Original Article

Effect of Celiprolol on Cardiac Hypertrophy in Hypertension

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The present study was undertaken to clarify whether celiprolol and atenolol, β1-selective β blockers with and without intrinsic sympathomimetic activity (ISA), respectively, might improve ischemic damage in the isolated perfused hearts of spontaneously hypertensive rats (SHR), and whether long-term treatment with celiprolol may reduce left ventricular hypertrophy (LVH) in patients with essential hypertension. Atenolol (50 mg/kg/day) or celiprolol (300 mg/kg/day) for 7 weeks significantly reduced the blood pressure in SHR to the same degree, and both drugs decreased the heart rate, but the magnitude of the fall in heart rate was significantly higher with atenolol treatment than with celiprolol treatment. Both treatments significantly reduced the ratio of LV weight to body weight in SHR and significantly improved the coronary reserve in SHR to the same extent. Both treatments significantly improved the extent of recovery of the pressure-rate product and the extent of percent recovery of the coronary flow after reperfusion following 30 min of ischemia in SHR. Celiprolol treatment in patients with essential hypertension for 12 months significantly decreased interventricular septal thickness (IVST)+LV posterior wall thickness (PWT) and LV mass index (LVMI), but there was no significant correlation between IVST+PWT or LVMI and blood pressure before and after treatment. IVST+PWT and LVMI were significantly decreased after 3 months of treatment and these LVH indices were significantly smaller after 6 and 12 months of treatment than after 3 months of treatment. In conclusion, both celiprolol and atenolol treatment reduced LVH and improved the ischemic damage in SHR. In essential hypertensive patients with LVH, celiprolol treatment effectively reduced blood pressure and achieved LVH regression. (Hypertens Res 2000; 23: 467-474)

Key Words: celiprolol, atenolol, cardiac hypertrophy, hypertension, spontaneously hypertensive rat

Introduction

Left ventricular hypertrophy (LVH), as well as blood pressure elevation, are important prognostic indicators in patients with hypertension (1-4). Lowering blood pressure decreases the morbidity of hypertensive patients, and LVH regression decreases it even further (5, 6). Therefore, both blood pressure reduction and LVH regression contribute to reduced morbidity when hypertensive patients with LVH are treated with antihypertensive drugs. β blockers without intrinsic sympathomimetic activity (ISA) have been used in many clinical studies in patients with hypertension, myocardial infarction or congestive heart failure (7-10), but β blockers with ISA only in a few studies (11). Further, β blockers do not always re-
duce cardiac hypertrophy in spontaneously hypertensive rats (SHR) or hypertensive patients (12-15). Celiprolol, a \( \beta \)-selective \( \beta \) blocker with ISA, is known to cause modest bradycardia and has no clinical effect on the conduction system or pump function of the heart. It compares favorably with older \( \beta \) blockers in achieving LVH regression in patients with essential hypertension (16). However, it is not well known whether \( \beta \) blockers with ISA improve ischemic damage in LVH as well as \( \beta \) blockers without ISA.

Echocardiography allows accurate noninvasive assessment of the magnitude of LVH and its change over time. A review of echocardiographic studies showed that long-term therapy with selected antihypertensive agents is required to effect LVH regression.

Therefore, the present study was undertaken to clarify whether celiprolol improves ischemic damage as effectively as atenolol, a \( \beta \)-selective \( \beta \) blocker without ISA, as measured by the mechanical function of the isolated perfused hearts of SHR, and whether long-term treatment with celiprolol reduces LVH in patients with essential hypertension.

**Methods**

**Experimental Study**

Six male normotensive Wistar-Kyoto rats (WKY: WKY/NCrj, Charles River Japan Inc., Japan) and 28 male SHR (WKY/NCrj, Charles River Japan Inc.) aged 19 weeks were divided into control WKY, control SHR, atenolol (50 mg/kg/day) and celiprolol (100 or 300 mg/kg/day) groups. Atenolol or celiprolol was administered through a gastric tube to the SHR from 19 to 26 weeks of age. All rats were housed under the same conditions and were fed rat chow (CE-2, Nihon Clea, Japan). Systolic blood pressure and heart rate were measured in the conscious state at 19 and 26 weeks of age by tail plethysmography (PE-300, Narco, Japan) after 20 min prewarming at 37°C. The 26-week-old rats were sacrificed by decapitation. The hearts were rapidly excised and blotted on filter paper, and then the ventricles were weighed.

Nineteen-week-old WKY \((n=7)\) and SHR \((n=20)\) were divided into control WKY, control SHR, atenolol (50 mg/kg/day) and celiprolol (300 mg/kg/day) groups. Atenolol or celiprolol was administered to the SHR for 7 weeks. Rats (26 weeks of age) were anesthetized with pentobarbital sodium (50 mg/kg, i.p.). The hearts were rapidly excised and perfused using the Langendorff technique with a Krebs-Henseleit bicarbonate buffer (37°C) containing 11 mM glucose equilibrated with 95% O\(_2\)-5% CO\(_2\). The pulmonary artery and left atrium were cannulated, and both the caval veins were ligated. After 10 min of Langendorff perfusion, hearts were perfused using the working heart technique (17) with a left atrial filling pressure of 9 mmHg and a hydrostatic aortic pressure of 60 mmHg. After 15 min of working heart perfusion, global ischemia was induced for 30 min by lowering the aortic pressure from 60 to 0 mmHg. The reduction in aortic pressure resulted in a coronary flow of almost zero and cessation of the heart beat. When the heart was reperfused, the aortic pressure was again raised to 60 mmHg. The period of reperfusion was 30 min. The peak aortic pressure and heart rate were recorded with an RJJ-4121 recorder (Nihon Koden) and an MPU-0.5A pressure transducer (Nihon Koden). Coronary flow was determined by collecting the perfusate that dripped from the pulmonary arterial cannula. Twenty-four hours after the last administration, hearts from atenolol-treated SHR or celiprolol-treated SHR were used for perfusion.

**Clinical Study**

**Patients**

Twelve previously treated or untreated mild-to-moderate essential hypertensive patients with LVH were enrolled in the study (10 males and 2 females, mean age, 55.4±3.1 years). The diagnosis of essential hypertension was based on a systolic blood pressure of >160 mmHg or diastolic blood pressure of >95 mmHg during two random measurements on different days. In all patients, secondary causes of hypertension were eliminated using routine screening tests. The study procedures were explained to the patients in detail, and informed consent was obtained from each patient.

Patients were excluded from the study if they had cerebral or myocardial infarction, insulin-dependent diabetes mellitus, congestive heart failure, angina pectoris, bradycardia, second- or third-degree atrio-ventricular blocks, renal impairment, history of drug hypersensitivity, collagen disease or technically inadequate echocardiographic images. Pregnant women were also excluded. In treated patients, antihypertensive therapy was discontinued at least 4 weeks before the start of the study.

Celiprolol therapy was started at a dose of 100 or 200 mg once a day according to the physicians' judgment. If a satisfactory antihypertensive effect (normalization of blood pressure, i.e. <140/90 mmHg, or a decrease in blood pressure of more than 20/10 mmHg) was not obtained, the daily dose was increased to 400 mg/day, and if this also failed to produce the desired antihypertensive effect, a dihydropyridine calcium channel blocker or diuretic was added. Patients were seen at the hospital every 2 to 4 weeks throughout the 12-month treatment period. Casual blood pressure and heart rate in the sitting position were determined every 2 to 4 weeks during celiprolol administration. At the end of the observation (4 weeks) and treatment periods, laboratory tests, chest X rays and electrocardiography (ECG) were checked and an oral glucose tolerance test was performed using 75 g of
Symptoms and their severity were recorded by the physician during the observation and the treatment periods.

**Echocardiography**

Two-dimensional and M-mode echocardiographies were performed using a duplex Doppler system (SSD2200, ALOKA Co., Ltd., Japan) with a 3.5-MHz or 2.5-MHz mechanical sector transducer before and after 3, 6 and 12 months of celiprolol treatment. Echocardiographic images were recorded and measured by the same experienced investigator according to the guidelines of the American Society of Echocardiography (18). The interventricular septal thickness (IVST), LV posterior wall thickness (PWT), LV end-diastolic dimension (LVDd), LV end-systolic dimension (LVDs), stroke index (SI) and cardiac index (CI) were measured using echocardiography. The percentage FS was calculated using the following formula: %FS (%) = \((\text{LVDd} - \text{LVDs})/ \text{LVDd} \times 100\). LV mass (LVM) was determined using the method described by Devereux and Reichek (19): LVM (g) = 1.04 × \((\text{LVDd} + \text{IVST} + \text{PWT})^3 - \text{LVDd}^3\) − 13.6, and the LVM index (LVMI) was calculated.

LVH was diagnosed when the sum of IVST and PWT was 23 mm or greater, or when the sum of IVST and PWT was 21 mm or greater and the sum of SV1 and RV5 on ECG was 3.5 mV or greater.

**Statistical Analysis**

All values are expressed as the means±SE. Statistical significance was determined using the paired Student’s t-test, unpaired Student’s t-test or multiple comparison test (Bonferroni/Dunn). Linear regression analysis was used to determine the correlation between the parameters. P values less than 0.05 were considered to indicate statistical significance.

**Results**

**Effects of Atenolol and Celiprolol on Blood Pressure, Heart Rate and Ventricular Weight in SHR**

In 19-week-old rats, the body weight of SHR (n=28) was significantly lower than that of WKY (n=6) (332±3 vs. 373±3 g, p<0.01). The systolic blood pressure of SHR was significantly higher than that of WKY (194±2 vs. 125±3 mmHg, p<0.01) and the heart rate of SHR was significantly faster than that of WKY (391±7 vs. 333±9/min, p<0.01).

In 26-week-old rats, the body weights of all SHR groups were significantly lower than those of control WKY (Table 1). Treatment with either atenolol (50 mg/kg/day) or celiprolol (100 or 300 mg/kg/day) for 7 weeks significantly decreased systolic blood pressure and heart rate in SHR, and there was a significant difference in heart rate between atenolol-treated SHR and celiprolol-treated SHR (Table 1). Both the ratio of the LV weight to body weight and the ratio of the whole heart weight to body weight in control SHR were significantly higher than those in control WKY. Treatment with either atenolol (50 mg/kg/day) or celiprolol (100 or 300 mg/kg/day) significantly decreased these ratios, and there was no significant difference in these ratios between atenolol (50 mg/kg/day)-treated SHR and celiprolol (300 mg/kg/day)-treated SHR (Table 1).
Effects of Atenolol and Celiprolol on Mechanical Function in Perfused Rat Hearts

The peak aortic pressure×heart rate (pressure-rate) products before ischemia were not significantly different among control WKY, control SHR, atenolol (50 mg/kg/day)-treated SHR and celiprolol (300 mg/kg/day)-treated SHR (24.5±1.8, 24.6±0.6, 25.8±1.1, and 25.6±1.9×10^3 mmHg/min, respectively). The coronary flow before ischemia in control WKY was significantly larger than that in control SHR, atenolol-treated SHR or celiprolol-treated SHR (19.7±0.6 vs. 15.8±0.7, 15.7±0.9, and 16.5±0.9 ml/min, p<0.05). The ratio of the coronary flow to the ratio of heart weight to body weight, calculated by using the ratio of heart weight to body weight (Table 1), was significantly lower in control SHR than in control WKY (12.1±0.7 vs. 19.7±1.9 ml/min/g heart weight, p<0.05). Treatment with either atenolol or celiprolol significantly (p<0.01, respectively) improved this ratio in SHR (14.5±0.6 or 14.4±0.6 ml/min/g heart weight, respectively) and there was no significant difference in these ratios between atenolol-treated SHR and celiprolol-treated SHR.

After the onset of ischemia, the coronary flow rapidly fell to near 0 ml/min, and the pressure-rate product progressively decreased to 0 mmHg/min within 5 min in both control WKY and control SHR. Both the extent of pressure-rate product recovery and that of percent recovery of the coronary flow during reperfusion in control SHR were significantly lower than those in control WKY (Fig. 1 and 2). Treatment with either atenolol or celiprolol significantly improved these recoveries during reperfusion to the same extent (Fig. 1 and 2).

Fig. 1. Effects of long-term treatment with atenolol or celiprolol on peak aortic pressure×heart rate during reperfusion. The symbols ○, ●, □ and ◇ represent control WKY, control SHR, atenolol-treated SHR (50 mg/kg/day) and celiprolol-treated SHR (300 mg/kg/day), respectively. *p<0.05, compared with control WKY, #p<0.05, compared with control SHR.

Fig. 2. Effects of long-term treatment with atenolol or celiprolol on the percent recovery of coronary flow during reperfusion. The symbols ○, ●, □ and ◇ represent control WKY, control SHR, atenolol-treated SHR (50 mg/kg/day) and celiprolol-treated SHR (300 mg/kg/day), respectively. *p<0.05, compared with control WKY, #p<0.05, compared with control SHR.

Effect of Celiprolol on Blood Pressure, Heart Rate, CTR and SV1+RV5 and Echocardiographic Parameters in Essential Hypertensive Patients with LVH

Celiprolol was well tolerated and effective in all patients and a dihydropyridine calcium channel blocker was given to 3 patients. The final dose of celiprolol in all patients treated for 12 months was 225±41 mg/day. Body weight did not change before and after the study (62.3±3.5 or 62.3±3.9 kg, respectively).

Systolic blood pressure, diastolic blood pressure and heart rate significantly decreased after administration of celiprolol and were maintained to the same degree over 1 year of treatment (Table 2). No patient showed severe bradycardia. Systolic blood pressure and diastolic blood pressure before and after 12 months of treatment were 162±3/97±1 and 137±3/84±1 mmHg, respectively, in patients receiving celiprolol alone and 169±5/112±4 and 144±7/86±4 mmHg, respectively, in patients receiving celiprolol and a calcium channel blocker. The parameters for LVH such as CTR and SV1+RV5 significantly decreased during treatment with celiprolol (Table 2).

Celiprolol treatment for 12 months significantly decreased IVST, PWT, IVST+PWT and LVMI, but did not change LVDd, LVDs, %FS, SI or CI (Table 2). LVMI before and after 12 months of treatment was 154±7 and 134±7 g/m², respectively, in patients receiving celiprolol monotherapy and 176±19 and 144±11 g/m², respectively, in patients receiving combination therapy. There was no significant correlation between IVST+PWT or LVMI and systolic blood pressure, diastolic blood pressure or mean blood pressure before and after treatment or between changes in IVST+PWT or LVMI and changes in systolic blood pressure, diastolic blood pres-
Table 2. Blood Pressure, Heart Rate, CTR, SV$_1$+RV$_5$ and Echocardiographic Parameters before and after 12 Months of Treatment with Celiprolol

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before treatment</th>
<th>After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>164±3</td>
<td>139±3**</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>101±2</td>
<td>85±1**</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>72±2</td>
<td>67±1**</td>
</tr>
<tr>
<td>CTR (%)</td>
<td>49.9±1.3</td>
<td>48.7±1.3*</td>
</tr>
<tr>
<td>SV$_1$+RV$_5$ (mV)</td>
<td>4.77±0.27</td>
<td>4.48±0.25*</td>
</tr>
<tr>
<td>IVST (mm)</td>
<td>12.3±0.3</td>
<td>11.1±0.3**</td>
</tr>
<tr>
<td>PWT (mm)</td>
<td>12.0±0.3</td>
<td>10.6±0.3**</td>
</tr>
<tr>
<td>IVST+PWT (mm)</td>
<td>24.3±0.5</td>
<td>21.7±0.5**</td>
</tr>
<tr>
<td>LVDD (mm)</td>
<td>48.5±1.2</td>
<td>48.4±1.2</td>
</tr>
<tr>
<td>LVDS (mm)</td>
<td>30.9±1.7</td>
<td>30.9±1.0</td>
</tr>
<tr>
<td>%FS (%)</td>
<td>36.5±2.6</td>
<td>36.6±1.6</td>
</tr>
<tr>
<td>SI (ml/m$^2$)</td>
<td>49.4±3.4</td>
<td>50.7±3.5</td>
</tr>
<tr>
<td>Cl (l/min/m$^2$)</td>
<td>3.42±0.24</td>
<td>3.24±0.23</td>
</tr>
<tr>
<td>LVMI (g/m$^2$)</td>
<td>160±7</td>
<td>137±6**</td>
</tr>
</tbody>
</table>

* p<0.05, ** p<0.01, compared with values before treatment.

sure or mean blood pressure. To evaluate the progress of LVH regression, echocardiographic studies were done before and after 3, 6 and 12 months of celiprolol treatment in 9 patients (8 male and 1 female; mean age, 56.6±3.8 years). Mean blood pressure significantly decreased 3 months after administration of celiprolol, and its effect on lowering blood pressure continued at the same level until the end of the study (Fig. 3). On the other hand, both IVST+PWT and LVMI significantly decreased after 3 months of treatment, and further reductions in these LVH indices were observed after 6 and 12 months of treatment (Fig. 4).
The levels of blood lipids in 12 patients did not change significantly by treatment with celiprolol (Fig. 5). Treatment with celiprolol did not change the plasma glucose or insulin values in OGTT in 8 patients (Table 3). There were 4 or 5 patients with impaired GTT before and after treatment with celiprolol, respectively.

**Discussion**

Many clinical studies have shown that β blockers without ISA, such as atenolol, metoprolol or bisoprolol, have beneficial effects on primary or secondary prevention in patients with hypertension, myocardial infarction or congestive heart failure (7-10). On the other hand, the IPPPSH Collaborative Group (11) reported that oxprenolol, a β₁-selective β blocker with ISA, having partial agonist effects at the β₂-receptor, and direct vasodilating action (16). We previously reported that celiprolol enhanced renal dopamine production, which may contribute, at least in part, to its antihypertensive effect (20). Vyssoulis et al. (21) showed that celiprolol reverses LVH as effectively as propranolol, atenolol, metoprolol or pindolol in patients with essential hypertension. Cleophas et al. (22) reported that celiprolol exerts its beneficial effects, including complete cessation of attacks without a reduction in cardiac output, through its vasodilatory properties, in patients with unstable angina pectoris. However, Sanderson et al. (23) recently reported that in patients with heart failure, metoprolol, a β₁-selective β blocker without ISA, improved subjective symptoms and LV systolic function while celiprolol, which does not decrease heart rate, did not. It is unclear whether β blockers with ISA improve cardiac function and ischemic damage in LVH as effectively as β blockers without ISA.

We already reported that long-term treatment with atenolol in SHR reduced blood pressure, induced LVH regression and prevented ischemic myocardial damage in perfused rat hearts (24). Therefore, we attempted to clarify whether celiprolol, as well as atenolol, reversed LVH and improved ischemic damage in SHR. In the present study, both atenolol (50 mg/kg/day) and celiprolol (300 mg/kg/day) treatment for 7 weeks significantly reduced blood pressure to the same degree, and both drugs decreased heart rate, but the magnitude of fall in heart rate was significantly larger with atenolol treatment than with celiprolol treatment. Both atenolol and celiprolol treatment significantly reduced the ratio of LV weight to body weight and caused the LVH regression in SHR. The
coronary flow per unit of the whole heart weight in the control SHR was significantly lower than that in the control WKY, and both atenolol and celiprolol treatment significantly improved it to the same extent. After reperfusion following 30 min of ischemia, the extent of recovery of the pressure-rate product and the extent of percent recovery of the coronary flow in atenolol- or celiprolol-treated SHR were significantly greater than those in the control SHR. These results suggest that both celiprolol and atenolol treatment improve the coronary flow reserve and protect the myocardium from ischemic damage.

Schmieder et al. (25) have reported that the decrease in LVMI is more marked the greater the decline in blood pressure and the longer the duration of therapy. However, Vyssoulis et al. (21) showed that there was no correlation between reduction in blood pressure and LV regression in hypertensive patients treated with 5 different β blockers. Gottdiener et al. (26) reported that hypertensive patients with adequate blood pressure control on captopril (ACE inhibitor), hydrochlorothiazide (diuretics), and atenolol showed a reduction in LV mass after 1 year of treatment, whereas patients on diltiazem (a calcium channel blocker) or prazosin (an α blocker) did not. Vyssoulis et al. (27) showed that LVMI in older hypertensive patients decreased after 6 months of celiprolol treatment and that the magnitude of reduction in LVMI with celiprolol treatment was greater after 18 months of treatment than after 6 months of treatment.

Therefore, in this clinical study, we evaluated the correlation between LVH and blood pressure and the regression of LVH over time in patients with essential hypertension treated with celiprolol. Celiprolol treatment for 12 months significantly decreased IVST+PWT or LVMI, but there was no significant correlation between IVST+PWT or LVMI and blood pressure before and after treatment, or between changes in IVST+PWT or LVMI and changes in blood pressure. In 9 patients, echocardiographic studies were done before and after 3, 6 and 12 months of celiprolol treatment. Their mean blood pressure significantly decreased 3 months after administration of celiprolol, and the antihypertensive effect of celiprolol continued at the same level until the end of the study, whereas IVST+PWT and LVMI significantly decreased after 3 months of treatment, and these LVH indices were significantly smaller after 6 and 12 months of treatment than after 3 months of treatment. Blood pressure and LVMI before and after treatment were slightly higher in patients receiving a combination of celiprolol and a calcium channel blocker than in patients receiving celiprolol alone, but the magnitude of changes in these parameters was not different between the 2 groups. These results indicate that celiprolol has disparate effects on LV mass independent of the magnitude of blood pressure reduction in hypertensive patients with LVH, and that celiprolol treatment with adequate blood pressure control induces a reduction in LV mass after 1 year of treatment. However, the precise mechanism of LV mass regression by celiprolol treatment has yet to be clarified. Therefore, it is important to confirm the differences between different β blockers with large-scale double-blind studies.

Fogari et al. (28) reported that in hypertensive patients with hypercholesterolemia, celiprolol improved the lipids pattern, possibly because of its peculiar ancillary properties, while propranolol, atenolol and bisoprolol did not. Malmimemi et al. (29) reported that celiprolol improved the insulin sensitivity of hypertensive patients with dyslipidemia with long-term therapy. In the present study, celiprolol treatment did not change the levels of blood lipids or the plasma glucose and insulin values in OGTT. These results indicate that celiprolol does not adversely affect plasma lipids or glucose tolerance.

In conclusion, both celiprolol treatment and atenolol treatment reduced LVH and improved ischemic damage in SHR. In essential hypertensive patients with LVH, celiprolol treatment effectively reduced blood pressure and achieved LVH reduction.

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