Original Article

Morning Rise of Blood Pressure Assessed by Home Blood Pressure Monitoring Is Associated with Left Ventricular Hypertrophy in Hypertensive Patients Receiving Long-Term Antihypertensive Medication

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To assess the influence of morning rise of systolic blood pressure (SBP) as assessed by home blood pressure monitoring on the left ventricular mass index (LVMI) in relation to the blood pressure control status, we evaluated M-mode cardiac echocardiography in 626 hypertensive subjects (412 men and 214 women; mean age, 61.3±10.1 years) who were receiving antihypertensive medication. The subjects were requested to measure their blood pressure at home in the morning and evening over a 3-month period. They were distributed into the following four groups by the average (ME Ave) and the difference (ME Dif) of the morning and evening SBP. The well-controlled hypertensives with a morning rise of SBP (ME Ave<135 mmHg and ME Dif ≥10 mmHg; *n*=45; 7.2%) had a greater LVMI (122.9±22.7 *vs.* 92.7±15.6 g/m^2, *p*<0.001) than the well-controlled hypertensives without a morning rise of SBP (ME Ave<135 mmHg and ME Dif<10 mmHg; *n*=367; 58.6%). The uncontrolled hypertensives with a morning rise of SBP (ME Ave≥135 mmHg and ME Dif≥10 mmHg; *n*=91; 14.5%) also had a greater LVMI (136.8±21.9 *vs.* 100.2±17.5 g/m^2, *p*<0.001) than the uncontrolled hypertensives without a morning rise of SBP (ME Ave≥135 mmHg and ME Dif<10 mmHg; *n*=123; 19.6%). A stepwise multivariate regression analysis revealed that the ME Dif was the most important factor related to the LVMI (r^2=35.1% for all subjects, *p*<0001; r^2=39.7% for men, *p*<0.001; and r^2=18.7% for women, *p*<0.001). These results suggest that morning rise of blood pressure is an important factor influencing the development of left ventricular hypertrophy in hypertensive patients on antihypertensive medication. (*Hypertens Res* 2007; 30: 903–911)

***Key Words*: morning rise of blood pressure, left ventricular mass, β-blockers, insulin resistance**

Introduction

The prevalent practice of ambulatory blood pressure and home blood pressure monitoring has facilitated investigation of the predictive value of multiple blood pressure measurements outside the clinic setting (*1–3*). It has been reported that morning rise of blood pressure may be a predictor of hypertensive target organ damage, independent of the actual morning blood pressure level (*4–7*). The previously reported studies have been either population-based studies (*4*) or clinical studies in hypertensive patients (*5–7*), and to the best of our knowledge, there are no published clinical studies on the influence of morning rise of blood pressure on the development of hypertensive target organ damage in patients receiving antihypertensive medication. Recently, we reported that a morning rise of systolic blood pressure (SBP) of over 10 mmHg as compared to the evening SBP was a significant factor influencing the development of left ventricular (LV) hypertrophy in hypertensive patients under treatment with the long-acting calcium channel blocker, amlodipine (*8*). However, it remains unclear whether morning rise of SBP as

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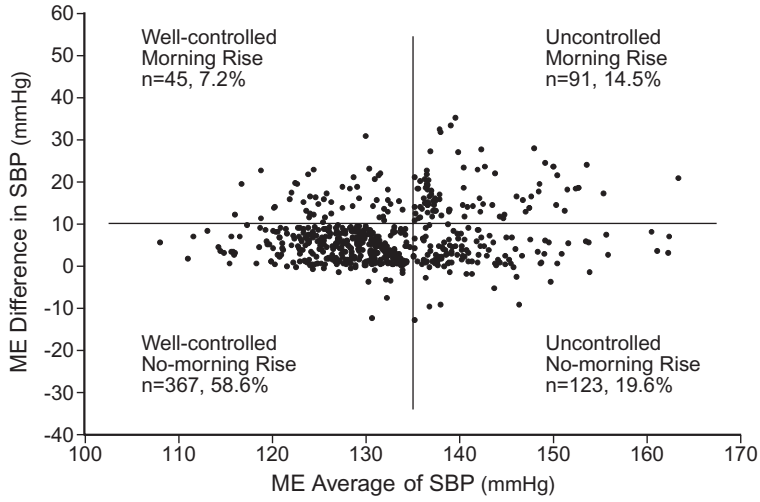

Fig. 1. *Blood pressure control as judged by the ME Ave of SBP (average of the morning and evening systolic blood pressure) and ME Dif in SBP (difference between morning and evening systolic blood pressure).*

assessed by home blood pressure monitoring would also be related with a higher risk of LV hypertrophy in well-controlled hypertensive patients. In order to ascertain the role of morning rise of blood pressure in the development of LV hypertrophy with reference to the control status of the blood pressure and the antihypertensive medication used, a cross-sectional study was designed to investigate the relationship between blood pressure values obtained by home blood pressure monitoring and echocardiographically determined left ventricular mass (LVM) in hypertensive patients under long-term antihypertensive medication.

Methods

Subjects and Study Design

This study was conducted in 626 Japanese subjects (421 men and 205 women; mean age, 61.3 years; range, 36 to 90 years) with established, moderate essential hypertension who had not changed their antihypertensive medication for at least 1 year. Subjects with secondary hypertension, body mass index (BMI)≥30.0 kg/m^2, diabetes mellitus (diagnosed according to the criteria of the World Health Organization [WHO] Consultative Committee [fasting plasma glucose levels≥126 mg/dL, 7.0 mmol/L; 2-h after glucose load≥200 mg/dL, 11.1 mmol/L]) (*9*), renal failure (serum creatinine level≥1.5 mg/dL, 133 μmol/L), or severe liver dysfunction (serum transaminase≥100 IU/L) were excluded from this study. Clinical information about the subjects was obtained from their medical records, and included the duration of hypertension and antihypertensive drug treatment, family history of hypertension, history of alcohol intake, and smoking history. Subjects enrolled in the study conducted home blood pressure monitoring over a 3-month period and underwent routine clinical evaluation, including biochemical measurements and echocardiography (as detailed below). The nature of the study and the potential risks associated with it were explained to all the subjects, and informed consent was obtained from each prior to his/her participation in the study. The study protocol was approved by the Institutional Review Board on Human Investigations of the 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 physicians with an Omron office digital blood pressure monitor (HEM-907; Omron Healthcare Co., Kyoto, Japan) (*10*) in their consultation chamber (time of measurements, 12:25±2:15 h; range, 9:05–17:46 h); the measurements were obtained with the patients in the sitting position, during their monthly visits to the outpatient clinic. The office blood pressure values used for the analysis were the average of the measurements obtained over 3 months. The subjects were provided instructions by the physicians on how to measure their own blood pressure at home according to the Japanese Society of Hypertension guidelines for self-monitoring of blood pressure at home (*11*). The monitors used in this study were cuff-oscillometric devices (Omron HEM-737 IntelliSense or its associated model, HEM-757 IntelliSense; Omron Healthcare Co.), which have been reported to fulfill the criteria of the Association for the Advancement of Medical Instrumentation for a general adult population across large ranges of age, blood pressure, body mass, and cuff circumference (*12*). Each device was checked before use by connecting it to a mercury sphygmomanometer with a Y-connector. The subjects were requested to obtain 2 consecutive measurements in the seated position in the morning (on awakening, before breakfast and

at the time of taking the antihypertensive drugs), and 2 additional measurements in the seated position in the evening (at bedtime), and to record the results in a diary for 3 months. The average values of the daily blood pressure and pulse rate measurements obtained at home by the patients themselves were used for the analysis, and only when the measurements had been conducted both in the morning and in the evening. The average of the morning and evening blood pressure measurements (ME Ave) was used as an index of the control status of home blood pressure. The difference between the morning and evening blood pressure values (ME Dif) was determined to define the morning rise of blood pressure in the study subjects.

Echocardiography

Echocardiograms were recorded with a SONOS 5500 Ultrasound Imaging System (Philips Medical Systems, Tokyo, Japan) equipped with a 2.0- to 4.0-MHz transducer. The echocardiographic examinations were performed by a trained physician who was unaware of the patients' clinical data. Two-dimensionally guided M-mode echocardiograms of the left ventricle (LV) were recorded at or just below the mitral valve with the patient in a partial left lateral decubitus position, and the average of 3 measurements was recorded. End-systolic and end-diastolic measurements of the inner dimension of the LV, interventricular septal thickness, and LV posterior wall thickness were obtained according to the American Society of Echocardiography recommendations (*13*). LVM was calculated using the formula developed by Devereux *et al*. on the basis of necropsy validation studies (*14*).

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) (*15*).

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 (*16*).

Biochemical Measurements

Blood samples for biochemical measurements were drawn from the patients after they had fasted for at least 12 h. The serum total protein and creatinine concentrations were measured by an enzymatic technique with an automatic analyzer (Model H 736; Hitachi, Tokyo, Japan). Plasma glucose was 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 EIA Test Insulin II BMY (Boehringer Mannheim, Mannheim, Germany). The homeostasis model assessment insulin resistance index (HOMA-IR) was calculated using the formula, glucose (mmol/L) $\times$ insulin (μU/mL)/22.5, and used as an index of insulin resistance (*17*).

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$\pm$SD. Intergroup comparisons were performed using one-way analysis of variance (ANOVA). When ANOVA showed an overall significance, Scheffe's test was used for multiple comparisons of the means among the groups. Analysis of covariance (ANCOVA) was used to adjust the LVMI and RWT in each group for 11 covariates: age, gender (1: men; 2: women), α-blocker use (1: use, 0: no use), β-blocker use (1: use, 0: no use), daily alcohol consumption, BMI, office SBP, morning and evening SBP, ME Ave of SBP, and ME Dif in SBP. The Pearson Product Moment formula was used for calculation of the coefficients of correlation between the LVMI and other continuous variables. Multiple linear stepwise regression analysis was used to determine which parameters accounted for the LVMI in the two models. Independent variables included in the models were selected from those that reached statistical significance ($p<0.05$) in the univariate analysis. The selected independent variables in the model 1 were the general characteristics and metabolic parameters, including age, gender, daily alcohol consumption, BMI, renin-angiotensin system (RAS) inhibitor use, β-blocker use, α-blocker use, glucose, HbA1c, insulin, and HOMA-IR. The independent variables for model 2 were those that were identified to be significant in model 1 and the blood pressure measurements (office SBP, morning and evening SBP, ME Ave of SBP, and ME Dif in SBP).

Results

Characteristics of the Subjects

The estimated duration of hypertension and antihypertensive drug treatment in the subjects were 14.0$\pm$9.8 years (range: 2–50 years) and 8.3$\pm$7.7 years (range: 1–47 years), respectively. Four hundred thirty-five subjects (77.4%) had a family history of hypertension. Two hundred ninety-four subjects (46.9%) were regular drinkers and 127 subjects (20.2%) were current smokers. With respect to the antihypertensive drug class prescribed, 87.3% of the patients were on calcium channel blockers, 22.5% were on RAS inhibitors (angiotensin II receptor blockers or angiotensin converting enzyme inhibitors), 11.8% were on β-blockers, 16.9% were on α-blockers, and 5.9% were on diuretics. The number of antihypertensive drugs taken per patient was 1.44$\pm$0.62 (1 to 4 drugs/day).

Table 1. Clinical, Laboratory and Echocardiographic Parameters in Patients Grouped According to the ME Ave and ME Dif in Systolic Blood Pressure

	Well-controlled patients		Uncontrolled patients		*p* (ANOVA)
	No-morning rise	Morning rise	No-morning rise	Morning rise	
Number (%)	367 (58.6)	45 (7.2)	123 (19.6)	91 (14.5)	
General characteristics					
Gender (% male)	67.0	82.2$^{\#}$	53.6	79.1$^{\#}$	<0.001
Age (years)	60.5±9.4	59.6±8.2	62.9±11.8	62.8±10.6	0.035
Body mass index (kg/m^2)	23.6±2.4	23.9±1.8	24.0±2.8	25.3±2.1*,$^{\#}$	<0.001
Alcohol consumption (g/day)	20.0±23.0	34.7±30.6*,$^{\#}$	17.4±21.2	26.8±25.4$^{\#}$	<0.001
Smoking (cigarettes/day)	4.2±9.3	7.2±12.3	4.6±10.5	2.7±7.7	0.083
Antihypertensive medication					
Calcium channel blocker use (%)	90.7	84.4	78.0*	87.9	0.003
RAS inhibitor use (%)	20.1	28.8	27.6	21.9	0.254
β-Blocker use (%)	8.4	26.6*,$^{\#}$	7.3	24.1*,$^{\#}$	<0.001
α-Blocker use (%)	21.2	6.6*	14.6	5.4*	0.001
Diuretic use (%)	4.3	11.1	5.6	9.8	0.095
Blood pressures					
Office					
Systolic blood pressure (mmHg)	136.1±9.1	136.1±6.8$^{\#}$	143.9±9.8*	140.0±10.7*,$^{\#}$	<0.001
Diastolic blood pressure (mmHg)	84.4±6.3	84.6±6.3	85.6±8.4	86.0±7.6	0.152
Home					
Morning					
Systolic blood pressure (mmHg)	129.9±4.7	135.2±5.0*,$^{\#}$	143.2±6.5*	150.0±6.8*,$^{\#}$	<0.001
Diastolic blood pressure (mmHg)	83.3±5.7	86.2±6.4	85.7±7.7*	89.7±8.3*,$^{\#}$	<0.001
Evening					
Systolic blood pressure (mmHg)	125.6±5.2	118.6±5.0*,$^{\#}$	140.6±6.1*	132.4±6.2*,$^{\#}$	<0.001
Diastolic blood pressure (mmHg)	77.9±5.9	73.0±5.8*,$^{\#}$	82.6±7.3*	77.7±7.8$^{\#}$	<0.001
ME Ave					
Systolic blood pressure (mmHg)	127.7±4.7	126.9±4.6$^{\#}$	141.9±6.0*	141.2±6.0*	<0.001
Diastolic blood pressure (mmHg)	80.6±5.5	79.6±5.8$^{\#}$	84.2±7.3*	83.5±7.3*	<0.001
ME Dif					
Systolic blood pressure (mmHg)	4.21±3.24	16.66±4.01*	2.58±3.80*	17.59±5.33*,$^{\#}$	<0.001
Diastolic blood pressure (mmHg)	5.40±4.01	13.19±3.90*	3.16±3.59*	12.01±6.37*,$^{\#}$	<0.001
Metabolic parameters					
Hematocrit (%)	0.426±0.032	0.422±0.034	0.422±0.040	0.431±0.025	0.199
Total protein (g/L)	70.7±3.9	70.0±3.7	70.9±3.7	71.0±4.3	0.519
Creatinine (μmol/L)	68.3±16.0	68.8±14.4	66.6±15.6	72.6±15.0	0.047
Glucose (mmol/L)	5.55±0.50	5.64±0.48	5.54±0.59	5.73±0.61*	0.024
Glycated hemoglobin A1c (%)	5.18±0.40	5.30±0.47	5.20±0.39	5.26±0.44	0.129
Insulin (μU/mL)	6.35±2.97	12.17±5.52*,$^{\#}$	6.77±3.09	13.18±6.21*,$^{\#}$	<0.001
HOMA-IR	1.57±0.77	3.08±1.53*,$^{\#}$	1.67±0.79	3.37±1.62*,$^{\#}$	<0.001
Echocardiographic findings					
Left ventricular end-diastolic dimension (mm)	45.6±4.2	49.2±4.5*,$^{\#}$	46.9±4.6	50.3±4.0*,$^{\#}$	<0.001
Left ventricular end-systolic dimension (mm)	26.7±4.5	30.1±4.4*,$^{\#}$	27.1±4.8	29.9±5.4*,$^{\#}$	<0.001
Interventricular septal thickness (mm)	9.8±1.2	11.2±1.1*,$^{\#}$	10.2±1.3	11.9±1.7*,$^{\#}$	<0.001
Left ventricular posterior thickness (mm)	9.6±1.1	11.1±1.1*,$^{\#}$	10.1±1.3*	11.6±1.3*,$^{\#}$	<0.001
Relative wall thickness	0.428±0.071	0.456±0.060*	0.435±0.070	0.466±0.07*,$^{\#}$	<0.001
Left ventricular mass (g)	153.3±29.5	209.6±44.4*,$^{\#}$	169.9±37.7*	232.7±47.3*,$^{\#}$	<0.001
Left ventricular mass index (g/m^2)	92.7±15.6	122.9±22.7*,$^{\#}$	100.2±17.5*	136.8±21.9*,$^{\#}$	<0.001

Values are mean±SD. *$p<0.05$ *vs*. well-controlled patients with no-morning rise group, $^{\#}p<0.05$ *vs*. uncontrolled patients with no-morning rise group. RAS, renin-angiotensin system; ME Ave, average of morning and evening; ME Dif, difference between morning and evening; HOMA-IR, homeostasis model assessment insulin resistance index.

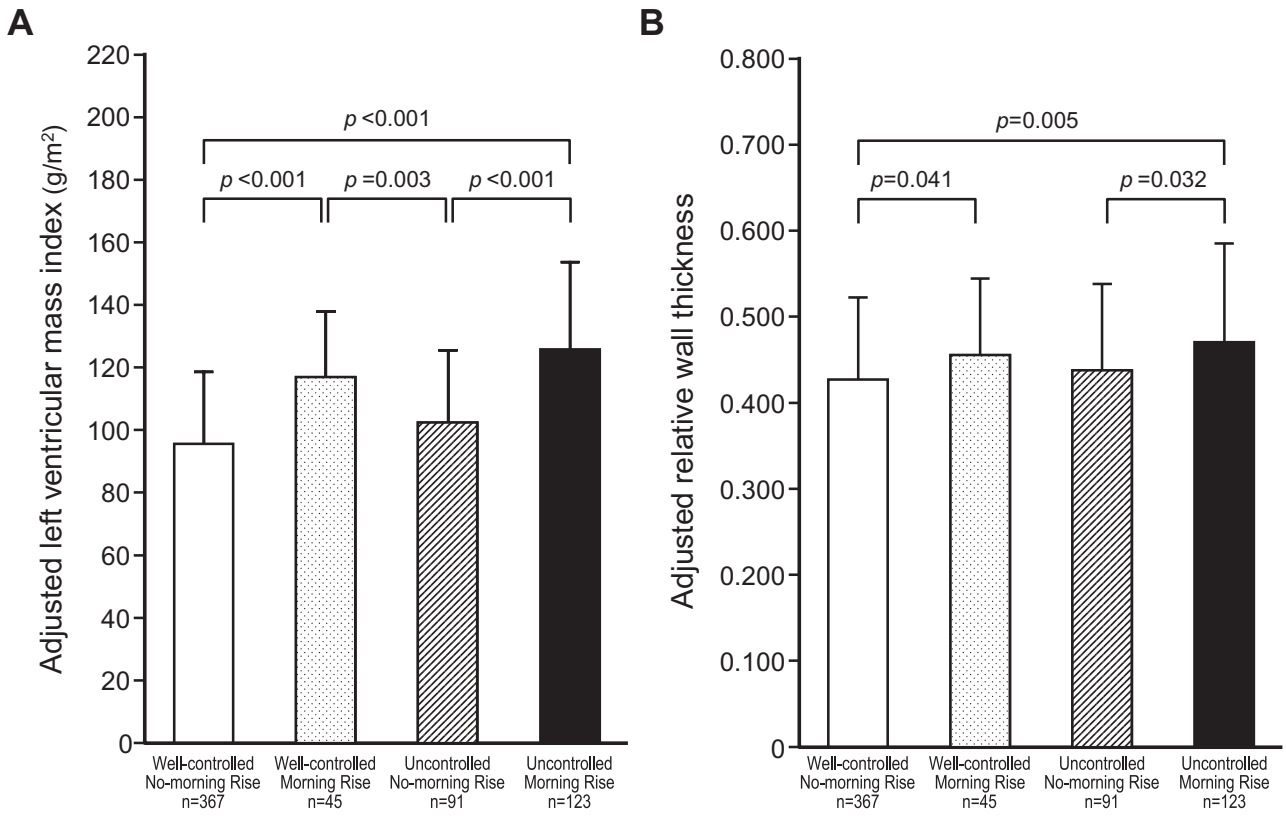

Fig. 2. *Adjusted left ventricular mass index (A) and relative wall thickness (B). The means are adjusted for 11 covariates (age, gender, α-blocker use, β-blocker use, daily alcohol consumption, body mass index, office systolic blood pressure [SBP], morning and evening SBP, ME Ave of SBP, and ME Dif in SBP). Vertical bars denote 1 SD.*

Control of Blood Pressure as Assessed by Home Blood Pressure Monitoring

The relationships between the ME Ave of SBP and the ME Dif in SBP in the 626 patients are shown in Fig. 1. Based on these relationships, the subjects were classified into the following four groups: a well-controlled no-morning rise group (367 cases; 58.6%): ME Ave of SBP<135 mmHg and ME Dif in SBP<10 mmHg; a well-controlled morning-rise group (45 cases; 7.2%): ME Ave of SBP<135 mmHg and ME Dif in SBP≥10 mmHg; an uncontrolled no-morning rise group (123 cases; 19.6%): ME Ave of SBP≥135mmHg and ME Dif in SBP<10 mmHg; and an uncontrolled morning-rise group (91 cases; 14.5%): ME Ave of SBP≥135mmHg and ME Dif in SBP≥10 mmHg.

Biochemical and Echocardiographic Characteristics of the Patients Grouped According to the ME Ave of SBP and the ME Dif in SBP

Among the well-controlled hypertensives, the group showing morning rise of SBP had a higher percentage of patients receiving β-blockers and of patients with a history of daily alcohol consumption, and a lower percentage of patients receiving α-blockers as compared to the no-morning rise of SBP group. This group also showed significantly higher values of the echocardiographic parameters, including the LV internal dimension, interventricular septal thickness, LV posterior wall thickness, RWT, and LVMI. The serum insulin levels were also significantly higher in this morning rise of SBP group than in the no-morning rise of SBP group, without a corresponding change of the plasma glucose level or HbA1c, which resulted in an increase in the HOMA-IR, indicative of increased insulin resistance. Among the uncontrolled hypertensives, the group that showed morning rise of SBP had a higher percentage of males, of patients receiving β-blockers and of patients with a history of daily alcohol consumption, and higher BMI as compared to the no-morning rise of SBP group. This group also showed significantly increased values of the metabolic and echocardiographic parameters as compared to the uncontrolled hypertensive group showing no-morning rise of SBP, similar to the findings in the corresponding well-controlled hypertensive groups (Table 1). The increased LVMI and RWT in the groups showing morning rise of SBP among both the well-controlled and uncontrolled hypertensives remained significant even after adjustment for age, gender, α-blocker use, β-blocker use, daily alcohol consumption, BMI, office SBP,

Table 2. Pearson Correlation Coefficients between Clinical Parameters and Left Ventricular Mass Index

Variables	All subjects		Men		Women	
	r	*p*	*r*	*p*	*r*	*p*
Age (years)	−0.033	0.407	−0.013	0.785	0.061	0.384
Gender (1: men, 2: women)	−0.129	0.001				
Alcohol consumption (g/day)	0.129	0.001	0.108	0.027	−0.073	0.302
Smoking (cigarettes/day)	0.062	0.123	0.033	0.501	0.008	0.908
Body mass index (kg/m^2)	0.211	<0.001	0.224	<0.001	0.126	0.073
Antihypertensive medication						
Calcium channel blockers (1: use, 0: no use)	−0.012	0.761	−0.040	0.418	0.049	0.489
RAS inhibitors (1: use, 0: no use)	−0.064	0.107	−0.033	0.500	−0.182	0.009
β-Blockers (1: use, 0: no use)	0.352	<0.001	0.336	<0.001	0.378	<0.001
α-Blockers (1: use, 0: no use)	−0.109	0.006	−0.137	0.005	−0.052	0.462
Diuretics (1: use, 0: no use)	0.074	0.064	0.117	0.016	0.016	0.819
Blood pressure						
Office						
Systolic blood pressure (mmHg)	0.023	0.565	0.051	0.301	0.049	0.487
Diastolic blood pressure (mmHg)	0.058	0.147	0.095	0.053	−0.054	0.442
Morning						
Systolic blood pressure (mmHg)	0.489	<0.001	0.541	<0.001	0.376	<0.001
Diastolic blood pressure (mmHg)	0.245	<0.001	0.266	<0.001	0.095	0.175
Evening						
Systolic blood pressure (mmHg)	0.075	0.062	0.081	0.095	0.129	0.066
Diastolic blood pressure (mmHg)	−0.069	0.085	−0.091	0.062	−0.056	0.427
ME Ave						
Systolic blood pressure (mmHg)	0.315	<0.001	0.359	<0.001	0.267	<0.001
Diastolic blood pressure (mmHg)	0.089	0.025	0.083	0.090	0.017	0.812
ME Dif						
Systolic blood pressure (mmHg)	0.594	<0.001	0.631	<0.001	0.437	<0.001
Diastolic blood pressure (mmHg)	0.405	<0.001	0.418	<0.001	0.274	<0.001
Metabolic parameters						
Creatinine (μmol/L)	0.048	0.232	−0.071	0.146	0.110	0.116
Glucose (mmol/L)	0.104	0.009	0.172	<0.001	−0.149	0.035
Glycated hemoglobin A1c (%)	0.122	0.003	0.186	<0.001	−0.073	0.305
Insulin (μU/mL)	0.511	<0.001	0.575	<0.001	0.268	<0.001
HOMA-IR	0.517	<0.001	0.585	<0.001	0.232	<0.001

RAS, renin-angiotensin system; ME Ave, average of morning and evening; ME Dif, difference between morning and evening; HOMA-IR, homeostasis model assessment insulin resistance index.

morning and evening SBP, ME Ave of SBP, and ME Dif in SBP (Fig. 2).

Factors Influencing the LVMI

Table 2 shows the univariate correlations between the LVMI and several clinical variables in the subjects, also classified according to the gender of the patients. The strongest correlation was found for the ME Dif in SBP (r=0.594 for all subjects, p<0.001; r=0.631 for men, p<0.001; r=0.437 for women, p<0.001). Other factors showing significant correlations were the gender, BMI, history of daily alcohol consumption, blood glucose, HbA1c, serum insulin, HOMA-IR, and several office and home blood pressure variables. With respect to the antihypertensive medication, significant correlation was found between the LVMI and β-blocker use (r=0.352 in all subjects, p<0.001; r=0.336 in men, p<0.001; r=0.378 in women, p<0.001). Use of RAS inhibitors was negatively correlated with the LVMI in women (r=−0.182, p=0.009). α-Blocker use was negatively correlated with the LVMI in the entire subject population (r=−0.109, p=0.006) as well as in men (r=−0.137, p=0.005). The results of a stepwise multivariate regression analysis revealed that the ME Dif in SBP, ME Ave of SBP, β-blocker use and HOMA-IR were significant contributory factors to the LVMI in the entire subject population. This regression model could explain 48.8% of the LVMI variability (Table 3). When factors contributing to the LVMI were deter-

Table 3. Multivariate Predictors of Left Ventricular Mass Index

Independent variables	Regression coefficient	Partially adjusted r^2	Sum of adjusted r^2	p
Model 1				
All subjects				
HOMA-IR	17.63	26.6%	26.6%	<0.001
β-Blocker use (use: 1, no use: 0)	8.89	5.2%	31.8%	<0.001
Men				
HOMA-IR	9.79	33.7%	33.7%	<0.001
β-Blocker use (use: 1, no use: 0)	14.73	3.8%	37.5%	<0.001
Glycated hemoglobin A1c (%)	5.12	0.6%	38.1%	0.025
Women				
β-Blocker use (use: 1, no use: 0)	23.70	15.0%	15.0%	<0.001
HOMA-IR	3.86	9.0%	16.9%	0.006
Glucose (mmol/L)	−6.34	0.3%	17.2%	0.023
Model 2				
All subjects				
ME Dif in SBP (mmHg)	1.41	35.1%	35.1%	<0.001
ME Ave of SBP (mmHg)	0.60	5.2%	40.3%	<0.001
β-Blocker use (use: 1, no use: 0)	15.01	5.1%	45.4%	<0.001
HOMA-IR	4.30	3.4%	48.8%	<0.001
Men				
ME Dif in SBP (mmHg)	1.41	39.7%	39.7%	<0.001
HOMA-IR	5.21	8.2%	47.9%	<0.001
ME Ave of SBP (mmHg)	0.66	4.0%	51.9%	<0.001
β-Blocker use (use: 1, no use: 0)	13.96	3.3%	55.2%	<0.001
Women				
ME Dif in SBP	1.24	18.7%	18.7%	<0.001
β-Blocker use (use: 1, no use: 0)	0.52	6.2%	24.9%	<0.001
ME Ave of SBP (mmHg)	19.78	4.9%	29.8%	<0.001

ME Ave, average of morning and evening; ME Dif, difference between morning and evening; SBP, systolic blood pressure; HOMA-IR, homeostasis model assessment insulin resistance index.

mined in men and women, the ME Dif in SBP, HOMA-IR, ME Ave of SBP and β-blocker use were selected in the men, and the ME Dif in SBP, β-blocker use and ME Ave of SBP were selected in the women. These regression models could explain 55.2% and 29.8% of the LVMI variability in men and women, respectively.

Discussion

We found that the LVMI was increased in subjects showing morning rise of SBP, even after adjustment for confounding factors. Morning rise of blood pressure as defined by an ME Dif in SBP accounted for 35.1% of the total variability of the LVMI, and all of the remaining factors, including the ME Ave of SBP, use of β-blockers and the HOMA-IR accounted for 13.7% of the variability. Morning rise of blood pressure has been reported to be a predictor of hypertensive target organ damage, independent of the actual morning blood pressure levels (*4*–*8*). A population-based study in Ohasama showed that untreated hypertensive subjects with morning rise of blood pressure, defined as a greater than 10 mmHg difference in the diastolic blood pressure between the morning and evening, had a relatively high hazard ratio of cardiovascular mortality (*4*). The change in blood pressure after arising in the morning has been reported to be better correlated with the LVMI than the office blood pressure (*5*, *6*). A prospective study by Kario *et al*. (*7*) demonstrated that subjects with a morning surge of SBP had a higher baseline prevalence of cerebral infarction as detected by brain magnetic resonance imaging and a higher incidence of stroke during a follow-up period of 41 months. We recently found that having a morning SBP more than 10 mmHg higher than the evening SBP is a significant factor associated with the development of LV hypertrophy in hypertensive patients receiving the long-acting calcium channel blocker, amlodipine (*8*). These lines of evidence, as well as the results of this study, support the contention that morning rise of blood pressure may be a strong predictor of LV hypertrophy in hypertensive patients on long-term antihypertensive medication.

With respect to the antihypertensive medication, the percentage of patients receiving β-blockers was higher in the groups showing morning rise of SBP among both the well-

controlled and uncontrolled hypertensives, and a stepwise regression analysis revealed a significant association of β-blocker use with the LVMI. β-Blockers have been used as first-line therapy for hypertension in the hope of reducing the cardiovascular mortality associated with coronary heart disease and congestive heart failure (*18*). However, some investigators have challenged the use of β-blockers as an optimal treatment for uncomplicated hypertension (*19*, *20*). Messerli *et al*. (*19*) reported that diuretics were superior to β-blockers in every end-point study included in their meta-analysis of randomized trials conducted in elderly hypertensive patients. A more recent meta-analysis of 13 randomized controlled trials that compared the use of β-blockers for the treatment of hypertension with other antihypertensive drugs showed that β-blockers have less significant effects on cardiovascular outcomes as compared with other antihypertensive drugs (*20*). Furthermore, it was reported that β-blockers were less effective at reducing the LVMI than RAS inhibitors or Ca antagonists, even after adjustment for differences in the blood pressure among the treatment groups (*21*, *22*). Despite producing a similar degree of reduction of blood pressure as the RAS inhibitors, β-blockers appear to have only a small effect on the LVMI. This might be related to the smaller effect of β-blockers on the central aortic blood pressure, which is the main hemodynamic determinant of the development of LV hypertrophy. Previous short-term studies have demonstrated that the β-blocker atenolol is less effective for lowering the central aortic SBP than Ca antagonists or angiotensin converting enzyme inhibitors despite having a similar effect on the brachial arterial pressure (*23–26*). Recently, the Conduit Artery Function Evaluation (CAFE) study, a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), has shown that atenolol-based treatment is much less effective than amlodipine-based treatment for lowering the central aortic pressure (*27*). Further prospective evaluation is necessary to clarify the usefulness of β-blockers in the treatment of hypertensive patients with morning rise of blood pressure and LV hypertrophy.

Another important finding of the present study was the influence of insulin resistance on the LVMI. The HOMA-IR was significantly related to the LVMI and was determined, by stepwise regression analysis, to be one of the significant factors influencing the LVMI, accounting for 3.4% of the total variability of the LVMI. The existence of a relationship between insulin sensitivity and LV hypertrophy has also been shown in previous population-based studies (*28*, *29*) and cross-sectional studies conducted in untreated hypertensive patients (*30*, *31*). Our data are consistent with these reports even in hypertensive patients under treatment. It will be necessary to perform further clinical studies by glucose clamping to clarify the relationship between insulin resistance and LVMI in relation to antihypertensive drug treatment.

In conclusion, our observations indicate that morning rise of blood pressure, as assessed by home blood pressure monitoring, is an important factor influencing the development of LV hypertrophy in both well-controlled and uncontrolled hypertensive patients.

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