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ARTICLE

Higher blood pressure during light exercise is associated with increased left ventricular mass index in normotensive subjects

Min Seok Oh[1] · Soo Jin Cho[2] · Jidong Sung[3] · Kyung Pyo Hong[3]

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Abstract

An exaggerated blood pressure response during an exercise test reflects a future risk of hypertension and is related to increased left ventricular mass (LVM) in hypertensive patients. However, whether this relationship exists in normotensive subjects is not known. We enrolled 7923 health normotensive screening volunteers. Systolic blood pressure (SBP) at stage 1 of the exercise test was used as an indicator of the exercise BP response. Two-dimensional echocardiography was used to obtain the LVM index. Exercise SBP was significantly correlated with the LVM index ($r = 0.11$, $P < 0.001$). Higher exercise SBP at stage 1 was associated with an increased LVM index after adjusting for age, sex, body mass index, hemoglobin, SBP at rest, and peak oxygen consumption ($P < 0.001$). Higher SBP during low-intensity exercise was associated with an increased LVM index in normotensive subjects.

Introduction

An exaggerated blood pressure (BP) response to exercise in people who are normotensive or prehypertensive is associated with future development of hypertension [1–3]. Elevated exercise systolic blood pressure (SBP) at an early stage suggests the presence of hypertension and a higher 24 h ambulatory BP [4]. Furthermore, an increased SBP response during a treadmill test (TMT) may be a predictor of future cardiovascular risk in hypertensive patients [5].

Increased left ventricular mass index (LVMI) is a marker of target organ damage in hypertensive patients, and is more commonly found in hypertensive than normotensive individuals [6,7]. In hypertensive patients, an exercise BP response is related to higher LVMI [8–10]. However, limited data are available on this issue in normotensive subjects.

The objective of this study was to investigate the relationship between LVMI and the SBP response to light exercise during a TMT in normotensive subjects without overt cardiovascular diseases.

Methods

Study population and data collection

From January 1999 to December 2012, volunteers for health screenings at the Center for Health Promotion, Samsung Medical Center, Seoul, Republic of Korea who underwent both echocardiography (echoCG) and a TMT were enrolled. The inclusion criteria were (1) SBP less than 120 mmHg and (2) diastolic blood pressure (DBP) less than 80 mmHg. The exclusion criteria were (1) previous history of diagnosis of hypertension or taking BP-lowering medication, (2) echocardiographic evidence of cardiomyopathy, (3) ejection fraction (EF) less than 55% on echoCG, (4) previous history of ischemic heart disease or stroke, or (5) positive/equivocal/incomplete result on TMT.

The previous medical history and lifestyle patterns (e.g., smoking, alcohol intake, and exercise) were collected via self-administered questionnaires. Laboratory findings were obtained from medical records. This study was approved by

✉ Jidong Sung
jidong.sung@samsung.com

1 Cardiovascular Center, Department of Internal Medicine, Bundang Jesaeng General Hospital, Seongnam-si, Gyeonggi-do, Republic of Korea

2 Center for Health Promotion, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

3 Division of Cardiology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

the Institutional Review Board of Samsung Medical Center, Seoul, Republic of Korea, and written consent was waived due to the retrospective nature of the study.

BP measurement, exercise test and echoCG

After at least 5 min rest, baseline BP was measured with an electronic sphygmomanometer (Eagle 1000, GE Medical Systems IT, Inc., Milwaukee, Wisconsin, USA, or Dinamap Procare 300, GE Medical Systems IT, Inc., Milwaukee, Wisconsin, USA) using the nondominant upper arm with an appropriately sized cuff considering the arm circumference in a sitting position. The baseline BP measurement was taken separately from the exercise test and echoCG but on the same day, and the sequence of these three tests was random.

The exercise test was performed using the Bruce protocol. A Quinton Q4500 (Cardiac Science Corp., Bothell, Washington, USA) was used for the test. We measured BP manually with the subject in a standing position just before the test (stage 0) and at the 2-min point at each stage of the TMT. Heart rate and electrocardiography were obtained in the same manner. To determine maximal oxygen uptake, the JAEGER system (VIASYS Healthcare, Hoechberg, Germany) was used. Dynamic breath-by-breath respiratory gas analysis was performed, and various parameters of oxygen uptake, carbon dioxide output, and minute ventilation were measured. Subjects were allowed to put their hands on the machine, but leaning on the bar or tightly grabbing the bar were not permitted. Subjects with positive findings (significant ST changes, BP drops or arrhythmias during the test) were excluded from the study. The test was otherwise terminated according to the usual criteria for exercise stress testing: (1) exhaustion, (2) reaching >90% of the maximal heart rate (220 – age), (3) respiratory quotient ≥1.15, and (4) plateau of oxygen consumption.

Echocardiograms were obtained (Vivid 7, GE Medical Systems IT, Inc., Milwaukee, Wisconsin, USA) with a 1.5–5.0-Mhz adult cardiac probe. Two-dimensional measurements were made following the guidelines from the American Society of Echocardiography [11]. The LV dimension and wall thickness were measured by M-mode echoCG.

Terms and formulas

The Systolic and diastolic LV volumes were calculated with the Treicholz formula ($\text{Volume} = \left[\frac{7}{\{2.4+(\text{Inner dimension})\}}\right] \times (\text{Inner dimension})^3$), and EF was derived from the volume data ($\text{Ejection fraction} = \frac{\{(\text{End}-\text{diastolic volume})-(\text{End}-\text{systolic volume})\}}{(\text{End}-\text{diastolic volume})\times 100}$) [12]. LV mass was calculated with the Devereux formula ($0.8 \times 1.04 \times [\{(\text{LV inner diameter at diastole}) + (\text{inter-ventricular septum dimention at diastole}) + \text{LV posterior wall thickness at diastole})\}^3 - (\text{LV inner diameter at diastole})^3 + 0.6$) [12]. The Mosteller formula ($\text{Body surface area} = \sqrt{\frac{\text{Height (cm)}\times\text{Weight (kg)}}{3600}}$) was used for body surface area calculations [13]. LVMI was calculated as the LV mass divided by the body surface area.

Table 1 Clinical characteristics and laboratory findings ($n = 7923$)

Variables	Values
Age, years	50.0 ± 7.5
Sex, male	69.4
Diabetes mellitus	5.9
Hyperlipidemia	15.6
Never smoker	41.6
Alcohol drinking three or more times per week	17.2
BMI (kg/m^2)	23.6 ± 2.7
Blood pressure at rest (mmHg)	
Systolic	106.6 ± 8.2
Diastolic	67.3 ± 7.1
Laboratory (mg/dL)	
Hemoglobin (g/dL)	14.6 ± 1.4
Fasting blood glucose	94.1 ± 18.6
Hemoglobin A1c (%)	5.5 ± 0.7
Creatinine	0.9 ± 0.2
Total cholesterol	196.3 ± 33.7
HDL-C	53.9 ± 14.0
LDL-C	126.5 ± 30.0
TG	126.5 ± 73.5
hsCRP	0.12 ± 0.30

Values are expressed as mean ± SD or %

BMI body mass index, *HDL-C* high-density lipoprotein cholesterol, *hsCRP* high sensitivity C-reactive protein, *LDL-C* low density lipoprotein cholesterol, *TG* triglyceride

Statistical analysis

Categorical variables are presented as the number and proportion of subjects and were compared using chi-square or Fisher's exact tests. Continuous variables are described as the mean ± standard deviation and were analyzed with *t*-tests for independent samples or Mann–Whitney *U* tests. The hypothesis of normality was checked with the Kolmogorov–Smirnov test between systolic BP at stage 1 TMT and all of the variables in Tables 1 and 2. Bivariate analysis with Pearson or Spearman correlations was performed to calculate the correlation coefficients. Univariate and multiple linear regression analyses were performed to evaluate associations between exercise SBP and LVMI. We selected the starting set of variables for a stepwise regression model from variables with significant associations in

Table 2 Treadmill test and echocardiographic findings ($n = 7923$)

Variables	Values
Treadmill test	
SBP (mmHg)	
just before starting the test	114.6 ± 11.0
stage 1	127.4 ± 13.4
peak	164.6 ± 19.2
Δ SBP during exercise (mmHg)	
(stage 1) - (at rest)	8.0 ± 10.5
(stage 1) - (stage 0)	12.9 ± 10.0
(peak SBP) - (at rest)	47.8 ± 16.3
Heart rate (per min)	
baseline	61.6 ± 8.3
stage 1	97.1 ± 12.1
VO_{2peak} (ml/kg/min)	31.8 ± 6.2
Maximal METs	9.1 ± 6.2
Exercise duration (s)	565.8 ± 107.2
Echocardiography	
LVEF (%)	64.3 ± 4.9
LVMI (g/m^2)	83.2 ± 16.9

Values are expressed as mean ± SD

LVEF left ventricular ejection fraction, *LVMI* left ventricular mass index, *LAVI* left ventricular volume index, *METs* metabolic equivalents, *SBP* systolic blood pressure, VO_{2peak} peak oxygen consumption

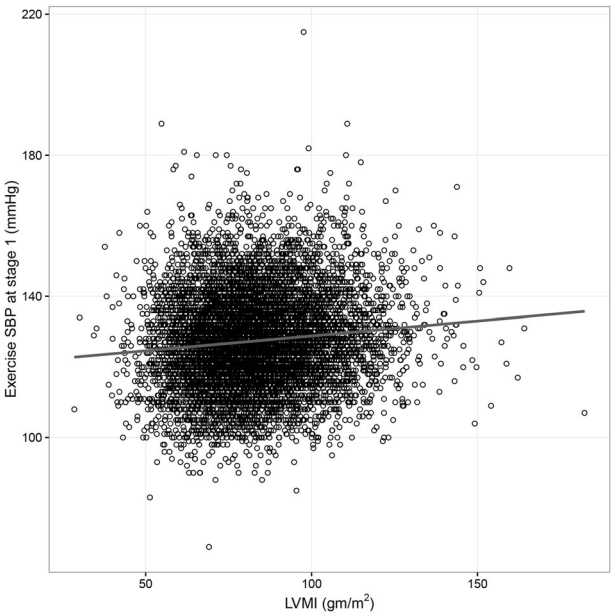

Fig. 1 Scatter plot for SBP at stage 1 during the treadmill test and LVMI showing a significant correlation. *LVMI* left ventricular mass index, *SBP* systolic blood pressure

univariate regression analysis, and additional empirical exploration for the final multivariable-adjusted model was performed considering biological plausibility and explanatory power.

SPSS 22.0 (SPSS, Inc., Chicago, Illinois, USA) was used for all statistical analysis. Two-tailed $P < 0.05$ was considered statistically significant.

Results

The baseline clinical characteristics and laboratory findings for the 7923 included subjects are shown in Table 1. The mean age was 50 years (range 15–81 years), and 69.4% of subjects were men. The mean SBP was 106.6 mmHg and mean DBP was 67.3 mmHg. The mean waist circumference was 83.2 cm, and 29.4% were overweight (body mass index [BMI] ≥ 25.0 kg/m^2). Never-smokers were 41.6%, and approximately 2% drank alcohol almost every day.

The parameters of TMT and echoCG are shown in Table 2. More than six metabolic equivalents were reached in 98.4% of subjects, and the mean exercise duration was 9.4 min. Systolic BP taken at rest was lower than SBP just before TMT (106.6 vs. 114.6 mmHg, $P < 0.001$), and SBP increased significantly at stage 1 TMT compared to at rest and just before TMT (106.6 vs. 127.4 mmHg, respectively, $P < 0.001$). The mean maximal increase in SBP during the exercise TMT was 47.8 mmHg. The mean LVMI was 83.2 g/m^2 (85.3 in men, and 78.5 in women).

Systolic BP at stage 1 was higher in subjects with increased LVMI (≥135 ml/m^2 in men, ≥110 ml/m^2 in women) compared to normal LVMI (130.3 vs. 127.4 mmHg, respectively, $P = 0.017$). This trend was significant both in men ($n = 5502$, 133.7 vs. 129.3 mmHg, $P = 0.050$) and women ($n = 2421$, 129.0 vs. 122.8 mmHg, $P < 0.001$).

In bivariate analysis, exercise SBP at stage 1 was significantly correlated with LVMI ($r = 0.11$, $P < 0.001$) (Fig. 1). As SBP at stage 1 increased by 10 mmHg, LVMI was increased by 1.40 g/m^2. This tendency was also significant in both men and women (0.57 vs. 1.67 g/m^2 per 10 mmHg of SBP elevation, $P < 0.001$, respectively). The correlations between LVMI and other parameters are shown in Table 3. Age, smoking, BMI, peak SBP, peak oxygen consumption during the TMT, and exercise duration showed relatively higher correlations with LVMI than the other parameters described in the table.

The final multiple regression model with maximal explanatory power is shown in Table 4. Higher exercise SBP at stage 1 was associated with increased LVMI after adjusting for age, sex, BMI, hemoglobin, SBP at rest and peak oxygen consumption ($r^2 = 0.13$, $P < 0.001$). Exercise duration, smoking, and HDL were associated with LVMI, but added minimal explanatory power to the model. High-sensitivity C-reactive protein, fasting blood glucose, hemoglobin A1c, lipid profile, waist circumference,

metabolic equivalents, LV ejection fraction, and left atrial volume index were not significant variables in the multivariate analysis. Though peak SBP during exercise was also a significant predictor, SBP at stage 1 provided a better explanatory power for the multiple regression model. This tendency was consistent both in men ($r^2 = 0.09$, $P < 0.001$) and women ($r^2 = 0.11$, $P < 0.001$).

Table 3 Correlation of left ventricular mass index to measured parameters ($n = 7923$)

Variables	Pearson correlation coefficient (r)	P value
Age (years)	0.16	<0.001
BMI (kg/m^2)	0.21	<0.001
Smoking	0.12	<0.001
SBP at rest (mmHg)	0.10	<0.001
DBP at rest (mmHg)	0.07	<0.001
Hemoglobin (g/dL)	0.07	<0.001
Fasting blood glucose (mg/dL)	0.06	<0.001
hsCRP (mg/dL)	0.02	0.087
LDL-C (mg/dL)	0.02	0.035
HDL-C (mg/dL)	−0.10	<0.001
TG (mg/dL)	0.06	<0.001
During exercise test		
SBP at stage 1 (mmHg)	0.11	<0.001
Peak SBP (mmHg)	0.15	<0.001
ΔSBP [(stage 1) − (at rest)]	0.09	<0.001
ΔSBP [(stage 1) − (stage 0)]	−0.02	0.060
ΔSBP [(peak) − (at rest)]	0.09	<0.001
V_{O2peak} (ml/kg/min)	0.17	<0.001
Exercise duration (s)	0.14	<0.001
LVEF (%)	0.00	0.98

BMI body mass index, *DBP* diastolic blood pressure, *HDL-C* high density lipoprotein cholesterol, *hsCRP* high sensitivity C-reactive protein, *LAVI* left ventricular volume index, *LDL-C* low density lipoprotein cholesterol, *LVEF* left ventricular ejection fraction, *METs* metabolic equivalents, *SBP* systolic blood pressure, *TG* triglyceride, *VO2 peak* peak oxygen consumption

Discussion

The main finding of our study was that SBP during light exercise was related to LVMI in normotensive subjects. LVMI was correlated with resting SBP, age, and BMI [14, 15]. After adjusting for these confounders in multiple regression analysis, exercise SBP at stage 1 was an independent predictor of LVMI.

While exercise BP was previously shown to be a predictor of masked hypertension or risk of future hypertension, most of those studies focused on peak exercise BP and had limitations. A study by Gottdiener et al. analyzed the relationship between LVMI and exaggerated BP response during exercise (peak exercise SBP of more than 210 mmHg in men and 190 mmHg in women) [16], in which the number of subjects was small and only older veteran men were enrolled. Lauer et al. analyzed the Framingham Heart Study population and concluded that normotensive subjects with exaggerated BP response had higher LVMI [17]. However, they dichotomously defined an exaggerated BP response, and a quantitative correlation between exercise SBP and LVMI was not reported. Our large-volume study showed a linear relationship between SBP during low-intensity exercise and LVMI in normotensive subjects. Exercise SBP at stage 1, rather than at peak exercise, predicted LVMI. These results seem to be clinically relevant because the BP at stage 1 of the exercise test is more likely to represent the BP level during physical activities in daily life.

The author's research group previously reported the relationship between SBP during stage 1 of the exercise test and pulse wave velocity, which suggested that a frequent BP increment during light physical activity could lead to stiffer arteries [18]. Increased LVMI could result from increased afterload during daily activities, and arterial stiffness may augment this mechanism.

Table 4 Multiple regression model for prediction of left ventricular mass index ($r^2 = 0.13$, $n = 7923$)

Variables	Regression coefficient (β)	Standard error	Test statistics (t)	P value
Age (years)	0.45	0.03	17.78	<0.001
Sex (female)	−4.70	0.61	−7.78	<0.001
BMI (kg/m^2)	1.25	0.07	17.06	<0.001
Hemoglobin (g/dL)	−1.79	0.15	−9.76	<0.001
SBP at rest (mmHg)	0.07	0.02	2.72	0.007
SBP at stage 1 (mmHg)	0.07	0.01	4.52	0.001
VO_{2peak} (ml/kg/min)	0.55	0.03	16.10	<0.001

BMI body mass index, *SBP* systolic blood pressure, VO_{2peak} peak oxygen consumption

Patients with masked hypertension could have been enrolled in our study population. However, we could not differentiate these subjects from subjects with true normotension because of a lack of ambulatory BP or home BP measurement. An exaggerated BP response to exercise in masked hypertension could be associated with increased LVMI and subclinical cardiovascular disease [8, 19]. Moreover, inflammatory status in normotensive subjects, which affects various vascular events, is related to an exaggerated BP response [20]. Further studies using ambulatory BP monitoring may be needed to determine whether the relationship between exercise BP and LVMI in apparent normotensive subjects is due to the presence of masked hypertension.

The hemoglobin level showed a negative correlation with LVMI in our data. Patients with chronic kidney disease, atrial fibrillation, renal transplantation, and newly diagnosed hypertension also have such an association [21–24]. Furthermore, lower hemoglobin implies a higher future cardiovascular risk [25]. Erythropoietin or fibroblast growth factor may contribute to this finding [26, 27]. A small-volume, retrospective study showed that LVMI was higher in an iron deficient anemia group than a control group in subjects without overt heart disease [28]. In our study, we did not measure these biomarkers.

As analyzed in previous studies, an exaggerated BP response, which represents ΔSBP at stage 0 and maximal BP during exercise, predicted LVMI [8–10]. However, BP during light exercise can better reflect daily life BP than maximal BP. Furthermore, by measuring SBP at stage 1, we can predict future cardiovascular outcomes or new-onset hypertension, even in patients who failed to exercise for a sufficient duration during the TMT. Clinicians should closely observe normotensive subjects with high stage 1 BP for detecting new-onset hypertension or hidden target organ damage.

This study has some limitations. First, it was a single-center, retrospective, registry-based study. As only cross-sectional relationships could be analyzed, causal effect reversal could not be ruled out in this study. Second, the ethnicity of the study subjects was 100% Korean. Third, because clinic BP measurements were performed only once and ambulatory or home BP data were not available, some misclassification of BP status could have occurred. Fourth, as presented in the results, the strength of association between LVMI and exercise BP was only moderate, probably because the exclusion of the non-optimal clinic BP resulted in a narrow range of both BP and LVMI in our study subjects.

In conclusion, higher SBP during low-intensity exercise was associated with increased LVMI in normotensive subjects. This relationship may be explained by a higher BP load during daily physical activities and/or the presence of masked hypertension.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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