Prediction of Progression of Left Ventricular Hypertrophy in Mild Hypertension: 5-Year Observations without Pharmacological Intervention

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We investigated the clinical implications of blood pressure changes after 20 min of rest and during exercise in particular for predicting the progression of left ventricular hypertrophy (LVH) in unmedicated male subjects with borderline and mild hypertension. We studied 155 subjects who were enrolled in a hypertension management program that included routine annual physical check-ups and cardiovascular follow-up studies, including echocardiography and treadmill exercise stress testing, every 3 years. Sixty-nine subjects were followed for 5 years without pharmacological intervention. Left ventricular mass index (LVMI) was correlated with systolic pressure at peak exercise (max Ps) and 20-min resting systolic pressure in 155 subjects. Stepwise multiple linear regression analysis showed that the initial LVMI and max Ps had significantly higher percent explained variances in relation to the LVMI increase over the 5-year observation period compared with other variables. Hyper-responders, subjects with an initial max Ps above 200 mmHg, showed a greater increase in LVMI than subjects with an initial max Ps below 200 mmHg, although there was a small but significant increase in LVMI, without any increase in the blood pressure variables, even in those showing a normal response. In conclusion, max Ps appears to be a simple and reliable predictor of LVH progression. (*Hypertens Res* 1992; 15: 155-161)

Key Words: left ventricular hypertrophy, mild hypertension, systolic pressure at peak exercise

Because the final goal of management of essential hypertension is to improve and/or prevent cardiovascular morbidity and mortality (1), timely and appropriate intervention is essential. Most physicians who treated hypertensive patients are dissatisfied with the currently recommended WHO/ISH guidelines on the definition and management strategies of mild hypertension based on casually determined blood pressure levels (2-5).

Epidemiologic and clinical studies have shown that left ventricular hypertrophy (LVH) has an important role in the morbidity and mortality associated with hypertension (6-8). We therefore investigated the predictive value of various clinical variables for the progression of LVH in the early stage of essential hypertension in unmedicated male subjects.

Methods

Subjects

Male subjects who were found to satisfy the following criteria during an annual physical check-up at the Life Planning Center (LPC, Tokyo, Japan) were

enrolled in a continuous hypertension management program: 1) initial diagnosis between the ages of 30 to 49 years; 2) diastolic blood pressure between 90 to 105 mmHg on three consecutive measurements; 3) no pharmacological intervention during the previous three years; and 4) no regular physical exercise. Patients with secondary hypertension or other coexisting serious medical problems requiring specific treatment were excluded. Informed consent was obtained from all subjects. The present study involved subjects who were enrolled in the program after March 1981 and whose most recent follow-up cardiovascular studies were completed by the end of December 1990.

Methods

Blood Pressure Measurements

Upon admission to the program, casual blood pressures were measured in the office with the patients seated after at least 10 min of rest using the conventional cuff method with a mercury manometer. Systolic and diastolic pressures were determined at the 1st and 5th phases, respectively, of Korotkoff's sounds. Twenty-min resting blood pressure was

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measured at 2-min intervals over a 20-min period with subjects in the semisupine position using a fully automated unit (Dynamap 950, Tampa, USA). We determined the mean of 5 measurements taken over the last 10 min. Blood pressures during exercise were obtained by the ordinary K-sound method using a mercury manometer. Blood pressure at peak exercise was defined as the pressure measured at the peak of the symptom-limited maximal treadmill exercise stress test according to the conventional Bruce protocol (9).

Echocardiographic Measurements

M-mode echocardiograms, guided by two-dimensional echocardiography, were obtained using a Sonolayer (SSH-1, Toshiba Co. Tokyo, Japan) with a 2.5-MHz transducer. Data were printed on a split chart-recorder with a recording speed of 50 mm/s. Interventricular septal thickness (IVS), left ventricular internal diameter (LVD), and posterior wall thickness (PWT) were measured at end-diastole according to the recommendations of The American Society of Echocardiography and the Penn Convention (10, 11). Each dimension was defined as the mean of two measurements, obtained from an M-mode recording, performed by different investigators.

Left ventricular mass (LVM), cardiac output (CO), ejection fraction (EF), and mean velocity of the left ventricular circumference (mVcf) were calculated by the following formulae: $LVM = 1.04 \times \{(LVDd + PWTd + IVSTd)^3 - LVDd^3\} - 13.6$, $CO = (EDV - ESV) \times HR$; $EF = (1 - LVDd^3/LVDs^3) \times 100$; and $mVcf = \{(LVDd - LVDs)/LVDd\} \times ET$. Abbreviations: LVDd (end-diastolic left ventricular diameter); LVDs (end-systolic left ventricular diameter); PWTd (end-diastolic posterior wall thickness); IVSTd (end-diastolic interventricular septal thickness); EDV (end-diastolic left ventricular volume); ESV (end-systolic left ventricular volume), and ET (ejection time). Both EDV and ESV were

derived by Teichholtz's method (12). The left ventricular mass and cardiac indices (LVMI and CI) were calculated by dividing LVM and CO by the body surface area (BSA).

Program Follow-Up

Following routine health education, subjects entered the follow-up program, which involved annual physical check-ups and a cardiovascular evaluation every 3 years. If a subject's casual diastolic pressure exceeded 105 mmHg, he was asked to withdraw from the program, and pharmacological intervention was recommended.

Statistical Analysis

Data, arranged for the statistical package STAX, were expressed as the mean $\pm$ 1 SD. Linear regression analysis was used to evaluate the correlation between LVMI and blood pressure variables. The relation of LVMI to initial blood pressure variables at the end of the follow-up period and the change in LVMI during the observation period (Δ LVMI) were evaluated using stepwise multiple linear regression analysis. Results are expressed as a percentage of the explained variance (R^2). We selected the following independent variables for analysis: LVMI; casual, rest and maximal blood pressures; age; body mass index; and duration of follow-up period. A probability value of less than 0.05 was considered statistically significant.

Results

General Observations

Suitable echocardiograms allowing for reliable measurement were obtained in 155 of 243 eligible subjects. Data from these 155 subjects (mean age 43 ± 8 years) were analyzed. By the end of 1990, 69 of 155 subjects had been followed for over 3 years without pharmacological intervention. The median duration of follow-up was 4.9 ± 1.8 years. Of the remaining 86 subjects, 6 were recommended for phar-

Table 1. Demographics, Blood Pressure and Echocardiographic Variables in 155 Males

Age	43 $\pm$ 8
Body weight (kg)	66 $\pm$ 5
Casual Ps (mmHg)	138 $\pm$ 13
Casual Pd (mmHg)	91 $\pm$ 8
20 min resting Ps (mmHg)	130 $\pm$ 13
20 min resting Pd (mmHg)	82 $\pm$ 10
Maximal Ps (mmHg)	199 $\pm$ 23
Maximal Pd (mmHg)	94 $\pm$ 14
Maximal HR (bpm)	174 $\pm$ 14
Treadmill time (sec)	709 $\pm$ 118
LVMI (g/m ²)	105.9 $\pm$ 29.6
Cardiac index (l/m ²)	2.6 $\pm$ 0.7
Ejection fraction (%)	64.6 $\pm$ 8.6
mVcf (circ/sec)	1.1 $\pm$ 0.2

Abbreviations: casual Ps (casual systolic pressure); casual Pd (casual diastolic pressure); 20-min resting Ps (20-min resting systolic pressure); 20 min resting Pd (20-min resting diastolic pressure); maximal Ps (systolic pressure at peak exercise); maximal Pd (diastolic pressure at peak exercise); maximal heart rate (heart rate at peak exercise); LVMI (left ventricular mass index); mVcf (mean velocity of circumferential shortening).

macological intervention, 8 did not have a suitable echocardiogram at the second examination, 28 had been followed for less than 3 years, and 44 did not return for a second examination.

Table 1 shows the demographics, blood pressure and echocardiographic variables obtained in the 155 subjects at the initiation of the program. Anthropometric measurements and physical fitness levels showed that they were representative of typical middle-aged Japanese men with mild or borderline hypertension (13).

At the beginning of the observation period, 20-min resting blood pressure and blood pressure at peak exercise were more strongly correlated with LVMI than was casual blood pressure (Fig.1). Blood pressure at peak exercise showed the best correlation with LVMI ($r=0.57$, $p<0.001$).

Progression of LVH

After a follow-up period of 4.9 years, there was a marked decrease in physical fitness and no change in body weight, probably because of poor compliance with recommended non-pharmacological treatment regimens (Table 2). Although there were no changes in any blood pressure variables, LVMI showed a significant increase of +16.7%.

Prediction of LVMI

Figure 2 shows the percent explained variance of each variable for the prediction of the final LVMI and delta LVMI. When the initial LVMI was included in independent variables, Table 3 shows partial correlation coefficients and partial regression coefficients in that analysis. The initial LVMI had the greatest explained variance of 77.5% variability and other variables such as max Ps, the duration of follow-up, and age at the initiation of the observation only revealed 2.4%, 2.3%, and 0.9% levels of explained variance, respectively (Fig. 2). Table 4 shows partial correlation coefficients and partial regression coefficients when the initial LVMI was excluded from analysis. The initial max Ps emerged to be the most important predictor with a 30.5% explained variance level (Fig. 2). The initial max Ps was also the strongest predictor of delta LVMI when initial LVMI was excluded from analysis, with a 14.1% explained variance (Fig. 2).

Association between the Initial Max Ps and LVMI Increase

Preliminary data suggested that a max Ps of 200 mmHg was a useful predictor of progression in LVH (14). Therefore, we divided subjects into two

Fig. 1. Correlations of LVMI with blood pressure variables in 155 subjects at the beginning of the observation period.

Table 2. Body Weight, Blood Pressure and Echocardiographic Variables in 69 Untreated Males Followed for 5 Years

	Initial	Follow-up	<i>p</i> value
Body weight (kg)	65±7	65±8	ns
Casual Ps (mmHg)	141±12	139±15	ns
Casual Pd (mmHg)	92±8	92±10	ns
20-min resting Ps (mmHg)	130±10	131±13	ns
20-min resting Pd (mmHg)	82±8	81±9	ns
Maximal Ps (mmHg)	199±22	200±24	ns
Maximal Pd (mmHg)	94±14	95±13	ns
Maximal HR (bpm)	175±18	173±16	ns
Treadmill time (sec)	715±117	662±105	<i>p</i> <0.05
LVMI (g/m ²)	106.7±20.7	124.5±28.8	<i>p</i> <0.01
Cardiac index (l/m ²)	2.6±0.8	2.6±0.6	ns
Ejection fraction (%)	66±7	67±9	ns
mVcf (circ/sec)	1.1±0.2	1.1±0.2	ns

Abbreviations: casual Ps (casual systolic pressure); casual Pd (casual diastolic pressure); 20-min resting Ps (20-min resting systolic pressure); 20-min resting Pd (20-min resting diastolic pressure); maximal Ps (systolic pressure at peak exercise); maximal Pd (diastolic pressure at peak exercise); maximal heart rate (heart rate at peak exercise); LVMI (left ventricular mass index); mVcf (mean velocity of circumferential shortening).

Table 3. Predictive Value of Independent Variables Including Initial LVMI for Final LVMI

	partial correlation coefficient	partial regression coefficient	<i>p</i> value
LVMI	0.836	1.073	<i>p</i> <0.01
Casual Ps	-0.228		ns
Casual Pd	-0.250		ns
20-min resting Ps	0.269		ns
20-min resting Pd	-0.247		ns
Maximal Ps	0.404	0.207	<i>p</i> <0.01
Maximal Pd	0.107		ns
Age	0.184	0.416	<i>p</i> <0.05
Body mass index	-0.028		ns
Duration	0.262	0.170	<i>p</i> <0.01

Abbreviations: casual Ps (casual systolic pressure); casual Pd (casual diastolic pressure); 20-min resting Ps (20-min resting systolic pressure); 20-min resting Pd (20-min resting diastolic pressure); maximal Ps (systolic pressure at peak exercise); maximal Pd (diastolic pressure at peak exercise); maximal heart rate (heart rate at peak exercise); LVMI (left ventricular mass index); mVcf (mean velocity of circumferential shortening).

subgroups based on their initial max Ps; subjects with a max Ps $\geq$ 200 mmHg were classified as hyper-responders and subjects with a max Ps<200 mmHg were classified as normal responders. Initial casual systolic blood pressure was not significantly different between the two subgroups. This variable showed no significant intragroup changes during the observation period, but the casual systolic blood pressure was significantly higher in hyper-responders than in normal responders after the 5-year observation period (Fig. 3). Initial LVMI was significantly greater in hyper-responders compared with normal responders, and hyper-responders showed a significantly greater increase in LVMI after 5 years than did normal responders.

Discussion

Clinical trials have demonstrated the effectiveness of treating essential mild hypertension (15, 16). Because of the high cost of antihypertensive treatment to all patients with providing mild hypertension, and because of the relatively low incidence of cardiovascular events in this group, treatment is not universally provided to such patients (17). Casual blood pressure is not considered to be a reliable measure of blood pressure or a valid indication of target organ damage, especially of LVH (18). Therefore, better measures are needed to evaluate the cardiovascular status of patients with mild hypertension.

Table 4. Predictive Value of Variables Excluding Initial LVMI

	partial correlation coefficient	partial regression coefficient	p value
Casual Ps	-0.017		ns
Casual Pd	-0.231		ns
20-min resting Ps	0.358	0.264	$p < 0.01$
20-min resting Pd	-0.185		ns
Maximal Ps	0.385	0.367	$p < 0.01$
Maximal Pd	-0.003		ns
Age	0.298	0.235	$p < 0.01$
Body mass index	-0.001		ns
Duration	0.325	0.235	$p < 0.01$

Abbreviations: casual Ps (casual systolic pressure); casual Pd (casual diastolic pressure); 20-min resting Ps (20-min resting systolic pressure); 20-min resting Pd (20-min resting diastolic pressure); maximal Ps (systolic pressure at peak exercise); maximal Pd (diastolic pressure at peak exercise); maximal heart rate (heart rate at peak exercise); LVMI (left ventricular mass index); mVcf (mean velocity of circumferential shortening).

Fig. 2. Results of stepwise multiple linear regression analysis of variables for prediction of final LVMI after a 5-year follow-up and increase in LVMI during follow-up. The vertical line represents the percent explained variances of independent variables. The horizontal line represents dependent variables. Abbreviations: LVMI (left ventricular mass index); 20RPs (20-min resting systolic pressure); max Ps (systolic pressure at peak exercise); Duration (the duration of follow-up); final LVMI included initial LVMI (The final LVMI is the dependent variable and the initial LVMI is included in independent variables.); final LVMI excluded initial LVMI (The final LVMI is the dependent variable and the initial LVMI is excluded from independent variables.); delta LVMI (Change in LVMI during the observation period is the dependent variable).

Our results showed that max Ps was a useful indicator of the current state of LVH, and that both the initial LVMI and max Ps were independent predictors of the progression of LVH. Subsequent analysis showed that a blood pressure level at peak exercise above 200 mmHg was the most reliable predictor of LVH progression. Although systolic

blood pressure at exercise has been identified as a predictor of LVH in cross-sectional studies, the present study is the first longitudinal study to our knowledge, to investigate the clinical significance of max Ps for prediction of LVH progression.

Casual blood pressure has not been found to be a reliable measure of LVH (18). The 20-min resting

Fig. 3. Changes in blood pressure and LVMI variables in subjects classified according to systolic pressure at peak exercise. Open circles represent the normal responder group and closed circles represent the hyper-responder group. Abbreviations: CSLPs (casual systolic pressure); LVMI (left ventricular mass index); delta LVMI (change of LVMI during the observation period).

blood pressure measure used in the present study represented the average of 5 consecutive measurements obtained at 2-min intervals over the final 10 min using a fully automated device. This 20-min resting blood pressure measurement has been found to be significantly correlated with the 24-h average and midnight sleep blood pressure levels (19). Although the average 24-h systolic pressure has been reported to be well correlated with LVH (20, 21), the 20-min resting systolic blood pressure is relatively easy to obtain and our results showed that it was significantly correlated with LVMI. This measure would seem to be useful for estimating the presence of LVH, but its low percent of explained variance suggests that it is not a good predictor of LVH progression.

Fagard *et al.* reported that blood pressure measurement obtained during exercise did not offer any additional precision in predicting cardiovascular morbidity and mortality over the use of resting blood pressure and age (22). However, the age range in their patient population was extremely wide, and more than half of their subjects had moderate hypertension. Cardiovascular morbidity in patients with mild hypertension between the ages of 40 and 60 years is lower than in those over 60 years of age (23). Therefore, the clinical significance of the exercise blood pressures in the Fagard *et al.* study is questionable because of the relatively older age of their patients and, consequently, their relatively advanced hypertension. Max Ps may be a clinically useful prognostic factor only in the relatively early stage of hypertension.

Koren *et al.* reported that LVMI and left ventricular geometry are more useful than casual blood pressure for predicting cardiovascular events (24). Echocardiography is simpler and more cost-effective than the exercise test. However, our results showed that max Ps was a predictor of final LVMI and progression of LVMI independently of initial

LVMI. Thus, max Ps may provide useful information in addition to echocardiographic study for estimating the progression of mild hypertension.

The present study raises the question of why an exaggerated blood pressure response during exercise is one of the best predictors of LVH progression. It has been suggested that both hemodynamic and neurohormonal factors contribute to the progression of LVH (25). Gottodinner *et al.* reported that LVH was present even in normotensives whose systolic blood pressure at peak exercise exceeded 210 mmHg (26), suggesting that a hyperdynamic response to peak exercise is not a cause of LVH, but a result (27). It may be that both hypertension and LVH are caused by some other as yet unspecified factors, and that they may progress simultaneously, with systemic effects. Further studies are needed to clarify these issues.

Many blood pressure variables showed no change during the 5-year observation period. However, when subjects were classified as hyper-responders or normal responders according to their initial max Ps, casual systolic pressures differed significantly after 5 years in association with a relatively large LVH progression in the hyper-responder group. Studies have shown that blood pressure is not always elevated in its course and sometimes improves without pharmacological intervention (15, 28). Our results also support these findings, and indicate that a max Ps above 200 mmHg is a reliable measure for predicting the progression of mild hypertension. The present study demonstrated small but significant increases in LVMI without progressive elevation of blood pressure variables, providing further evidence that LVH may progress in the absence of increases in blood pressure.

In conclusion, max Ps emerged as a simple and useful factor for predicting the progression of LVH. Further study is required to confirm its long-term prognostic significance.

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