Original Article

Add-On Effect of Bedtime Dosing of the α_1-Adrenergic Receptor Antagonist Doxazosin on Morning Hypertension and Left Ventricular Hypertrophy in Patients Undergoing Long-Term Amlodipine Monotherapy

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High morning blood pressure is related to target organ damage and future cardiovascular events. Chronobiologic therapies focusing on the early morning period may be an important strategy for antihypertensive therapy. The aim of this study was to clarify the add-on effects of bedtime dosing of the α_1-adrenergic receptor antagonist doxazosin on morning blood pressure in patients with essential hypertension who were under long-acting calcium channel blocker amlodipine monotherapy. The add-on effects of doxazosin at the maximum dose of 6 mg at bedtime on home blood pressure and left ventricular geometry for 1 year were investigated in 49 subjects (37 men and 12 women, aged 57.5±9.1 years) with morning hypertension who had been treated with amlodipine alone for more than 1 year. Doxazosin induced a significant decrease in morning blood pressure (145.6±5.6/91.5±5.4 to 132.4±3.7/83.6±5.6 mmHg, $p \leq 0.001/<0.001$) without a change of evening blood pressure (128.9±5.1/79.8±5.1 to 127.7±6.0/78.8±6.2 mmHg, $p=0.056/0.051$). Left ventricular mass index (LVMI; 124.8±19.8 to 95.6±15.7 g/m^2, $p<0.001$), relative wall thickness (0.457±0.061 to 0.405±0.047, $p<0.001$) and homeostasis model assessment of the insulin resistance index (HOMA-IR; 2.62±1.43 to 1.33±0.75, $p<0.001$) were decreased after doxazosin therapy. A stepwise multivariate regression analysis revealed that the changes in morning systolic blood pressure (adjusted $r^2=34.9\%$, $p<0.001$) and HOMA-IR (adjusted $r^2=4.5\%$, $p=0.046$) were significant contributory factors to the change in LVMI after doxazosin therapy. These results suggest that bedtime dosing of doxazosin is useful for the control of morning blood pressure and regression of left ventricular hypertrophy. (*Hypertens Res* 2007; 30: 1097–1105)

***Key Words*: doxazosin, morning hypertension, left ventricular hypertrophy, insulin resistance, amlodipine**

Introduction

Epidemiologic studies have shown that adverse cardiovascular events tend to cluster in the early morning (*1*, *2*) as blood pressure tends to increase rapidly between awakening and the onset of physical activity (*3*). High morning blood pressure is closely related to organ damage (*4*) and future cardiovascular events (*5*–*7*). These chronobiologic findings in hypertension have suggested that the inhibition of blood pressure increase in the early morning by long-acting antihypertensive drugs or combination therapies centered on pharmacodynamic effects may be an important strategy in antihypertensive therapy (*8*, *9*). Calcium channel blockers (CCBs), particularly the dihy-

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dropyridine derivatives, are being used increasingly both as a first-line monotherapy and in combination therapies for long-term control of hypertension and regression of left ventricular (LV) hypertrophy (*10*, *11*). In Japan, physicians continue to prescribe CCBs (either as monotherapy or a part of combination therapy) for up to 75% of their patients with hypertension (*12*, *13*), despite the fact that recent guidelines for the treatment of hypertension recommend diuretics or β-blockers as the optimal first-line therapy (*14–17*). Among the dihydropyridine derivatives, amlodipine has a distinct pharmacokinetic profile with a long half life of 34 h; thus, single daily dosing enables steady-state plasma concentrations to be achieved (*18*). Clinical studies based on ambulatory blood pressure monitoring (ABPM) have confirmed that amlodipine is more effective in controlling morning blood pressure after awakening than other CCBs with short plasma half lives (*19*) or angiotensin converting enzyme inhibitors (*20*). However, we have previously observed that 19% of patients under long-term amlodipine monotherapy experience morning hypertension with an average morning systolic blood pressure (SBP) over 135 mmHg, despite the fact that their average evening SBPs are adequately controlled at below 135 mmHg (*21*). The aim of this study was to clarify the efficacy of combination therapy consisting of amlodipine plus a bedtime dose of the α_1-adrenergic receptor antagonist (α-blocker) doxazosin on morning blood pressure and LV hypertrophy.

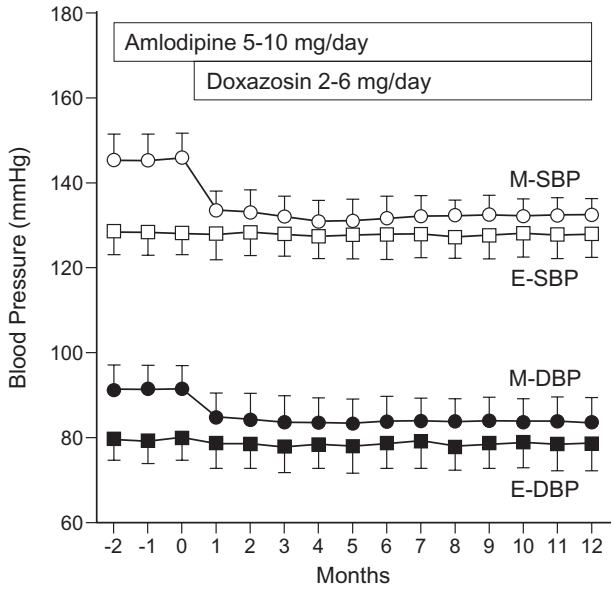

Fig. 1. *Changes in home blood pressure after bedtime dosing of doxazosin. M-SBP, morning systolic blood pressure; E-SBP: evening systolic blood pressure; M-DBP, morning diastolic blood pressure; E-DBP, evening diastolic blood pressure. Vertical bars denote 1 SD.*

Methods

Subjects

This was an open-label study on the add-on effects of doxazosin on morning blood pressure in patients with morning hypertension under long-term amlodipine monotherapy. Forty-nine subjects (37 men and 12 women; mean age, 57.5 years; range, 39–75 years) were recruited from among patients being treated with amlodipine monotherapy at the Hypertension Clinic of NTT Kanto Medical Center. All subjects met the following inclusion criteria: 1) Receipt of constant amlodipine monotherapy once daily in the morning for more than 1 year; 2) Patients who were defined as morning hypertension whose average evening SBP was well controlled at <135 mmHg but average morning SBP at ≥135 mmHg after more than 1 year of amlodipine monotherapy; 3) Absence of diabetes (fasting plasma glucose levels <7.0 mmol/L; 2 h after glucose load <11.1 mmol/L), of obesity (body mass index [BMI] <30.0 kg/m^2; 4 male cases with BMI 32.1–34.1 kg/m^2 were excluded from the study), and of renal failure (serum creatinine level <133 μmol/L); and 4) Absence of any history of cerebrovascular or cardiovascular diseases. Clinical information on the subjects was obtained from their medical records, and included the duration of hypertension and amlodipine monotherapy, family history of hypertension, history of alcohol intake, and smoking history. The estimated durations of hypertension and amlodipine monotherapy were 15.2±8.8 years (range: 1–38 years) and 4.0±1.9 years (range: 1–7 years), respectively. Thirty-nine subjects (79.6%) had a family history of hypertension. Thirty-five subjects (71.4%) consumed alcohol every day and 12 subjects (24.5%) were current smokers.

Study Design

Each subject was studied for a maximum of 15 months, consisting of 3 months of baseline treatment with amlodipine monotherapy (dose: 7.0±2.4 mg/day; range: 5–10 mg/day), a titration period of doxazosin add-on therapy of 1 to 3 months, and 9 to 11 months of maintenance therapy consisting of doxazosin combined with amlodipine. After the baseline clinical evaluation, including biochemical measurements and echocardiography (details below), patients started on 2 mg doxazosin once daily in the evening, taken just before going to bed. The dose of doxazosin was increased at a monthly interval, until 1) the average morning SBP was <135 mmHg, and/or 2) a maximum daily dose of 6 mg doxazosin had been reached. Subjects were withdrawn from the study if they showed any kind of adverse reaction during the titration phase. Subjects that completed the titration phase were transferred to a maintenance phase on the same dose of doxazosin for 9 to 11 months. At the end of the maintenance therapy, clinical evaluations were performed as at baseline.

The nature and potential risks of the study were explained to all subjects, and each gave his/her informed consent to par-

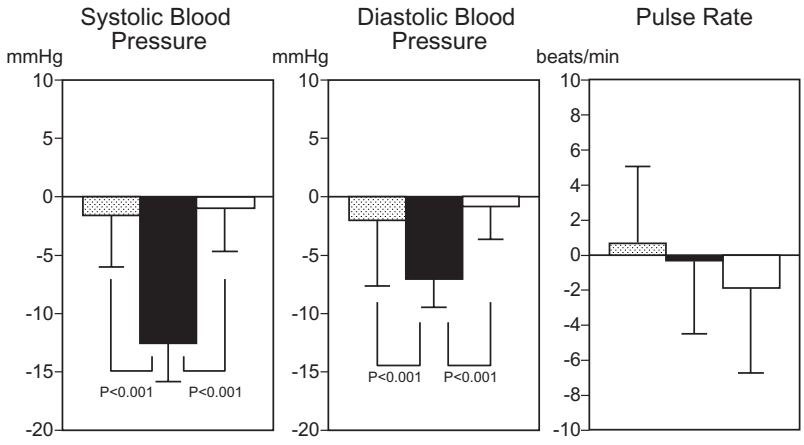

Fig. 2. *Changes in office (dotted bars), morning (solid bars) and evening (open bars) blood pressure and pulse rate after bedtime dosing of doxazosin. Vertical bars denote 1 SD.*

ticipate in the study. The study protocol was approved by the Institutional Review Board on Human Investigations of NTT Kanto Medical Center.

Blood Pressure Measurements

Office blood pressure and pulse rate were measured as the average of the last 2 of 3 readings obtained by a physician using an Omron office digital blood pressure monitor (HEM-907; Omron Healthcare, Kyoto, Japan) (*22*) during the monthly outpatient visits with the subject in the sitting position. Subjects were instructed by the physician on how to measure their blood pressure at home according to the Japanese Society of Hypertension guidelines for self-monitoring of blood pressure at home (*23*) using a cuff-oscillometric device (Omron HEM-737 IntelliSense; Omron Healthcare), as described previously (*21*). The morning and evening blood pressure were expressed as the average of 2 consecutive measurements in the morning and evening, respectively. The means of all the measurements for each month were calculated for each patient and used as the respective monthly blood pressures during the experimental period. The average blood pressure and pulse rate values during the 3 months before the start of doxazosin administration (months −2, −1, and 0 in Fig. 1) and the last 3 months of doxazosin administration (months 10, 11, and 12 in Fig. 1) were used for the analysis of the add-on effect of doxazosin.

Echocardiography

Echocardiography was performed according to the standard procedure, which has been described in detail previously (*21*). End-diastolic and end-systolic measurements of the inner dimension of the left ventricle (LV), interventricular septal thickness, and LV posterior wall thickness were calculated according to the American Society of Echocardiography recommendations (*24*), and the average of 3 measurements was considered for the analysis. Left ventricular mass (LVM) was measured by an anatomically validated method developed by Devereux *et al*. (*25*). The LVM index (LVMI) was calculated for each subject by dividing the LVM by the body surface area. The relative wall thickness (RWT) was calculated as 2 × (LV posterior wall thickness)/(LV internal dimension) (*26*). LV end-diastolic and end-systolic volumes were obtained by using the Techholz formula (*27*), which has been proven accurate in the absence of regional abnormalities of contraction (*28*). Stroke volume was calculated as the difference between LV end-diastolic and LV end-systolic volume. The ejection fraction was calculated as the ratio of the stroke volume to the LV end-diastolic volume. Individual values of the LV end-diastolic and LV end-systolic volumes and stroke volume were indexed by body surface area (LV end-diastolic volume index, LV end-systolic volume index, and stroke index, respectively). Only patients whose echocardiograms were of adequate quality for performing M-mode measurements of the LVM were included in this study. Individuals with more than trivial mitral or aortic regurgitation as detected by Doppler echocardiography were excluded from the study in order to eliminate the effect of valvular regurgitation on the LVM (*29*). Six cases with morning hypertension receiving amlodipine monotherapy were excluded from the study because of mild mitral regurgitation and/or aortic regurgitation detected by Doppler echocardiography.

Biochemical Measurements

Blood samples for biochemical measurements were drawn from the patients after they had fasted for over 12 h. The serum total protein, creatinine, total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides were measured by enzymatic techniques in an automatic analyzer (Model H 736; Hitachi, Tokyo, Japan). Plasma glucose was

Table 1. Changes in Blood Pressure, Metabolic Parameters and Left Ventricular Geometry after Bedtime Dosing of Doxazosin

Variables	Before doxazosin	After doxazosin	*p*
General characteristics			
Height (cm)	162.5±7.6	162.4±7.6	0.472
Weight (kg)	63.8±8.7	63.8±8.6	0.885
Alcohol consumption (g/day)	26.4±22.3	28.1±21.9	0.372
Smoking (cigarettes/day)	6.0±10.7	6.3±11.0	0.183
Body mass index (kg/m^2)	24.1±2.8	24.1±2.5	0.939
Body surface area (m^2)	1.68±0.13	1.68±0.13	0.964
Blood pressure and pulse rate			
Office			
Systolic blood pressure (mmHg)	137.9±5.4	136.3±6.3	0.029
Diastolic blood pressure (mmHg)	87.7±5.5	85.2±5.6	0.002
Pulse rate (beats/min)	66.3±3.5	67.9±5.7	0.043
Home			
Morning			
Systolic blood pressure (mmHg)	145.6±5.6	132.4±3.7	<0.001
Diastolic blood pressure (mmHg)	91.5±5.4	83.8±5.6	<0.001
Pulse rate (beats/min)	70.4±8.0	69.9±7.9	0.293
Evening			
Systolic blood pressure (mmHg)	128.9±5.1	127.7±6.0	0.056
Diastolic blood pressure (mmHg)	79.8±5.1	78.8±6.2	0.051
Pulse rate (beats/min)	76.9±8.2	74.5±7.5	0.002
Metabolic parameters			
Hematocrit	0.424±0.027	0.419±0.031	0.169
Total protein (g/L)	70.4±4.5	72.2±16.8	0.517
Creatinine (μmol/L)	72.2±16.8	69.1±16.7	0.029
Glucose (mmol/L)	5.60±0.48	5.59±0.57	0.897
Glycated hemoglobin A1c (%)	5.14±0.35	5.12±0.37	0.729
Insulin (μU/mL)	10.42±5.40	5.28±2.80	<0.001
HOMA-IR	2.62±1.43	1.33±0.75	<0.001
Total choresterol (mmol/L)	5.47±1.07	5.15±0.86	0.002
HDL cholesterol (mmol/L)	1.58±0.47	1.60±0.38	0.493
Triglycerides (mmol/L)	1.50±0.81	1.21±0.58	0.002
Echocardiography			
Left ventricular end-diastolic dimension (cm)	4.93±0.38	4.76±0.39	<0.001
Left ventricular end-systolic dimension (cm)	3.10±0.50	2.62±0.41	<0.001
Interventricular septal thickness (cm)	1.12±0.12	0.96±0.11	<0.001
Left ventricular posterior wall thickness (cm)	1.12±0.12	0.96±0.09	<0.001
Relative wall thickness	0.457±0.061	0.405±0.047	<0.001
Left ventricular diastolic volume index (mL/m^2)	68.8±11.0	63.5±10.8	<0.001
Left ventricular systolic volume index (mL/m^2)	23.4±8.2	15.5±5.6	<0.001
Stroke index (mL/m^2)	45.3±9.7	48.0±8.2	0.028
Ejection fraction (%)	66.0±10.8	75.8±6.7	<0.001
Left ventricular mass (g)	210.2±38.7	161.0±30.0	<0.001
Left ventricular mass index (g/m^2)	124.8±19.8	95.6±15.7	<0.001

Values are mean±SD. HOMA-IR, homeostasis model assessment of insulin resistance index; HDL, high-density lipoprotein.

measured by the glucokinase method in an automatic analyzer. Glycated hemoglobin A1c (HbA1c) was measured by high-performance liquid chromatography. The serum level of insulin was measured by competitive enzyme immunoassay with a double antibody procedure using an EIA Test Insulin II kit [BMY] (Boehringer Mannheim, Mannheim, Germany). The homeostasis model assessment of the insulin resistance index (HOMA-IR) was calculated using the formula {glucose (mmol/L) × insulin (μU/mL)/22.5} and used as an index of insulin resistance (*30*).

Table 2. Pearson's Correlation Coefficients between Changes in Left Ventricular Mass, Relative Wall Thickness and Clinical Parameters

Variables	Change in left ventricular mass index		Change in relative wall thickness	
	r	*p*	*r*	*p*
Changes in body mass index (kg/m^2)	−0.184	0.227	−0.102	0.506
Changes in alcohol consumption (g/day)	0.132	0.388	0.131	0.391
Changes in smoking (cigarettes/day)	−0.030	0.844	0.053	0.730
Changes in blood pressures				
Office				
Systolic blood pressure (mmHg)	−0.170	0.265	0.000	0.416
Diastolic blood pressure (mmHg)	0.081	0.595	0.109	0.475
Home				
Morning				
Systolic blood pressure (mmHg)	0.617	<0.001	0.305	0.043
Diastolic blood pressure (mmHg)	0.585	<0.001	0.218	0.151
Evening				
Systolic blood pressure (mmHg)	0.006	0.968	0.049	0.748
Diastolic blood pressure (mmHg)	0.110	0.470	0.004	0.980
Changes in the metabolic parameters				
Hematocrit	−0.155	0.316	−0.113	0.464
Total protein (g/L)	−0.157	0.303	−0.060	0.698
Creatinine (μmol/L)	0.067	0.661	−0.008	0.959
Glucose (mmol/L)	0.171	0.262	−0.068	0.658
Glycated hemoglobin A1c (%)	0.014	0.928	−0.207	0.184
Insulin (μU/mL)	0.437	0.003	0.375	0.011
HOMA-IR	0.464	0.001	0.405	0.006
Total choresterol (mmol/L)	−0.202	0.183	−0.222	0.144
HDL cholesterol (mmol/L)	0.037	0.811	0.039	0.801
Triglycerides (mmol/L)	0.290	0.053	0.002	0.998

HOMA-IR, homeostasis model assessment of insulin resistance index; HDL, high-density lipoprotein.

Statistical Analysis

The software package SPSS 12.0J for Windows (SPSS Inc., Chicago, USA) was used for the statistical analysis. Data were expressed as the mean±SD. Differences in clinical, biochemical and echocardiographic measurements before and after doxazosin treatment were tested using a paired *t*-test. Changes in blood pressure and pulse rate in the office, morning and evening were examined using one-way analysis of variance (ANOVA). When ANOVA showed an overall significance, Fisher's protected least significance difference was used for inter-group comparison. Pearson's product moment formula was used to calculate coefficients of correlation between the changes in LVMI and RWT and other changes in the continuous variables after doxazosin therapy. Multiple linear stepwise regression analysis was used to determine which changes in parameters accounted for the changes in LVMI and RWT. Independent variables included in the model were those that reached statistical significance ($p<0.05$) in the univariate analysis.

Results

Of the 49 subjects enrolled in this study, 4 were withdrawn due to adverse events (1 case of urinary incontinence and 3 cases of vasodilatory edema). Forty-five subjects completed the study without any significant adverse reactions. The maintenance dose of doxazosin was 2.4±1.1 mg/day (range: 2–6 mg/day). Doxazosin induced a significant decrease in morning blood pressure without altering evening blood pressure during the follow-up period of 1 year (Fig. 1). Decreases in morning SBP and diastolic blood pressure (DBP) were significantly greater than the decreases in evening and office SBP and DBP. There was no change in pulse rate (Fig. 2). LVMI and RWT decreased significantly by 23.4% and 11.3%, respectively, after the addition of the bedtime dose of doxazosin. The ejection fraction increased by 14.8%, indicating improvement in the systolic function of the LV. The serum insulin decreased without a corresponding change of the plasma glucose or HbA1c, with a decrease of the HOMA-IR by 49.2%, indicating an improvement of insulin resistance. Concerning the effects of the add-on therapy on the serum

Table 3. Multivariate Predictors of Changes of Left Ventricular Mass Index and Relative Wall Thickness

Indipendent variables	Regression coefficient	Partially adjusted r^2	Sum of adjusted r^2	p
Change of leftventricular mass index				
Change of morning SBP (mmHg)	1.26	34.9%	34.9%	0.0004
Change of HOMA-IR	2.95	4.5%	39.4%	0.0468
Change of relative wall thickness				
Change of HOMA-IR	0.01	14.5%	14.5%	0.0057

SBP, systolic blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance index.

lipid profile, the serum levels of total cholesterol and triglycerides decreased by 5.8% and 19.3%, respectively (Table 1).

Table 2 shows the univariate correlation between the changes in LVMI or RWT and those of several clinical variables after doxazosin therapy. A significant correlation was observed between changes in LVMI and those in morning SBP and DBP, serum insulin and HOMA-IR. The change in RWT was correlated with the changes in the morning SBP and HOMA-IR. The results of a stepwise multivariate regression analysis revealed that the change in morning SBP and HOMA-IR were significant contributory factors to the change in LVMI. This regression model accounted for 39.4% of the LVMI variability (Table 3). When factors contributing to the change in RWT were determined, only the change in HOMA-IR was selected as a significant contributory factor to the change in RWT (Table 3). The change in HOMA-IR accounted for 14.5% of the change in RWT after doxazosin therapy.

Discussion

In this study, bedtime dosing of doxazosin induced a good control of morning blood pressure and a regression of LV hypertrophy. The decrease in LVMI induced by doxazosin was closely related to the decreases in morning SBP and HOMA-IR, indicating an improvement in insulin sensitivity. These results indicate that bedtime dosing of doxazosin is an effective part of a combination therapy for patients who have morning hypertension and metabolic syndrome, particularly insulin resistance. The Hypertension and Lipid Trial (HALT) study conducted by Pickering *et al*. (*31*) reported that doxazosin achieved its greatest reduction in blood pressure in the early morning (10±12 mmHg systolic and 9±9 mmHg diastolic at an average bedtime dose of 8.9 mg/day). They noted that these findings were consistent with the kinetic profile of doxazosin, since the drug achieves its greatest pharmacodynamic effects when the α-adrenergic tone is at its peak. Similar results were obtained in the Japanese HALT study conducted in elderly Japanese hypertensive patients by Kario *et al*. (*32*). They observed that early morning blood pressure was reduced by a maximum of 15.0 mmHg systolic and 6.9 mmHg diastolic with bedtime dosing of doxazosin monotherapy at an average dose of 3.7 mg/day. In the present study, blood pressure change after doxazosin add-on therapy was evaluated by office and home blood pressure monitoring. The lack of blood pressure data by ABPM is a weakness of this study. Although it has been reported that home blood pressure monitoring has superior reproducibility compared to both office blood pressure measurement and ABPM, and can improve the accuracy of antihypertensive drug trials (*33*), it may be necessary to clarify in detail the time course of the effect of doxazosin by ABPM.

In this study, the morning blood pressure, but not the pulse rate, was efficiently decreased by the addition of a bedtime dose of doxazosin. Even long-acting CCBs such as amlodipine produced a slight increase in the pulse rate and a sustained increase in the plasma norepinephrine levels after chronic therapy, indicating sympathetic nervous activation (*34*). It is possible that doxazosin resets the baroreceptor reflex range to lower levels. These lines of evidence as well our study results indicate the potential beneficial effect of the addition of a bedtime dose of doxazosin on the control of morning hypertension. To the best of our knowledge, this is the first report suggesting the beneficial effect of a chronotherapeutic approach focusing on morning hypertension to treat hypertensive target organ damage in patients with essential hypertension. Kamoi and Ikarashi examined the effect of bedtime administration of doxazosin on morning hypertension and albuminuria in hypertensive patients with type-2 diabetes (*35*). They reported that bedtime administration of doxazosin at a mean daily dose of 2.9 mg/day decreased the urinary albumin excretion rate from 62 to 19 mg/g creatinine and decreased the morning SBP by 17–18 mmHg, and that the two effects were positively correlated. Along with our present findings, these results indicate that the control of morning hypertension by the addition of a bedtime dose of doxazosin may improve the surrogate markers of hypertensive vascular complications. However, it remains to be clarified whether a chronotherapeutic approach focusing on the control of morning hypertension can prevent future cardiovascular events in hypertensive patients.

Modest yet statistically significant declines in the use of doxazosin and other α-blockers in the United States (*36*) coincided with the early termination of the doxazosin arm of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (*37*). Recent guidelines

for the treatment of hypertension did not include α-blockers as a recommended first step therapy (*13–16*). However, the results of this study provide additional evidence that the combination therapy of bedtime dosing of doxazosin with amlodipine is a useful strategy for selected patients with morning hypertension and LV hypertrophy.

Another important finding of the present study was the influence of insulin resistance after doxazosin therapy on LV hypertrophy. The change in HOMA-IR, an indicator of insulin resistance, was significantly related to the changes in LVMI and RWT. The change in HOMA-IR accounted for 4.9% and 14.5% of the total variability of the changes in LVMI and RWT, respectively. The existence of a relationship between insulin sensitivity and LV hypertrophy has been shown in population-based studies (*38*) and cross-sectional studies conducted in untreated hypertensive patients (*39*). In our previous study, HOMA-IR was an independent predictor for echocardiographically determined LVMI in hypertensive patients who were on long-term amlodipine monotherapy (*21*). With respect to the relationship between improvement in insulin sensitivity and antihypertensive medication, α-blockers have been well documented to markedly improve insulin resistance (*40*), while long-acting Ca antagonists have been reported to slightly improve (*41*) or have no effect on (*42*) insulin sensitivity. These findings and our present results suggest that the regression of LV hypertrophy induced by doxazosin is, in part, due to the improvement in insulin sensitivity induced by the drug.

Significant decreases in the serum total cholesterol and triglycerides levels were observed in this study, consistent with previous reports (*43–45*). However, the changes in the serum levels of total cholesterol and triglycerides showed no significant correlations with the changes in the LVMI or RWT. Thus, the beneficial effects of doxazosin on cardiac hypertrophy may not be directly related to the improvement in the lipid profile induced by the drug. However, the improvement of the lipid profile by doxazosin may contribute to the reduction of other cardiovascular events in the future.

Four subjects were withdrawn from the study due to adverse reactions to doxazosin: 1 female subject had temporal urinary incontinence and 3 subjects (2 males and 1 female) had vasodilatory edema. In women, urinary incontinence has been reported to be triggered by α-blockers and to be reversible upon withdrawal of the offending drug (*46*). It has been reported that vasodilatory edema is dose-dependent and most common with direct arteriolar dilators such as minoxidil or hydralazine, and in decreasing order of frequency with CCBs, α-blockers and antiadrenergic drugs (*47*). In this study, vasodilatory edema was observed in 3 patients after 4 weeks when 4 mg of doxazosin was used in combination with amlodipine. In the future, therefore, patients should be closely monitored for these distressing adverse reactions when being treated with the combination of doxazosin and amlodipine.

There were several limitations to the present study. First, this study lacked a placebo or active control group. It is thus possible that the reduction of morning blood pressure associated with the improvement of LV hypertrophy observed in this study may have been induced by some other antihypertensive drug therapy. Indeed, Hashimoto *et al*. reported that the bedtime administration of the central α_2-agonist, guanabenz, and clonidine effectively suppressed the morning blood pressure in patients already under therapy but without adequate control of morning blood pressure (*48*). However, these authors did not evaluate the change of LV hypertrophy after reduction of morning blood pressure by the bedtime administration of α_2-agonist. In this study, the decrease in the LVMI induced by doxazosin was correlated with the decreases in morning home SBP and HOMA-IR. These lines of evidence strongly indicate that the reduction of LVMI induced by doxazosin was attributable to the improvements in morning hypertension and insulin sensitivity. However, it should be pointed out that this study was an open-label study, and thus the results should be regarded with caution. In particular, the risk of excessive depressor effects and other adverse reactions should be considered before adding a bedtime dose of doxazosin to amlodipine therapy in clinical practice. A blinded or comparative study with other antihypertensive drugs will be needed to definitively confirm the relationship between the decrease of LVMI and the control of morning blood pressure by a bedtime dose of doxazosin. Secondly, LVMI was indexed by body surface in this study. This indexation tends to result in an over-emphasis on body weight and an underestimation of LV hypertrophy (*49*). To avoid this possibility in this study, obese patients with body mass index over 30 kg/m^2 were excluded.

In conclusion, our observations indicate that bedtime dosing of doxazosin in combination with amlodipine is useful for controlling morning blood pressure and regressing LV hypertrophy associated with insulin resistance.

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