Original Article

Long-Term and Strict Blood Pressure Lowering by Imidapril Reverses Left Ventricular Hypertrophy in Patients with Essential Hypertension: An Evaluation Using a Novel Indicator of Burden on the Left Ventricle

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Left ventricular hypertrophy is an independent risk factor for cardiovascular disease. We evaluated the effect of long-term and strict antihypertensive therapy with and without the angiotensin-converting enzyme inhibitor (ACEI) imidapril on left ventricular hypertrophy using a novel indicator of chronic burden on the left ventricle, the area under the blood pressure curve $\times$ the duration of high blood pressure (AUSBP and AUDBP), in patients with essential hypertension. The patients were divided into 2 groups: an ACEI group, in which imidapril was used in addition to antihypertensive drugs such as Ca channel blockers, β -blockers, diuretics or angiotensin II antagonist; and a non-ACEI group, in which Ca channel blockers and diuretics were used. Systolic and diastolic blood pressures (SBP and DBP) were both maintained at below 140 and 90 mmHg, respectively, for 2 years. There was no significant difference in the left ventricular mass (LVM) assessed by echocardiography at baseline and that at 2 years of follow-up in the non-ACEI group. However, the LVM in the ACEI group was significantly decreased at 2 years of follow-up as compared to that at the baseline visit. There was no difference in the mean AUSBP and AUDBP between the ACEI and non-ACEI groups. Changes in the LVM were not correlated with the AUSBP or AUDBP in both the ACEI and non-ACEI groups. These findings suggest that the decrease in the LVM in the ACEI group was mediated through mechanisms other than the blood pressure lowering-effect and that AUSBP and AUDBP may be novel indicators of the long-term burden on the left ventricle. (*Hypertens Res* 2006; 29: 89–94)

Key Words: left ventricular mass, imidapril, burden on the left ventricle, blood pressure

Introduction

Hypertension and left ventricular (LV) hypertrophy are major risk factors for cardiovascular disease (1, 2). Therefore, the reduction of LV hypertrophy as well as the reduction of systemic blood pressure are important objectives of antihypertensive therapy in patients with hypertension. High blood

pressure causes LV hypertrophy. However, since not only the level of high blood pressure but also the duration contributes to the development of LV hypertrophy, a new indicator which accounts for both the level and duration is needed to evaluate the long-term effect of high blood pressure on LV hypertrophy. Therefore, we propose a new indicator which incorporates both factors: the area under the blood pressure curve $\times$ the duration of high blood pressure (mmHg month) (AUSBP

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and AUIDBP). In the present study, we used this new indicator to evaluate the effect of long-term and strict antihypertensive therapy with and without use of the angiotensin-converting enzyme (ACE) inhibitor (ACEI) imidapril on LV hypertrophy.

Methods

Subjects

We prospectively studied 31 patients with mild to moderate hypertension whose initial systolic blood pressure (SBP) was more than 140 mmHg and/or diastolic blood pressure (DBP) was more than 90 mmHg. All patients had been outpatients of Gifu University Hospital, and had been diagnosed with essential hypertension and determined not have secondary hypertension at least 6 months before entry into this study, and had been treated with antihypertensive drugs for more than 3 months in an attempt to maintain SBP and DBP of less than 140/90 mmHg. The selection of antihypertensive drugs was made by each doctor based on the guidelines for the management of hypertension (JSH 2000). These patients were divided into 2 groups: an ACEI group ($n=15$) with a mean age of 64.6 ± 2.6 years and a non-ACEI ($n=16$) group with a mean age of 67.3 ± 2.4 years. Patients in the ACEI group were treated with imidapril alone ($n=6$), imidapril+diuretics ($n=1$), imidapril+ β -blockers ($n=1$), imidapril+Ca channel blockers ($n=6$) and imidapril+angiotensin II receptor blocker ($n=1$), and those in the non-ACEI group were treated with Ca channel blockers ($n=15$) or diuretics ($n=1$).

The study protocol was approved by the Ethical Committee of Gifu University School of Medicine. Informed consent was obtained from each patient before starting the study.

Follow-Up

All subjects were followed-up by doctors at the outpatient clinic of Gifu University Hospital and were treated with the aim of reducing SBP and DBP below 140/90 mmHg by standard lifestyle modification and pharmacological intervention. We aimed to maintain blood pressure strictly below 140/90 mmHg throughout the 2-year follow-up period. Blood pressure was measured using a sphygmomanometer once a month at the outpatient office and echocardiography was undertaken before and after 2 years of follow-up. None of the patients experienced any cardiovascular events during the 2-year follow-up period.

Blood Pressure Measurement

Office blood pressure was measured with a standard mercury sphygmomanometer after the subject had been seated for at least 10 min. Three consecutive measurements were obtained and the mean of the last two was regarded as the blood pressure.

Table 1. Main Characteristics of All Patients at Baseline

	ACEI group ($n=15$)	Non-ACEI group ($n=16$)
Age (years old)	64.6 ± 2.6	67.3 ± 2.4
Gender (male/female)	8/7	9/7
Body weight (kg)		
Baseline	56.9 ± 2.6	58.3 ± 2.8
2 years follow-up	57.3 ± 2.7	58.3 ± 2.8
BMI (kg/m^2)	22.9 ± 0.9	23.1 ± 0.7
Systolic blood pressure (mmHg)	140.7 ± 4.6	133.0 ± 3.4
Diastolic blood pressure (mmHg)	74.9 ± 2.6	74.8 ± 2.1
Heart rate (beats/min)	68.0 ± 2.3	68.2 ± 2.2
Diabetes mellitus (%)	4/15 (27)	5/16 (31)
History of hypertension (years)	5.6 ± 0.7	6.3 ± 0.6
BUN (mg/dl)	17.4 ± 0.8	16.9 ± 1.4
Creatinine (mg/dl)	0.70 ± 0.05	0.83 ± 0.07

BMI, body mass index; BUN, blood urea nitrogen.

An Indicator of Burden on the Left Ventricle

Time-course changes in SBP and DBP were measured at an interval of once per month for 2 years, and the least-squares lines for SBP and DBP were plotted against the duration of high blood pressure for each case. Then, we obtained the area under the least-squares lines for the SBP and DBP, respectively. We regarded the area under the SBP curve (AUSBP) or the area under the DBP curve (AUIDBP) over the 2-year follow-up period as an indicator of the burden on the left ventricle.

Echocardiography

An M-mode echocardiographic study of the left ventricle was performed under cross-sectional control with a commercially available machine (Prosound II SSD-6500 SV; Aloka, Tokyo, Japan). Echocardiographic examinations were conducted by two expert physicians and tracings were read by two other investigators. At the time of the echocardiographic examination, all investigators were unaware of the patients' clinical data, including office blood pressure, medications and cardiovascular complications. LV mass (LVM) was determined according to the formula introduced by Devereux *et al.* (3):

$$\text{LVM} = 1.04 [(\text{IVSTd} + \text{LVDd} + \text{PWTd})^3 - \text{LVDd}^3] - 13.6 \text{ (g)},$$

where IVSTd is interventricular septal thickness in diastole; LVDd is LV diameter in diastole; and PWTd is posterior wall thickness in diastole.

We used an absolute value of LVM but not LVM index (LVMI) corrected by body surface area to investigate the

Fig. 1. Two-year time-course changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) in the ACEI and non-ACEI groups.

Fig. 2. A typical case of time-course changes in the systolic and diastolic blood pressures (SBP/DBP) over the 2-year follow-up period and the least-squares lines for these blood pressure values in the non-ACEI group.

Fig. 3. The mean value of the area under the systolic blood pressure curve (AUSBP) and the area under diastolic blood pressure curve (AUDBP) in the non-ACEI and ACEI groups.

change of LV hypertrophy based on the report by Dahlof *et al.* (4). This is because body weight change substantially affects the body surface area and results in change of LVMI, and therefore we considered that the absolute LVM is a good indicator of LV hypertrophy without any influence of body weight change.

Statistical Analysis

All values are expressed as the mean $\pm$ SEM. Differences between groups were assessed by the Student's *t*-test and $p < 0.05$ was considered to indicate statistical significance.

Results

Table 1 shows the main characteristics of all patients at baseline in the ACEI and non-ACEI groups. There were no significant differences in SBP, DBP, heart rate, body mass index (BMI) or body weight between the ACEI and non-ACEI groups at the baseline visit. There were also no abnormal laboratory findings in either group.

Time-Course Changes in Blood Pressure

Time-course changes in SBP and DBP over the 2 years of follow-up in the ACEI and non-ACEI groups are shown in Fig. 1.

An Indicator of Burden on Left Ventricle

Figure 2 shows a typical case of time-course changes in SBP and DBP over the 2-year follow-up period and the least-squares lines for SBP and DBP in the non-ACEI group. Here,

Fig. 4. Left ventricular mass (LVM) at the baseline visit and at the end of the 2-year follow-up period in the non-ACEI and ACEI groups.

AUSBP was obtained from the area under the least-squares line for the SBP, and AUDBP was obtained from the area under the least-squares line for the DBP. In this case, the AUSBP was 3,137 mmHg months and AUDBP was 1,681 mmHg months.

Figure 3 shows the mean values of AUSBP and AUDBP in the ACEI and non-ACEI groups. There were no differences in the mean AUSBP and AUDBP between the two groups.

Changes in LVM

Figure 4 shows the LVM before (baseline visit) and after 2 years of follow-up. There were no significant differences in LVM between baseline and the end of the 2-year follow-up in the non-ACEI group. However, the LVM in the ACEI group was significantly decreased at the end of the 2-year follow-up as compared to that at the baseline visit.

Relationship between Changes in LVM and AUSBP or AUDBP

Figure 5 shows the relationship between changes in the LVM and AUSBP or between changes in the LVM and AUDBP in the ACEI and non-ACEI groups. In both the ACEI and non-ACEI groups, there was no relation between changes in the LVM and the AUSBP or AUDBP.

Discussion

The present study found that strict blood pressure lowering for 2 years in the ACEI group but not in the non-ACEI group reversed the degree of LV hypertrophy in patients with essential hypertension.

Fig. 5. The relationships between changes in the LVM and AUSBP and between changes in the LVM and AUBP.

LV hypertrophy in essential hypertension is pathological in nature and gives the best indication of cardiovascular events (5). A reduction in the LVM during treatment is a favorable prognostic marker that can be used to predict a lesser risk for subsequent cardiovascular morbid events (6). Therefore, it is clinically important to reduce the LVM in patients with essential hypertension.

To date, many meta-analyses have examined the ability of various antihypertensive drugs to reduce LV hypertrophy. Some earlier meta-analyses found that the ability of ACEIs to reduce LVM was more pronounced than that of diuretics, β -blockers or Ca channel blockers (4). Other meta-analyses have revealed that ACEIs and Ca channel blockers are more potent at reducing the LVM than β -blockers, with diuretics being in the intermediate range (7). Recent meta-analyses have shown that angiotensin II receptor antagonists, Ca channel blockers and ACEIs are more effective in reducing the LVM than are β -blockers (8). Furthermore, there is no signif-

icant difference in the reduction in LVM between enalapril and long-acting nifedipine (9) or between lisinopril and amlodipine (10).

A reduction in blood pressure causes a reduction in the LVM (11). However, when the blood pressure is already reduced below 140/90 mmHg, it is unclear whether maintenance of blood pressure lowering for a longer period of time is still effective in reducing the LVM, and whether ACEIs are more effective in reducing the LVM remains unclear. In the present study, patients with essential hypertension were treated with imidapril, an ACEI, or Ca channel blockers, and blood pressure levels were maintained below 140/90 mmHg for 2 years.

It has been reported that the changes in LVM over time showed a significant association with the changes in ambulatory blood pressure monitoring (ABPM) (12, 13) and a weaker association with those in casual blood pressure (12, 14). Therefore, the degree of 24-h blood pressure control over

time may have an important influence on the degree of LVM. However, even ABPM might not be adequate to express the degree of blood pressure control over years if it is performed only on a single follow-up day. Therefore, in the present study, we used new indicators of longer-term (*i.e.*, 2-year) burden on the LV, the AUSBP and AUDBP. This is the first report to use AUSBP and AUDBP as indicators of the burden on the LV. There was no significant difference in the AUSBP or AUDBP between the ACEI and non-ACEI groups. However, there was a reduction in the LVM assessed by echocardiography in the ACEI group but not in the non-ACEI group. The reduction in the LVM in the ACEI group may have been mediated through the inhibition of ACE activity by imidapril but not through the maintenance of lowered blood pressure for 2 years since the LVM was not affected in the non-ACEI group in spite of the blood pressure being maintained below 140/90 mmHg. Angiotensin II, which is produced from angiotensin I by activating ACE, is a potent growth factor of cardiomyocytes and causes LV hypertrophy (15). Therefore, inhibition of ACE activity by imidapril inhibits the generation of angiotensin II from angiotensin I at the tissue level and in the circulating blood. This may have led to a further reduction in the LVM even when the blood pressure was strictly maintained below 140/90 mmHg in the ACEI group. This may also be supported by the fact that there is an association between ACE gene polymorphisms and LV hypertrophy (16). Furthermore, it has been reported that the regression of LV hypertrophy by imidapril treatment for 6 months was correlated with a decrease in serum procollagen type III aminoterminal peptide levels in hypertensive patients, suggesting that the reduction in LVM may be at least partly due to a decrease in the collagen content of the hypertrophied heart (17).

Other factors that may affect the LVM include life-style modifications such as exercise, diet and weight control, which may affect the activity of the renin-angiotensin system or sympathetic nervous system. In the present study, we encouraged all our patients to make life-style modifications. However, whether or not they actually made such modifications is unclear, and it is difficult to evaluate life-style modifications quantitatively. Therefore, in the present study, we could not precisely evaluate the effect of life-style modification on LV hypertrophy.

In conclusion, long-term and strict antihypertensive combination therapy with the ACEI imidapril, but not that without it, reduces the LVM, and AUSBP and AUDBP may be novel indicators of long-term burden on the left ventricle.

References

1. Levy D, Garrison RJ, Savage DD, Kannel EB, Castelli WP: Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med* 1990; **322**: 1561–1566.
2. Kannel WB: Left ventricular hypertrophy as a risk factor: the Framingham experience. *J Hypertens* 1991; **9** (Suppl):

- S3–S9.
3. Devereux RB, Alonso DR, Lutas EM, *et al*: Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol* 1986; **7**: 450–458.
4. Dahlöf B, Pennart K, Hansson L: Reversal of left ventricular hypertrophy in hypertensive patients. A metaanalysis of 109 treatment studies. *Am J Hypertens* 1992; **5**: 95–110.
5. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH: Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. *Ann Int Med* 1988; **114**: 345–352.
6. Verdecchia P, Schillaci G, Borgioni C, *et al*: Prognostic significance of serial changes in left ventricular mass in essential hypertension. *Circulation* 1998; **97**: 48–54.
7. Schmieder RE, Schlaich MP, Klingbeil U, Martus P: Update on reversal of left ventricular hypertrophy in essential hypertension (a meta-analysis of all randomized double-blind studies until December 1996). *Nephrol Dial Transplant* 1998; **13**: 564–569.
8. Klingbeil AU, Schneider M, Martus P, Messerli FH, Schmieder RE: A meta-analysis of the effects of treatment on left ventricular mass in essential hypertension. *Am J Med* 2003; **115**: 41–46.
9. Devereux RB, Palmieri V, Sharpe N, *et al*: Effects on once-daily angiotensin-converting enzyme inhibition and calcium channel blockade-based antihypertensive treatment regimens on left ventricular hypertrophy and diastolic filling in hypertension. The prospective Randomized Enalapril Study Evaluating Regression of Ventricular Enlargement (PRESERVE) Trial. *Circulation* 2001; **104**: 1248–1254.
10. Terpstra WF, May JF, Smit AJ, *et al*: Long-term effects of amlodipine and lisinopril on left ventricular mass and diastolic function in elderly, previously untreated hypertensive patients: the ELVERA trial. *J Hypertens* 2001; **19**: 303–309.
11. Casale PN, Devereux RB, Milner M, *et al*: Value of echocardiographic left ventricular mass in predicting cardiovascular morbid events in hypertensive men. *Ann Intern Med* 1986; **105**: 173–178.
12. Grossman E, Alster Y, Shemesh J, Nussinovitch N, Rosenthal T: Left ventricular mass in hypertension: correlation with casual, exercise and ambulatory blood pressure. *J Hum Hypertens* 1994; **8**: 741–746.
13. Ono A, Fujita T: Predictors of controlled ambulatory blood pressure in treated hypertensive patients with uncontrolled office blood pressure. *Hypertens Res* 2004; **27**: 805–811.
14. Devereux RB, Savage DD, Sachs I, Laragh JH: Relation of hemodynamic load to left ventricular hypertrophy and performance in hypertension. *Am J Cardiol* 1983; **51**: 171–176.
15. Liu Y, Leri A, Li B, *et al*: Angiotensin II stimulation *in vitro* induces hypertrophy of normal and postinfarcted ventricular myocytes. *Circ Res* 1998; **82**: 1145–1159.
16. Saeed M, Saleheen D, Siddiqui S, Khan A, Butt ZA, Frossard PM: Association of angiotensin converting enzyme gene polymorphisms with left ventricular hypertrophy. *Hypertens Res* 2005; **28**: 345–349.
17. Sasaguri M, Noda K, Tashiro E, *et al*: The regression of left ventricular hypertrophy by imidapril and the reduction of serum procollagen type III aminoterminal peptide in hypertensive patients. *Hypertens Res* 2000; **23**: 317–322.