Table 1. Baseline clinical characteristics of study patients

Number		40
Sex (M/F)		(23/17)
Age (years)		59.7 ± 9.4
Known diabetes duration (years)		12.3 ± 7.9
Body mass index (kg/m^2)		23.4 ± 2.7
HbA_{1c} *(%)*		7.24 ± 0.9
Treatment *(%)*		
(Diet/Oral hypoglycemic agent/Insulin)		14/40/46
Retinopathy *(%)*		
(nil/simple/proliferative)		44/17/39
Urinary albumin excretion rate (μg/min)		82.23 ± 187.7
Serum creatinine (mg/dl)		0.8 ± 0.4
Creatinine clearance (ml/min)		94.5 ± 27.6
Systolic blood pressure (mmHg)		137.4 ± 15.1
Diastolic blood pressure (mmHg)		77.9 ± 9.3
Previous antihypertensive treatment *(%)*		52.5
Duration of antihypertensive treatment (years)		5.0 ± 0.7
Number of treatments with:	ACE inhibitor	6
	beta-blocker	1
	calcium antagonist	16
	diuretics	2
	alpha-blocker	2

Data are mean ±SD.

Table 2. Values in 37 patients with type 2 diabetes before and after treatment with low dose valsartan

	Before	After	*p*-value
Body mass index (kg/m^2)	23.0 ± 2.7	23.1 ± 1.7	NS
HbA_{1c} *(%)*	7.2 ± 0.8	7.2 ± 1.0	NS
Systolic blood pressure (mmHg)	137.6 ± 15.3	136.4 ± 14.5	NS
Diastolic blood pressure (mmHg)	78.1 ± 9.2	76.7 ± 9.2	NS

Data are mean ±SD.

ed the effects of low-dose (40 mg/day) valsartan on LVH in patients with Type 2 diabetes. The low dose of valsartan used in our study had no clinical effects on blood pressure.

PATIENTS AND METHODS

Subjects and design

Patients with type 2 diabetes mellitus (according to the World Health Organization criteria) were recruited from outpatients followed at Niigata University Hospital. Inclusion criteria were: glycosilated hemoglobin and arterial blood pressure were stable for more than six months. Exclusion criteria were: type 2 diabetes for <1 year; history of myocardial infarction; history of angina as defined by the Rose questionnaire[14]; abnormality of segmental wall motion in the left ventricle on echocardiography; heart failure; uncontrolled hypertension (blood pressure >180/100 mmHg); significant aortic stenosis; known serious arrhythmia; left bundle branch block; previous coronary artery bypass surgery; atrial fibrillation; treatment with digoxin; severe chronic or acute illness; and renal disease other than diabetic nephropathy or urinary tract infection. Other antihypertensive medi-

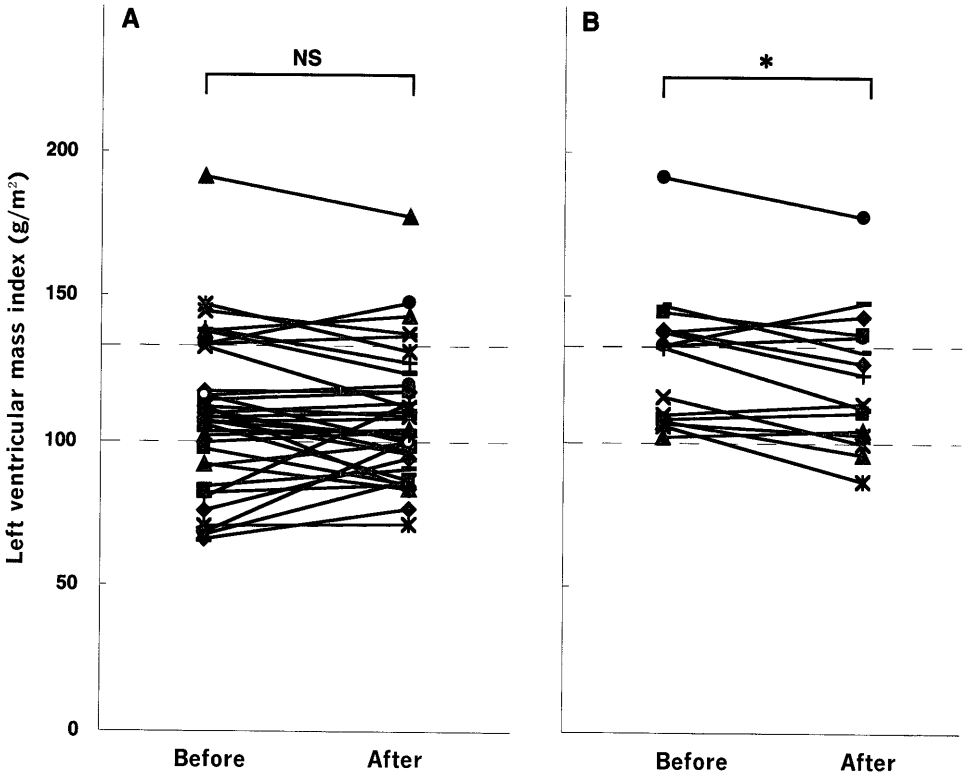

Fig. 1. LVMI before and after 6 months of treatment with valsartan. **A.** all patients (n=37), **B.** Patients with LVH (n=16; 8 males, 8 females). $*P<0.05$.

cations and/or antidiabetic drugs, including insulin, were permitted during the study. In addition, patients were not required to follow a protein- or salt-restricted diet. All patients provided informed consent.

All patients received 40 mg valsartan once daily, a dose that has been shown to have no clinical effect on blood pressure levels. Urinary albumin excretion (UAE) and creatinine clearance were determined from overnight urine samples collected by the patients at home. Patients were instructed to empty their bladders before going to bed, and then during the night to void into a plastic container. The times at which urine was collected were noted. Overnight urine samples were collected once at the baseline and at the end of the 6-month treatment period.

Echocardiography

Echocardiography was performed according to the recommendations of the American Society of Echocardiography[15] using a Hewlett Packard SONOS 2500 equipped with a 2.5 MHz transducer at the baseline and at the end of the 6-month treatment period. The M-mode was guided by a two-dimensional image in the parasternal long axis. The following variables were measured: left ventricular end-diastolic diameter (LVDD) and end-systolic diameter (LVDS), ventricular septal thickness (STD) and posterior wall thickness in diastole (PWTD). Left ventricular mass was calculated according to Penn's formula: $1.04[(STD+LVDD+PWTD)^3-(LVDD)^3]-13.6$[16]. The left ventricular mass index (LVMI) was calculated by dividing LVM by the body surface area (g/m^2), and the latter was calculated according to the Dubois formula $[0.0001\times71.84\times(\text{weight in Kg})^{0.425}\times(\text{height in cm})^{0.275}]$[17]. Left ventricular hypertrophy was considered present if LVMI was $>131\ g/m^2$ in males and $>100\ g/m^2$ in females[18]. Relative posterior wall thickness was calculated according to the formula: $[2\times PWTD/LVDD]$[19]. Elevated relative posterior wall thickness with increased LVMI was identified as concentric hypertrophy, and in the presence of normal LVMI was identified as concentric left ventricular remodeling. The normal range of relative posterior thickness with increased LVMI was identified as eccentric hypertrophy. A partition value of 0.44 for relative wall thickness was used for both males and females[20]. Systolic function was assessed by calculating the fractional shortening (FS)

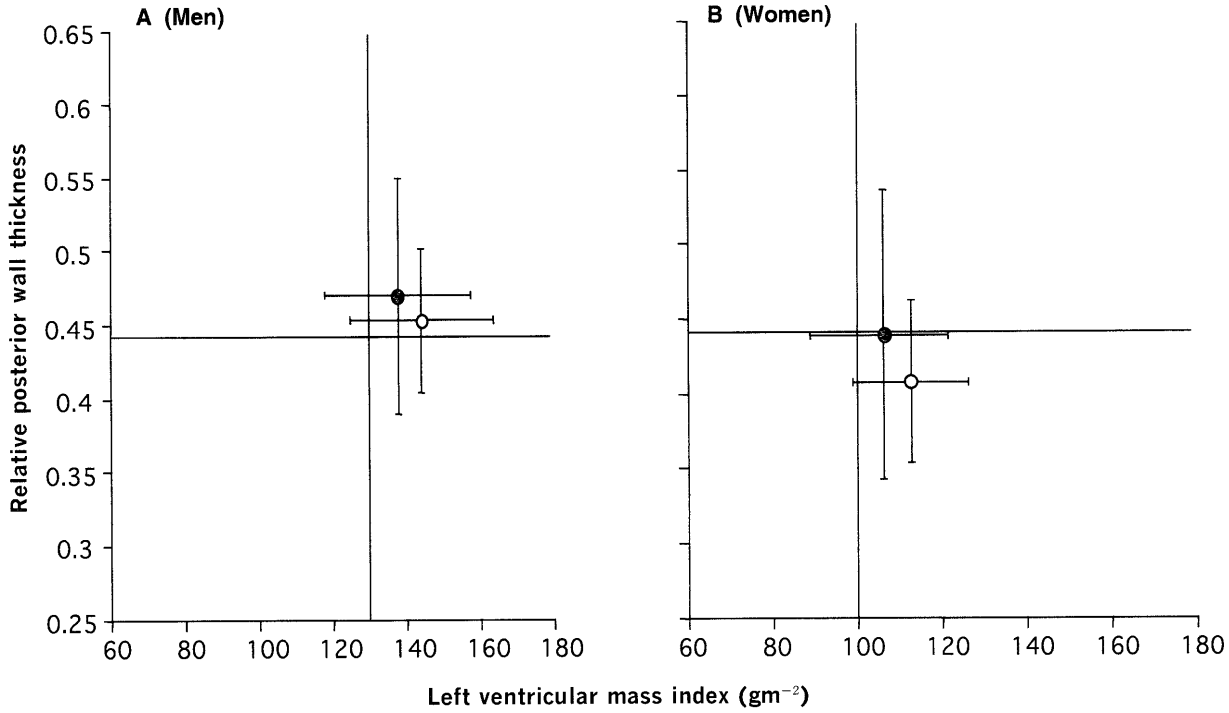

Fig. 2. Diagram divided into four fields by limits for left ventricular hypertrophy (100 gm^{-2} in females and 131 gm^{-2} in males), vertical line, and by 0.44 for relative wall thickness, horizontal line: **A.** males, **B.** females. The four fields correspond to different patterns of left ventricular geometry: normal left ventricle (*bottom left*), concentric remodeling (*top left*), concentric hypertrophy (*top right*), and eccentric hypertrophy (*bottom right*). ○ before, and ● after the treatment with valsartan in Type 2 diabetic patients with LVH.

Table 3. Echocardiographical parameters in 37 patients with Type 2 diabetes before and after treatment with low dose valsartan

	Before	After	*p*-value
LVDD (mm)	44.8 ± 4.3	44.4 ± 4.1	NS
LVDS (mm)	26.1 ± 4.1	26.1 ± 3.4	NS
STD (mm)	10.3 ± 1.7	10.2 ± 1.4	NS
PWTD (mm)	9.4 ± 1.2	9.7 ± 1.3	$p<0.05$
Fractional shortening of left ventricle *(%)*	41.8 ± 5.9	41.2 ± 5.0	NS
Relative posterior wall thickness	0.42 ± 0.05	0.43 ± 0.06	NS
LVMI (g/m^2)	109.0 ± 26.1	108.1 ± 22.0	NS

Data are means ±SD.

of the left ventricle, using the formula: [(LVDD−LVDS)/LVDD]×100. Systolic dysfunction was diagnosed if FS was ≤25%. Wall motion was analyzed in the 16 segments of the left ventricle defined by the American Society of Echocardiography[21]. All measurements were averaged over five cycles. Intraobserver error was <5%.

Clinical measurements

Arterial blood pressure was measured in the sitting position after 10 min of rest, using a standard sphygmomanometer with an appropriate-sized cuff. Measurements were taken three times at each office visit. Office blood pressure at the baseline and at the end of the 6-month treatment period was calculated

Table 4. Echocardiographical parameters in 16 Type 2 diabetic patients with LVH before and after treatment with low dose valsartan

	Before	After	*p*-value
LVDD (mm)	47.3 ± 4.0	46.3 ± 5.1	NS
LVDS (mm)	28.1 ± 4.2	27.6 ± 3.8	NS
STD (mm)	10.1 ± 1.2	10.3 ± 1.5	NS
PWTD (mm)	9.4 ± 1.2	9.7 ± 1.3	NS
Fractional shortening of left ventricle *(%)*	40.6 ± 6.6	40.3 ± 5.9	NS
Relative posterior wall thickness	0.43 ± 0.05	0.45 ± 0.08	NS
LVMI (g/m^2)	128.3 ± 22.9	121.9 ± 23.3	$p<0.05$

Data are means ±SD.

Table 5. Values in 16 diabetic patients with LVH before and after treatment with low dose valsartan

	Before	After	*p*-value
Body mass index (kg/m^2)	24.4 ± 3.2	24.5 ± 4.1	NS
HbA_{1c} *(%)*	7.2 ± 0.8	7.3 ± 1.3	NS
Systolic blood pressure (mmHg)	143.6 ± 10.6	142.3 ± 13.4	NS
Diastolic blood pressure (mmHg)	78.3 ± 9.6	77.3 ± 9.7	NS

Data are mean ±SD.

as the mean of all measurements. Presence of diabetic retinopathy was determined by fundus photography after pupillary dilatation and was graded as nil, simple, or proliferative.

Laboratory measurements

The urinary albumin concentration was measured using an enzyme immunoassay[22]. Glycosylated hemoglobin (HbA_{1c}) was measured by high performance liquid chromatography (Bio-Rad DIAMAT, Richmond, California). Our normal upper limit for HbA_{1c} is 5.8%. Serum and urinary creatinine levels were measured by standard laboratory techniques (clearance was corrected to a body surface area of 1.73 m^2).

Statistical analysis

Values are presented as mean ± standard deviation (SD). The significance of differences before and after treatment was evaluated by a paired t-test. A p value <0.05 was considered significant. All calculations were performed with commercially available programs (StatView-J 5.0, SAS Institute Inc., Cary, North Carolina).

RESULTS

Baseline clinical characteristics of all patients are shown in Table 1.

Twenty-one patients had undergone previous therapy for more than 6 months with 1 or more antihypertensive drugs. Of the 40 patients who entered the study, 37 (92.5%) completed it. Of these, 16 had LVH. Three patients (2 due to giddiness and 1 due to pruritus) discontinued the study. No side effects including hypotension, electrolyte imbalance, and liver dysfunction were attributed to valsartan.

Values before and after treatment with valsartan in the 37 patients who completed the study are shown in Table 2. There were no significant differences before and after treatment in BMI, HbA_{1c}, or systolic and diastolic blood pressure.

After 6 months of valsartan therapy, mean LVMI decreased slightly, from 109.0±26.1 to 108.1±22.0 g/m^2. In the subgroup of patients with LVH, a statistically significant decrease in LVMI (from 128.3±22.9 to 121.9±23.3 g/m^2, $P<0.05$) was observed (Fig. 1). Septal and posterior wall thicknesses in patients with LVH were not significantly reduced by valsartan (Table 4). Left ventricular internal diameters and

their derived parameters (relative posterior wall thickness and shortening traction of left ventricle) remained almost constant (Tables 3 and 4). In the subgroup, there were also no significant differences before and after treatment in BMI, HbA_{1c}, or systolic and diastolic blood pressure (Table 5).

In both males and females, treatment with valsartan for 6 months resulted in a movement of left ventricular geometry in the direction of concentric remodeling (Fig. 2).

DISCUSSION

Our study demonstrated that a low dose of the angiotensin-II-receptor antagonist valsartan significantly reduced LVMI in diabetic patients with LVH. The dose we used has been shown to have no clinical effects on blood pressure levels. To our knowledge, our study is the first to investigate the use of valsartan in patients with Type 2 diabetes.

Valsartan has reduced left ventricular weight in diabetic spontaneously hypertensive rats[23]. In patients with essential hypertension, Thürmann et al. observed a significant decrease of LVMI after treatment with valsartan[13], in accordance with our results. However, in their study, the effects observed could be attributed to the reduction in blood pressure brought about by valsartan, although the authors argued that the benefits observed exceeded those attributable to blood pressure changes alone. We found a significant effect of valsartan in a 6-month study, while the investigations by Thürmann et al. lasted for 8 months.

Thus, the present study clearly indicates that even the short-term use of a low dose of valsartan induces a regression of LVH. A low dose of this drug is preferable for patients with Type 2 diabetes because it is associated with few side effects and lower costs. In fact, in our study no patient had any side effect (based on laboratory data and symptoms) that could be attributed to valsartan.

Our study did not reveal the mechanism by which low-dose valsartan reduced LVMI without reducing blood pressure. ACE-inhibitor-induced regression of LVH might be mediated in part through the potentiation of kinins[24], a pathway that is not directly affected by valsartan. Although ACE inhibitors reduce the plasma concentration of angiotensin-II, valsartan increases it, which may result in the overstimulation of AT2 receptors. The function of AT2 receptors is unclear, but they are expressed mainly in the human myocardium, while the rat heart expresses mainly AT1 receptors[25]. These findings indicate that the stimulation of AT2 receptors may play an important role in the mechanism of selective AT1 receptor antagonists.

In patients with essential hypertension, left ventricular hypertrophy manifests initially as concentric remodeling, and then as concentric hypertrophy in the compensatory stage. In the decompensated stage, eccentric LVH is observed. During our 6-month study, treatment with valsartan resulted in a change of the left ventricular geometry from concentric LVH in males and eccentric LVH in females to concentric remodeling in both males and females. Long-term studies of valsartan treatment will be needed to elucidate whether valsartan can cause a further regression of LVH and a return to normal ventricular geometry. In our study with valsartan, no significant decreases in left ventricular internal diameters or wall thickness parameters were observed in patients with LVH. Thürmann et al., investigating an 8-month treatment regiven, found that only septal and posterior wall thickness were reduced. Therefore, it is possible that the effect of valsartan on wall thickness parameters can be observed only after 6 months of treatment, sometime between 6 and 8 months.

In conclusion, our findings demonstrated that in Type 2 diabetic patients with LVH, LVMI is reduced with low-dose valsartan treatment for 6 months. This reduction in LVMI occurred independently of any effect on blood pressure since no fall in systemic blood pressure was observed. Further long-term studies using end points such as cardiovascular events and mortality are needed to elucidate the clinical benefit of the LVH reduction achieved in Type 2 diabetic patients treated with valsartan.

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