HRQL by the questionnaire sheets than the amlodipine dose-up group, whereas the sufficient and similar BP lowering effects were observed in both treatment groups of patients with poorly controlled hypertension, despite taking a low dose of amlodipine.

Discussion

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Changes in Blood Chemistries

As shown in Table 3, both treatment groups did not show detectable changes in most parameters of blood chemistries except for a slight but significant increase of BNP in the betaxolol adding group.

Table 3 Effects of Treatment on Blood Chemistries

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Amlodipine dose-up group</th>
<th>Betaxolol adding group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>FBS (mg/dl)</td>
<td>99±15</td>
<td>94±16</td>
</tr>
<tr>
<td>Hemoglobin A1c (%)</td>
<td>5.2±0.6</td>
<td>5.2±0.7</td>
</tr>
<tr>
<td>Fasting insulin (IU/ml)</td>
<td>17±23</td>
<td>11±21</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>23±20</td>
<td>25±20</td>
</tr>
</tbody>
</table>

Data are mean±SD.
FBS, fasting blood sugar; BNP, brain natriuretic peptide.
*p<0.05 vs pre in the betaxolol adding group.

Reports have shown that impaired HRV indexes in patients with hypertension reflect the presence of either left ventricular hypertrophy or coronary artery disease, and that impaired HRV indexes are associated with a poor prognosis in patients with cardiovascular disease. Further prospective studies would be of benefit to determine whether improvements in HRV secondary to the autonomic nervous effect of betaxolol treatment result in more favorable patient outcomes.

Another important finding in the current study is that the administration of -blocker improves the HRQL of poorly controlled hypertensive patients. The betaxolol adding group showed a significantly improved HRQL. The earlier studies on the treatment using -blockers in cardiovascular disease have indicated controversial results on the HRQL. Some reports were concerned with the adverse effect of -blockers on the HRQL in cardiovascular patients whereas the other showed opposite findings. Although -blockers are reported to show the side-effects of fatigue, depression and sexual dysfunction that lead to impair the HRQL, betaxolol itself or amlodipine-betaxolol combination treatment might specifically maintain the HRQL in the hypertensive patients. Such a favorable finding agrees with a previous report.

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The current study has several limitations. First, we used the frequency domain analysis of HRV, although several time domain HRV indexes are also useful to predict the prognosis of cardiovascular disease. In our study, frequency domain analysis was chosen for the analysis because of the reason that sympathetic and parasympathetic nervous activities can be separately assessed. However, because HRV analysis has some limitations on assessing autonomic nervous function, measurements of resting blood catecholamine concentrations and muscle sympathetic nervous activity (eg, in the peroneal nerve) might be necessary.
we measured HRV during 30 min in a supine resting condition.\textsuperscript{3,12} CANA during the daily life may be important to evaluate.\textsuperscript{29} However, the daily activity could have some of amlodipine and betaxolol for hypertensive patients.\textsuperscript{30} A large-scale, prospective, randomized study with a larger number of patients need to be performed. Finally, a than the amlodipine monotherapy. Future studies with a scores were different between the 2 groups, it might be difficult to conclude that the combination treatment is better than the amlodipine monotherapy. Future studies with a larger number of patients need to be performed. Finally, a large-scale, prospective, randomized study with an additional betaxolol alone group seems to be more appropriate for verifying a clinical benefit of the combination treatment of amlodipine and betaxolol for hypertensive patients.\textsuperscript{30} In conclusion, combined treatment of amlodipine and betaxolol is more useful than the amlodipine dose-up therapy in poorly controlled hypertensives, because combined treatment favorably affects CANA assessed by HRV and HRQL evaluated by the questionnaire sheets.

References