Candesartan Cilexetil Improves Left Ventricular Function, Left Ventricular Hypertrophy, and Endothelial Function in Patients With Hypertensive Heart Disease

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Patients with hypertension often develop left ventricular (LV) hypertrophy and deterioration of the cardiac and endothelial functions. Recent clinical trials have shown the added benefits of angiotensin II receptor blockers in hypertensive patients. Twenty-nine patients with hypertensive heart disease (HHD) underwent echocardiography, radionuclide ventriculography and the measurement of endothelial function before and after administration of candesartan (8 mg/day). The subjects were divided into poorly controlled blood pressure (BP) (group P, n=6) and well controlled BP (group C, n=23). Endothelial function was evaluated from flow-dependent dilation, which was calculated as the percent change of the radial artery diameter during reactive hyperemia after upper arm occlusion, measured with a high-resolution ultrasound system. In group C, LV diastolic function and endothelial function were significantly (p<0.05) improved at 3 months after administration, LV systolic function and hypertension were significantly (p<0.05) improved after 6 months and these effects were maintained at 12 months. Even in group P, LV function, LV hypertrophy, endothelial function and brain natriuretic peptide were significantly (p<0.05) improved at 6 months after administration. In patients with HHD, candesartan improves LV systolic and diastolic function, LV hypertrophy and endothelial function within 6 months of administration, regardless of the control of BP. (Circ J 2002; 66: 993–999)

Key Words: Angiotensin II receptor blocker; Candesartan cilexetil; Endothelial function; Hypertensive heart disease; Left ventricular function; Left ventricular hypertrophy

Patients

Thirty-four patients with HHD were recruited and received candesartan (8 mg/day) therapy. However, 5 patients took the agent either irregularly or ceased taking it entirely and they were excluded. We divided the remaining 29 patients into 2 groups on the basis of BP control: poor control (group P, n=6) and good control (group C, n=23). The six patients in group P had systolic BP ≥170 mmHg or diastolic BP ≥100 mmHg at 6 months after drug administration and required other antihypertensive agents, so only the data up until 6 months were analyzed and compared with the data from group C.

The 23 patients in group C were followed for 12 months. All patients in groups P and C had a history of primary hypertension, with systolic BP ≥160 mmHg and diastolic BP ≥90 mmHg measured at the outpatient clinic at the beginning of this study, with and without previous antihypertensive therapy. They had LV hypertrophy (interventricular septal (IVS) thickness ≥12 mm) and diastolic dysfunction was evaluated by echocardiography. In our study, an A/E ratio (ratio of the peak velocity of atrial filling (A) to that of early diastolic filling (E) for transmitral
Simpson's method. The LV filling velocities were calculated by the modified ejection fraction (LVEF) was calculated by the modified method of mode echocardiography according to the method of Simpson. LV mass was calculated from the M-mode echocardiograms were derived from the 2-dimensional images. LV dimensions, wall thickness and cavity size were measured. LV mass was calculated from the M-mode echocardiography according to the method of Devereux and Reichek and the LV mass index (LVMI) was calculated as LV mass/body surface area. The LV ejection fraction (LVEF) was calculated by the modified Simpson's method. The LV filling velocities were recorded with pulse Doppler echocardiography by an apical approach, together with a phonocardiogram, on a strip chart at a paper speed of 100 cm/s. The sample volume was set at the level of the mitral leaflet tip in diastole. The peak velocity of atrial filling (A) and early diastolic filling (E) and their ratio (A/E) were obtained (Fig 1). The deceleration time (DcT) of the LV early filling wave was also measured. All measurements were carried out at end-expiration.

Radionuclide Ventriculography R wave-gated equilibrium blood pool studies were performed at rest to measure the LVEF fraction and peak filling rate. Images were acquired using a large field of view gamma camera and a medium-sensitivity parallel-hole collimator oriented in the 45° left anterior oblique projection with caudal tilt.

Measurement of Flow-Dependent Dilation Endothelial function was evaluated from the flow-dependent dilation (%FDD) which was calculated as the percent change in the diameter of the radial artery (5 cm proximal to the wrist) of the nondominant arm during reactive hyperemia after upper arm occlusion. The radial artery diameter was measured using a high-resolution ultrasound system and the recordings were obtained with a 7.5-MHz transducer positioned perpendicular to the vessel; ultrasonic gel was applied to improve transmission. Occlusion was performed by inflating a cuff to 40 mmHg above systolic BP for 5 min and immediately after release of the cuff, the arterial diameter was measured.

Evaluation of the Effects of Candesartan LV systolic function was assessed from the LVEF measured by echocardiography and radionuclide ventriculography. Diastolic function was evaluated from the A/E ratio and the DcT on the Doppler echocardiographic studies, and the peak filling rate was assessed from the results of the radionuclide ventriculography. LV hypertrophy was assessed as the LVMI and the sum of the thicknesses of the IVS and posterior wall (PW) at end-diastole on M-mode echocardiography. Endothelial function was evaluated from the %FDD. Cardiac status was evaluated by the serum concentration of brain natriuretic peptide (BNP).

Statistical Analysis Data are expressed as the mean±SD. Comparisons of mean changes in groups C and P were performed by a 2-way ANOVA and post hoc test. Analysis of sequential changes was performed by repeated-measures ANOVA. Probability values of less than 0.05 were considered significant.

Results All patients continued their treatment and no side effects related to candesartan were noted.

Characteristics of Group C (Tables 1, 2) Group C consisted of 14 men and 9 women aged 63±11 years (mean±SD). Their body mass index was 23.6±1.5 kg/m² and they had had hypertension for 2.8±1.8 years. Three patients were smokers (13%) and 3 had hyperlipidemia (13%). The systolic and diastolic BP values were 168±7 mmHg and 99±7 mmHg, respectively.

BP and Heart Rate The systolic and diastolic BP values were significantly (p<0.05) decreased after 3 months of candesartan therapy (Fig 2A). The systolic BP had fallen by approximately 20 mmHg and the diastolic BP by approximately 10 mmHg at 3 months after administration and those
levels were maintained for 1 year. However, there was no significant change in the heart rate: 70±8 beats/min before the study, 68±6 beats/min at 3 months, 67±7 beats/min at 6 months and 67±6 beats/min at 12 months after administration.

Echocardiographic Study The LV end-diastolic internal dimension (LVDd) was 47±5 mm and the end-systolic internal dimension (LVDs) was 30±4 mm before the study. The LVDd did not change significantly after administration (Fig 2B) and although the LVDs had not improved after 3 months, it was significantly (p<0.05) improved after 6 months: 30±3 mm at 3 months, 28±2 mm at 6 months and 28±1 mm at 12 months after administration (Fig 2B).

The sum of the thicknesses of the IVS and PW (IVS + PW) was 25.5±1.4 mm before the study, 24.8±1.3 mm at 3 months, 24.0±1.5 mm at 6 months and 23.1±1.5 mm at 12 months after administration. The IVS + PW had not improved after 3 months, but was significantly (p<0.05) improved after 6 months. The LVMI had the same result (Fig 2C): 169±25 g/m² before the study, 165±21 g/m² at 3 months, 147±15 g/m² at 6 months and 141±14 g/m² at 12 months after administration. The A/E ratio was significantly (p<0.05) improved at 3 months: 1.42±0.20 before the study, 1.26±0.20 at 3 months, 1.15±0.23 at 6 months and 1.04±0.14 at 12 months after administration. The DcT was also significantly (p<0.05) improved at 3 months: 283±30 ms before the study, 259±25 ms at 3 months, 246±19 ms at 6 months and 235±14 ms at 12 months after administration. The LVEF on echocardiography was not improved after 3 months, but was significantly (p<0.05) improved at 6 months: 65±6% before the study, 68±5% at 3 months, 70±5% at 6 months and 71±4% at 12 months after administration.

Results of Radionuclide Ventriculography The LVEF on radionuclide ventriculography (Fig 2D), as on echocardiography, was not improved after 3 months, but was significantly (p<0.05) improved at 6 months. The peak filling rate was significantly (p<0.05) improved at 3 months (Fig 3A).

Endothelial function (Fig 3B) The %FDD was significantly (p<0.05) improved at 3 months and, moreover, at 6 months, it had further significantly (p<0.05) improved compared with that at 3 months.

Serum Concentration of BNP (Fig 3C) The serum BNP was measured for 15 patients in group C and of those, 3 were in the normal range and the other 12 were above normal before the study. The BNP tended to decrease after candesartan administration.

Table 1 Individual Data for Group C Patients (n=23) With Hypertensive Heart Disease

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age/sex</th>
<th>Height/weight (cm²)/(kg)</th>
<th>BMI (kg/m²)</th>
<th>History of HT (years)</th>
<th>Therapy</th>
<th>Smoking</th>
<th>HL</th>
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<td>–</td>
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<td>152/52</td>
<td>22.5</td>
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<td>+, amlodipine 5 mg</td>
<td>–</td>
<td>+</td>
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<td>+, nifedipine 40 mg</td>
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<td>+</td>
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<tr>
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<td>152/60</td>
<td>26.0</td>
<td>0.5</td>
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Mean 63±11 159±7 23.6±1.5 2.8±1.8

M/F=14/9

BMI, body mass index; HT, hypertension; HL, hyperlipidemia.

Table 2 Echocardiographic Findings, Cardiac and Endothelial Function Before Administration of Candesartan in Group C Patients

<table>
<thead>
<tr>
<th>Echocardiography</th>
<th>LVDDd (mm)</th>
<th>LVDs (mm)</th>
<th>EF (%)</th>
<th>LVMI (g/m²)</th>
<th>IVS+PW (mm)</th>
<th>A/E ratio</th>
<th>DcT (ms)</th>
<th>EF (%)</th>
<th>PFR (%/s)</th>
<th>%FDD</th>
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</table>
| LVDDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; EF, ejection fraction; LVMI, left ventricular mass index; IVS, interventricular septal thickness; PW, posterior wall thickness; A/E ratio, ratio of the peak velocity of atrial filling (A) to that of early diastolic filling (E) for transmitral flow; DcT, deceleration time of early diastolic transmitral flow; PFR, peak filling rate; %FDD, flow-dependent dilation. Data are expressed as the mean±SD.
Characteristics of Group P (Table 3)

Group P consisted of 5 men and 1 woman aged 72±5 years, which was older than the group C patients (p=0.06). Their body mass index was 23.0±1.6 kg/m² and they had had hypertension for 3.8±1.5 years. One patient was a smoker and one had hyperlipidemia. The systolic and diastolic BP values before candesartan administration were 178±2 mmHg and 101±8 mmHg, respectively. The systolic BP was significantly higher than that in group C (p<0.01).

BP and Heart Rate

The systolic BP was significantly (p<0.05) decreased after 6 months (174±4 mmHg) of candesartan therapy (Fig 4A), falling by approximately 4 mmHg. The diastolic BP was unchanged (Fig 4B). There was no significant change in heart rate: 69±7 beats/min before the study, 68±6 beats/min at 3 months and 69±8 beats/min at 6 months after administration.

Echocardiographic Study

The LVDd was 49±2 mm and LVDS was 31±3 mm before the study and there were no significant difference between groups P and C. The LVDD did not changed significantly after administration (Fig 4C). The LVDSs had not improved after 3 months, but was significantly (p<0.05) improved after 6 months: 32±4 mm and 29±3 mm, respectively (Fig 4D).

The IVS + PW was 26.5±1.0 mm and the LVMI was 194±31 g/m² before the study. There was no significant difference between groups P and C, although the LVMI of group P tended to higher than that of group C (p=0.05). The IVS + PW was 25.9±0.7 mm at 3 months and 25.2±0.5 mm at 6 months after administration, and the LVMI was 185±27 g/m² and 175±20 g/m², respectively (Fig 5A).

The IVS + PW and the LVMI were not improved after 3 months, but were significantly (p<0.05) improved after 6 months.

The A/E ratio was 1.62±0.12 and the DcT was 292±14 ms before the study. There was no significant difference between groups P and C regarding the DcT before administration; however, the A/E ratio of group P was significantly (p<0.05) higher than that of group C. The A/E ratio was significantly (p<0.05) improved at 3 months: 1.54±0.14 at 3 months and 1.44±0.15 at 6 months after administration. The DcT was also significantly (p<0.05) improved at 3 months: 279±18 ms and 260±9 ms respectively.

The LVEF on echocardiography was 65±5% before the study and there was no significant difference between groups P and C. The LVEF was 64±4% and 69±4% respectively.

Results of Radionuclide Ventriculography

The LVEF was 69±4% at 6 months after administration. There was no significant difference between groups P and C regarding the LVEF at 6 months after administration.

Table 3 Individual Data for the 6 Patients (Group P) With Hypertensive Heart Disease Who Were Obliged to Discontinue the Study Because of Poor Blood Pressure Control

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age/sex (cm²/kg)</th>
<th>Height/weight (kg/m²)</th>
<th>BMI (years)</th>
<th>History of HT</th>
<th>Therapy</th>
<th>Smoking</th>
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<td>A</td>
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<td>+</td>
</tr>
<tr>
<td>B</td>
<td>68/M</td>
<td>163/65</td>
<td>24.5</td>
<td>2.0</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>C</td>
<td>69/M</td>
<td>167/60</td>
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<td>3.0</td>
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<tr>
<td>D</td>
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<td>E</td>
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<td>79/M</td>
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<td>–</td>
</tr>
<tr>
<td>Mean</td>
<td>72±5</td>
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<td>23.0±1.6</td>
<td>3.8±1.5</td>
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</table>

Data are expressed as the mean±SD.
Candesartan and Hypertensive Heart Disease

on radionuclide ventriculography was 64.0±5.4% before the study (Fig 5B) and there was no significant difference between groups P and C. As with the results on echocardiography, the LVEF was not improved after 3 months, but was significantly (p<0.05) improved at 6 months (64.7±3.8% and 69.1±3.9%, respectively). The peak filling rate was 229±14%/s before the study (Fig 5C) and there was no significant difference between groups P and C. It was significantly (p<0.05) improved at 3 months (246±20%/s) and at 6 months (271±14%/s) after administration.

Endothelial Function (Fig 5D)
The %FDD of group P was 3.6±1.1% before the study and was significantly lower than that of group C (p<0.05). It had not improved after 3 months, but was significantly (p<0.05) improved at 6 months (4.3±1.7% and 6.8±1.6%, respectively).

Serum concentration of BNP (Fig 5E) The serum BNP of group C was 41.0±8.2 pg/ml before the study and did not improve after 3 months; however, it was significantly (p<0.05) improved at 6 months (36.8±10.6 pg/ml and 31.0±9.6 pg/ml, respectively).

Discussion

Antihypertensive Effect of Candesartan

In the present study, systolic BP decreased by approximately 20 mmHg and diastolic BP by 10 mmHg on average at 12 months after administration of candesartan. However, other clinical studies on patients with HHD have shown equivalent or better BP responses so blocking the angiotensin II receptor with a selective angiotensin II receptor 1 antagonist has a therapeutic benefit in patients with hypertensive LV hypertrophy. There is clinical evidence of significant efficacy of treatment with ARBs in reversing the LV hypertrophy of hypertensive patients. Candesartan has been shown to induce regression of LV hypertrophy within 8–12 weeks of starting treatment, but in the present study, that was not significant until after 6 months of treatment.

The increase in LV mass in patients with hypertension is not only because of transverse and longitudinal enlargement of the cardiomyocytes, but also to alterations of the vasculature and intercellular matrices. Candesartan caused a decrease of LV weight, cardiomyocyte size, and LV interstitial collagen volume fraction in the hearts of stroke-prone spontaneously hypertensive rats, and prevented or caused the regression of myocardial fibrosis in adult rats. These results suggest that candesartan may cause regression of LV hypertrophy and improve cardiac function.

Improvement of Cardiac Function and LV Hypertrophy

In patients with HHD, the beneficial effect of losartan on diastolic function has already been reported but not the the effect of candesartan. Also, improvement of systolic function has never been documented after administration of ARBs. Our study showed candesartan improved both diastolic and systolic LV function, LV diastolic function first, then the systolic function, even though the present subjects had relatively good LV contraction before treatment. This indicates that candesartan has a beneficial effect on cardiac function in patients with HHD.
system\textsuperscript{28} Ghiadoni et al reported that treatment with candesartan increased tonic nitric oxide release and reduced the vasoconstricting effect of endogenous endothelin-1 in the forearm of patients with essential hypertension;\textsuperscript{2} indicating that candesartan improves endothelial function, although the effect was not seen after 2 months of treatment with candesartan, but revealed itself after 12 months.\textsuperscript{20} We did not directly evaluate nitric oxide and endothelin-1, but \%FDD is mediated by nitric oxide and our results indicate that endothelial function was improved after 3 months of drug administration. Moreover, endothelial function showed significantly more improvement at 6 months compared with 3 months, and the improvement lasted until 12 months.

**Candesartan Improves Cardiac Function, LV Hypertrophy and Endothelial Function**

This study demonstrated that patients with HHD who were given candesartan showed improvement in LV systolic and diastolic function, LV hypertrophy, serum concentration of BNP and endothelial function, even if BP control was poor. The results indicate that candesartan itself can improve these parameters.

**Possibility of Reduced Mortality and Morbidity**

The possibility of reduced mortality and morbidity from the regression of LV hypertrophy in patients with hypertension is an important consideration, because LV hypertrophy is associated with increased mortality,\textsuperscript{6,10,38} as well as an increased risk of nonfatal cardiovascular complications.\textsuperscript{39} As outlined by Devereux et al, there is a consistently higher risk of morbid events in subjects with LV hypertrophy when compared with subjects who do not have hypertrophy.\textsuperscript{40} Also, morbid events are more likely to occur in a high proportion of subjects with progressive LV hypertrophy when compared with those in whom hypertrophy shows regression. Several studies have provided information on the relationship between the regression of LV hypertrophy and subsequent morbidity and mortality.\textsuperscript{41–43} and the present findings indicate that candesartan may reduce the mortality and morbidity of the patients with hypertensive LV hypertrophy.

**References**


Candesartan and Hypertensive Heart Disease

999


