Candesartan, an Angiotensin II Receptor Blocker, Improves Left Ventricular Hypertrophy and Insulin Resistance

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A growing body of evidence indicates that the renin-angiotensin system and insulin resistance play crucial roles in left ventricular hypertrophy (LVH) in patients with essential hypertension (EH). Angiotensin II receptor blockers (ARB) have been reported to regress LVH and improve insulin resistance. We tested the hypothesis that candesartan, an ARB, could regress LVH, in association with improvement of insulin resistance in EH patients. The study participants were nondiabetic and never-treated EH patients (n = 10). Candesartan was administered at a mean final dose of 10.4 ± 2.1 mg/d for 24 weeks. Candesartan treatment resulted in a significant decrease of systolic and diastolic blood pressures, LV mass index (LVMI), homeostasis model assessment (HOMA) index, and plasma brain natriuretic peptide (BNP). A significant correlation was observed between the percent decrease in LVMI and that of both the HOMA index ($r = 0.83$, $P < .001$) and BNP ($r = 0.71$, $P < .005$). Stepwise regression analyses revealed that the percent decrease of HOMA index was an independent predictor for both percent decrease in LVMI and plasma BNP. Our findings suggest that pharmacological blockade of angiotensin II receptors by candesartan could improve LVH in never-treated EH patients, which may relate to the improvement of insulin resistance.

LEFT VENTRICULAR hypertrophy (LVH) is associated with high mortality in patients with essential hypertension (EH),[1] which is also associated with the development of coronary heart disease, heart failure, stroke, and other cardiovascular complications.[2] High blood pressure (BP) is the strongest factor for the development of LVH. Therefore, the regression of LVH is believed to be an important therapeutic goal in hypertensive patients to minimize the risk of cardiovascular mortality.[2] A meta-analysis trial comparing the effects of different drug classes on LVH suggested that angiotensin-converting enzyme (ACE) inhibitors are powerful drugs in this regard.[3,4] In contrast, a prospective trial comparing the effects of different drug classes revealed no relevant differences in terms of LVH reduction.[5] Thus, the question of whether antihypertensive drugs differ in their potency with regard to regression of LVH remains to be clarified.[6]

A chronic increase in pressure and/or volume overload and elevations in plasma ACE activity, plasma aldosterone levels,[7] and plasma angiotensin II concentrations also play a major role in the development of LVH.[8] Reduction of angiotensin II levels after ACE inhibition may be responsible for the beneficial effects of ACE inhibitors on regression of LVH beyond their BP-lowering activity. Apart from cleavage of angiotensin II by ACE, alternative pathways exist for the formation of angiotensin II. Despite ACE inhibition, a considerable amount of angiotensin II may be present, particularly in the heart.[9] Because most actions of angiotensin II are mediated via the AT-1 receptor subtype,[10] the recently introduced specific angiotensin II receptor blockers (ARB) might also be useful drugs in terms of LVH regression.[11]

Insulin resistance, and the accompanying compensatory hyperinsulinemia, has been reported to be critical in the development and progression of EH.[12] ARBs reportedly improve insulin resistance.[13,14] However, the effects of ARB on regression of LVH in relation to improvement of insulin resistance remain unclear at present. The present study was designed to test the hypothesis that candesartan, an ARB, could regress LVH, in association with the improvement of insulin resistance.

MATERIALS AND METHODS

The study participants comprised 10 consecutive Japanese patients (6 men, 4 women) aged 45 to 67 years (mean age, 59 ± 7 years, ±SD) with EH. The outpatient clinic designated as EH those patients who on at least three visits had a systolic BP of 140 mm Hg or higher, or a diastolic BP of 90 mm Hg or higher in the sitting position, based on the results of laboratory tests and guidelines of the World Health Organization.[15] No patients had been treated with antihypertensive medication prior to enrollment in the study. All patients underwent routine laboratory tests including assays for serum electrolytes, serum creatinine, blood urea nitrogen (BUN), fasting blood glucose, fasting immunoreactive insulin, chest x-rays, and electrocardiograms (ECGs). Patients with organic heart disease, renal failure, pulmonary heart disease, liver dysfunction, and/or a history of symptomatic cerebrovascular disease were excluded from the study.

All subjects gave written informed consent for participation in the study, and the study protocol was approved by the ethics committee of Oita Medical University.

Study Design

After the initial evaluation, each patient was treated orally with candesartan (Candesartan-cilexetil; Takeda Chemical Industries, Osaka, Japan) at a dose of 4 mg after breakfast. The starting dose was 4 mg once per day and this was increased until systolic and diastolic BP were reduced to 140 and 90 mm Hg, respectively. Subjects were excluded from the study if BP control was not achieved with candesartan monotherapy (maximum, 12 mg/d). The following examinations were determined before the initiation of therapy and after 24 weeks of candesartan treatment.

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Table 1. Clinical Characteristics at Baseline

Age (yr)	59 ± 7
Gender (men/women)	6/4
Body mass index (kg/m^2)	25.8 ± 1.6
Systolic BP (mm Hg)	165 ± 6
Diastolic BP (mm Hg)	97 ± 6
Heart rate (beats/min)	69 ± 7
BNP (pg/mL)	25.5 ± 6.3

NOTE. Data are mean ± SD.
Abbreviation: BNP, brain natriuretic peptide.

Echocardiography

Doppler recordings were obtained by using a phase-array echo-Doppler system. Echocardiograms were obtained in a standard manner using standard parasternal, short axis, and apical views. Left ventricular mass was calculated according to a previous study[16]: left ventricular mass = 1.04 ([LVIDd + IVSTd + PWTd]^3 − LVIDd^3) − 14 g, where LVIDd is the left ventricular internal dimension at end-diastole, IVSTd is intraventricular septal thickness at end-diastole, and PWTd is posterior wall thickness at end-diastole. Left ventricular mass was divided by body surface area to calculate the left ventricular mass index (LVMI). Pulsed Doppler recordings were made from the standard apical 4-chamber view. Mitral inflow velocity was recorded with the sample volume at the mitral annulus level; the average of ≥3 cardiac cycles was taken. The following measurements were made: peak velocity of early ventricular filling (E), peak velocity of late ventricular filling (A), their ratio (E/A), and deceleration time.

Measurement of Plasma BNP

After 30 minutes of supine rest, 10 mL of blood were drawn from an antecubital vein and immediately transferred into 2 chilled glass tubes, one containing ethylenediaminetetraacetic acid (EDTA, 1 mg/mL) and aprotinin (500 U/mL) for measuring plasma BNP. Blood was centrifuged immediately at 4°C, and the plasma was frozen and stored at −80°C until assayed. Plasma BNP levels were measured with specific immunoradiometric assays (Shionogi & Co, Osaka, Japan).

Insulin Resistance

Insulin resistance was evaluated by the homeostasis model assessment (HOMA) index = (fasting plasma insulin [μU/mL] × fasting plasma glucose [mmol/L])/22.5.[17]

Statistical Analysis

Data are presented as mean ± SD. Statistical analyses were performed using 1-way analysis of variance (ANOVA) to compare the mean values before and after candesartan treatment. When a significant difference was found, Scheffé's test was applied. To evaluate the effect of candesartan treatment on clinical variables, ANOVA was performed on repeated measurements. Simple regression analysis was carried out to compare the LVMI and BNP with other variables before and after treatment. Stepwise multiple regression analysis (F-to-enter value >4.00) was then carried out to determine the independent factors for percent decrease in both LVMI and BNP by candesartan treatment. A *P* value of less than .05 was considered significant.

RESULTS

Basic Clinical Characteristics of Patients

Table 1 lists the clinical characteristics of the studied patients at baseline before introduction of candesartan treatment.

Table 2. Effects of Candesartan Treatment on Body Mass Index and Hemodynamic Parameters

	Before	After	*P* Value
Body mass index (kg/m^2)	25.8 ± 1.6	25.4 ± 1.5	NS
Systolic BP (mm Hg)	165 ± 6	137 ± 2	<.0001
Diastolic BP (mm Hg)	97 ± 6	85 ± 3	<.0001
Heart rate (beats/min)	69 ± 7	66 ± 9	NS

NOTE. Data are mean ± SD.
Abbreviation: NS, not significant

Effects of 24-Week Candesartan Treatment

As shown in Table 2, candesartan treatment resulted in a decrease in both systolic and diastolic BP, but did not change the heart rate significantly. On echocardiographic findings, candesartan treatment did not significantly affect the LV ejection fraction and LV internal dimension (Table 3). However, it decreased LVMI and increased the E/A ratio. Among the metabolic factors, candesartan treatment did not significantly change total cholesterol, triglycerides, high-density lipoprotein (HDL)-cholesterol, or uric acid. However, it decreased fasting plasma glucose, fasting immunoreactive insulin, HOMA index, and plasma BNP (Table 4). Table 5 summarizes the simple correlation of percent decline of LVMI (D-LVMI) and that of BNP (D-BNP) with other clinical variables. There were significant correlations between D-LVMI and the percent changes in IVSTd (D-IVSTd), PWTd (D-PWTd), BNP (D-BNP), F-IRI (D-IRI), and HOMA-IR (D-HOMA index). There were significant correlations between percent decrease in BNP (D-BNP) and that of LVMI (D-LVM), IRI (D-IRI), and HOMA index (D-HOMA-IR). Table 6 summarizes the results of stepwise regression analysis, showing that HOMA-index was an independent predictor for both D-LVMI and D-BNP.

DISCUSSION

The main findings of the present study were that treatment with candesartan, an ARB, for 24 weeks improved LVH, and that percent decrease in HOMA index was an independent predictor for the percent decrease in LVMI in never-treated EH patients. To our knowledge, this is the first study demonstrating

Table 3. Echocardiographic Changes Induced by Candesartan Treatment

	Before	After	*P* Value
Ejection fraction (%)	71 ± 5	70 ± 5	NS
Left ventricular internal dimension at end-diastole (mm)	46.2 ± 2.5	45.9 ± 2.6	NS
Interventricular septal thickness at end-diastole (mm)	11.3 ± 0.5	10.4 ± 0.4	<.0005
Posterior wall thickness at end-diastole (mm)	11.7 ± 0.7	10.3 ± 0.5	<.0001
Left ventricular mass index (g/m^2)	142 ± 16	123 ± 14	<.01
E/A	0.89 ± 0.10	0.99 ± 0.09	<.05

NOTE. Data are mean ± SD.
Abbreviation: NS, not significant.

Table 4. Changes in Metabolic Parameters Induced by Candesartan Treatment

	Before	After	*P* Value
Total cholesterol (mg/dL)	217 ± 21	207 ± 23	NS
Triglyceride (mg/dL)	167 ± 35	155 ± 33	NS
HDL-cholesterol (mg/dL)	52 ± 4	55 ± 6	NS
Fasting plasma glucose (mg/dL)	109 ± 6	95 ± 7	<.0005
Fasting immunoreactive insulin (μU/mL)	7.7 ± 1.2	5.9 ± 0.8	<.01
HOMA index	2.1 ± 0.4	1.4 ± 0.3	<.0005
Uric acid (mg/dL)	6.8 ± 1.0	6.3 ± 0.4	NS
BNP (pg/mL)	25.5 ± 6.3	14.5 ± 5.1	<.01

NOTE. Data are mean ± SD.

Abbreviations: HDL, high-density lipoprotein; HOMA, homeostasis model assessment; BNP, brain natriuretic peptide; NS, not significant.

a close relationship between the antihypertrophic effects and insulin resistance improvement effects of an ARB in this population.

Effects of Angiotensin II Receptor Blockade

Our results demonstrated that candesartan treatment for 24 weeks caused a reduction of LVMI by 13.4%, which is consistent with results of previous studies using other ARB.[11,18] The antagonizing effects against cardiac hypertrophy by ARB have been demonstrated experimentally.[19-21] In spontaneously hypertensive rats (SHR), angiotensin II was most important factor to cause LVH.[19,20] In stroke-prone SHR, angiotensin II receptor blockade caused a decrease in cardiomyocyte size and LV interstitial collagen volume fraction in the heart, and prevented the regression of myocardial fibrosis.[19] This observation was confirmed by a recent study using SHR demonstrating that candesartan efficiently reduced BP with regression of cardiac remodeling.[20] More recently, it has been reported that, in the transgenic (mRen2)27 rat (TGRen2) overexpressing the Ren2 transgene in several tissues, with increased circulating angiotensin II concentration, treatment with an AT-1 blocker, but not an endothelin-1 blocker, regressed angiotensin II–induced cardiac fibrosis that was associated with both hypertension and LVH.[21] These mechanisms may explain the clinical efficacy of ARB in regression of LVH in hypertensive patients.[11,18,22]

Reduction of fasting plasma insulin concentration by candesartan treatment observed in the present study may be also involved in the regression of LVH, because insulin acts as a potent growth factor.[23,24] Insulin stimulates phosphoinositide 3- kinase (PI3-kinase) and its downstream serine-threonine kinase effector, Akt.[23] Activation of Akt subsequently provides a potent stimulus for cardiomyocyte growth.[23] In fact, inhibition of PI3-kinase was shown to attenuate the acceleration of protein synthesis and increase in cellular mass of protein or RNA in response to PI3-kinase stimulation in cultured adult ventricular myocytes.[24] Thus, candesartan-induced reduction plasma insulin levels might be, at least in a part, involved in the regression of LVH.

It is also important to know whether treatment with thiazolidinediones, insulin sensitizers, could induce regression of LVH. Several studies have reported that thiazolidinediones, eg, troglitazone and pioglitazone, reduced arterial BP in SHR.[25,26] However, their effects on LVH regression in this model remain to be elucidated. Clinically, a multicenter American study showed that 48-week troglitazone treatment did not significantly change the LVMI of normotensive patients with non–insulin-dependent diabetes mellitus (NIDDM).[27] On the other hand, in a small-scale Japanese study, 6-month troglitazone

Table 5. Correlations Between Changes in Left Ventricular Mass Index and Changes in Brain Natriuretic Peptide With Clinical Variables

	LVMI		BNP	
Parameters	*r*	*P* Value	*r*	*P* Value
Age	0.54	.11	0.09	.81
Body mass index	0.41	.24	0.02	.95
Systolic BP	0.47	.19	0.35	.36
Diastolic BP	0.31	.39	0.12	.74
Heart rate	0.11	.78	0.13	.7
Ejection fraction	0.36	.31	0.14	.69
LV internal dimension at end-diastole	0.29	.42	0.11	.76
IVS thickness at end-diastole	0.8	.005	0.53	.12
Posterior wall thickness at end-diastole	0.64	.04	0.55	.1
LVMI	—	—	0.71	.02
E/A	−0.31	.39	−0.54	.11
BNP	0.71	.02	—	—
Total cholesterol	0.29	.41	0.17	.64
Triglyceride	0.23	.52	0.32	.36
HDL-cholesterol	0.3	.41	0.07	.93
Fasting plasma glucose	0.33	.35	0.27	.45
Fasting immunoreactive insulin	0.75	.01	0.71	.02
HOMA index	0.83	.0027	0.75	.01
Uric acid	0.19	.59	0.17	.63

NOTE. Data are mean ± SD. Each clinical variable means the changes compared with baseline.

Abbreviations: LVMI, left ventricular mass index; BNP, brain natriuretic peptide; IVS, interventricular septal; HDL, high-density lipoprotein; HOMA, homeostasis model assessment.

Table 6. Stepwise Regression Analyses Between Changes in Left Ventricular Mass Index and Changes in Brain Natriuretic Peptide and Other Variables

Independent Variables	Regression Coefficient	Standard Error	Standard Regression Coefficient	*F* Value
To LVMI intercept	8.148			
HOMA index	0.18	0.042	0.835	18.37
To BNP intercept	15.687			
HOMA index	0.861	0.266	0.735	10.406

NOTE. Each clinical variable means the changes compared with baseline.

Abbreviations: LVMI, left ventricular mass index; BNP, brain natriuretic peptide; HOMA, homeostasis model assessment.

treatment reduced LVMI of male normotensive NIDDM patients but not hypertensive NIDDM patients.[28] The relatively weak BP-lowering effects without inhibitory effects on renin-angiotensin system of thiazolidinediones might explain these observations. However, their effects on LVH regression remain to be adequately investigated in patients with EH. We speculate that thiazolidinediones might be effective in LVH regression in mild to moderate EH patients associated with hyperinsulinemia. Large-scale studies focusing on this point will be needed in the future.

Several mechanisms may explain the improvement of insulin sensitivity by ARB. One hypothesis is a direct effect of angiotensin II on PI3-kinase and insulin receptor substrate-1 (IRS-1), because stimulation of angiotensin II receptors has been shown to inhibit PI3-kinase activation and IRS-1 phosphorylation in aortic smooth muscle cells.[29] Thus, the blockade of angiotensin II receptors may recover and restore activation of the glucose transporter via PI3-kinase and accelerate glucose influx. Another possible mechanism involves the vasodilatory effect of ARB.[13] Increased blood flow to skeletal muscles has been shown to activate and translocate the glucose transporter from the intracellular membrane component to the plasma membrane fraction.[13] It has been shown that the dose-response curve between insulin action and increased leg blood flow is shifted to the right in insulin-resistant patients.[30] Such an effect could be mediated by candesartan treatment in the present study.

The heart acts as an endocrine organ,[31] producing atrial natriuretic peptide (ANP) and brain natriuretic peptide.[32,33] In humans, ANP is secreted mainly from the atria and BNP from the ventricles, and plasma ANP and BNP are reportedly elevated in patients with EH.[34] This increase, especially plasma BNP, is closely related to LVH in EH patients.[34] Experimentally, the decrease in LV mass by long-term treatment with ACE inhibitors or ARB reduced the BNP secretion rate from the ventricles in hypertensive rats with LVH.[35] Clinically, an ACE inhibitor has also been reported to decrease plasma BNP concentrations, and the decrease in plasma BNP concentration correlated with a decrease in LVMI.[36] We have previously described the close relationship between BNP and LVH in never-treated EH patients.[37] Taken together, these findings indicate that the decrease in plasma BNP in response to candesartan treatment observed in the present study probably reflects the regression of LVH.

Our study also demonstrated a close relationship between improvement in insulin resistance and regression of LVH. What are the likely mechanisms that could reasonably explain these changes? Insulin resistance tightly relates to hyperfunction of the cardiovascular sympathetic nervous system.[38] As we reported previously, persistent activation of the cardiovascular sympathetic nervous system causes LVH, because such a condition is associated with a diminished nocturnal BP fall leading to persistent pressure overload.[31] Inhibition of sympathetic hyperfunction by improvement of insulin resistance with candesartan treatment is likely to underlie the regression of LVH in EH patients in the present study.

Study Limitations

Our study has several limitations. First, the study included a relatively small number of patients and did not include age-matched control subjects. Second, we did not compare the effect of candesartan with other antihypertensive and/or antihypertrophic drugs. The superiority of ARB for the regression of LVH in association with improvement of LVH should be further assessed.

Conclusions

Our findings suggest that pharmacological blockade of angiotensin II receptors with candesartan could improve LVH in never-treated EH patients, which may relate to an improvement in insulin resistance.

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