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Endothelial Dysfunction in Patients with Exaggerated Blood Pressure Response during Treadmill Test

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Summary

Background: The diagnostic and prognostic importance of exaggerated blood pressure response to exercise is controversial. Endothelial dysfunction has been demonstrated in patients with atherosclerosis and risk factors for coronary artery disease, but there is a paucity of information on patients with exercise-induced hypertension.

Hypothesis: We designed the study to evaluate endothelial function in patients with exaggerated blood pressure response during exercise.

Methods: Exercise-induced hypertension was defined as systolic blood pressure ≥ 210 mmHg in men and ≥ 190 mmHg in women during the treadmill test. Using a high-resolution ultrasound technique, endothelial function of the brachial artery in patients with exercise-induced hypertension (n = 25) and control subjects (n = 25) was investigated.

Results: Endothelium-dependent vasodilation was impaired in patients with exercise-induced hypertension compared with controls (7.77 ± 5.14 vs. 2.81 ± 2.29%, $p < 0.05$). On univariate analysis, the extent of vasodilation correlated negatively with age ($r = -0.43$, $p < 0.05$) and Δ systolic blood pressure ($r = -0.39$, $p < 0.05$). Even after adjustment for factors known to affect endothelial function, endothelium-dependent vasodilation was decreased in patients with exercise-induced hypertension ($\beta = 5.375$, $p = 0.02$).

Conclusion: Patients with exercise-induced hypertension have impaired endothelium-dependent vasodilation. This study also supports the concept that endothelial dysfunction may play an important role in exercise-induced hypertension.

Key words: exercise, blood pressure, endothelium

Introduction

Although an exaggerated increase of systolic blood pressure (SBP) in response to exercise has been observed often during treadmill stress testing, the exact mechanism and prognostic implication have been unclear so far. In many epidemiologic studies, exaggerated blood pressure response to exercise has been implicated to predict future cardiovascular events such as systemic hypertension, congestive heart failure, and ischemic heart diseases.[1–3]

During exercise tests, diastolic blood pressure (DBP) may not increase or may often decrease, but SBP has been increasing at a steady rate as a function of an increase in cardiac output against peripheral adaptation during exercise.[4] Nitric oxide released by the vascular endothelium has been known to relax vascular smooth muscle, thereby decreasing vascular resistance and blood pressure.[5, 6] Endothelial dysfunction was known to be associated with atherosclerosis, systemic hypertension, and congestive heart failure.[7–9]

Since the noninvasive measurement of endothelial function with ultrasound was established by Celermajer *et al.*,[10] endothelial function has been evaluated for prognosis and response to treatment as an independent predictor of future cardiovascular events.[11, 12]

Thus, we designed the study to evaluate endothelial function in patients with exaggerated blood pressure response during treadmill tests.

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Materials and Methods

Patient Population

Starting July 2000, the study enrolled 25 consecutive patients who visited Ajou University Hospital for health screening and were documented to have normal blood pressure at rest but exercise-induced SBP ≥ 210 mmHg in men and ≥ 190 mmHg in women, along with age- and gender-matched control subjects who showed normal SBP response during exercise.[13]

Exclusion criteria were: (1) hypertension, defined as the current use of antihypertensive medication or a resting SBP of ≥ 140 mmHg or resting DBP 90 mmHg at physical examination; (2) history or clinical evidence of coronary heart disease, congestive heart failure, or valvular or congenital heart disease; (3) use of cardiac medication; (4) age > 60 years; (5) any chronic disease of the liver, lungs, or kidneys, as well as diabetes mellitus.

We measured cardiac function and left ventricular (LV) mass index by echocardiography according to the method defined by Devereux *et al.*[14]

All patients took a multistage exercise treadmill test according to the Bruce protocol. Blood pressure, heart rate, and a 12-lead electrocardiogram (ECG) were recorded prior to exercise, during the last min of each 3-min exercise stage, and after 5 min during the recovery phase. All subjects gave informed consent, and the study protocol was approved by the institutional committee of medical ethics.

Measurement of Endothelial Function by Ultrasound[10–12]

The diameter of the brachial artery was measured within 1 week of the treadmill exercise test by B mode ultrasound, 10.0 MHz trapezoidal linear array transducer (axial resolution 0.12 mm, penetration depth 2–16 cm) with HP SONOS 5500 imaging system (Hewlett-Packard, Andover, Mass., USA). All procedures were recorded with super-VHS videocassette recorder (AG-MD830, Panasonic, Nakoya, Japan), and the images of the brachial artery were magnified eight times and printed out by a videographic printer (Sony UP 5600MDU, Toyko, Japan). All patients fasted overnight for 12 h before measurements were taken.

Every vessel diameter was measured by two observers blinded to the clinical details and the stage of the experiment. An arterial diameter was measured with ultrasonic calipers at a fixed distance from the bifurcation. Measurements were taken from the anterior to the posterior "m" line, the interface between media and adventitia, at end diastole gated on the R wave of the ECG. For a reactive hyperemia scan, another diameter measurement was taken 45–60 s after cuff deflation. Four cardiac cycles were analyzed for each scan and the measurements were averaged.

Sequence of measurement: In each patient scans were taken at rest, during reactive hyperemia, again at rest, and after administration of sublingual nitroglycerin. The subjects rested in supine position for at least 10 min before the first resting scan was recorded. Increased flow was then induced by inflation of a pneumatic tourniquet above the elbow to a pressure of 300 mmHg for 5 min. The second scan was taken 45–60 s after cuff deflation. A period of 15 min was allowed for vascular recovery, and consecutive resting scans were taken. Sublingual nitroglycerin (0.3 mg) was administered, and the last scan was recorded 3 min later. Each vessel diameter (VD) in scans after reactive hyperemia, 15 min at rest, and with nitroglycerin was calculated in percentages of the first control scan, that is, % diameter changes = VD (during reactive hyperemia or after nitroglycerin) − VD (resting) / VD (resting). The mean VD and percent dilatation for each patient were obtained by averaging the measurements taken during the procedures.

Reproducibility: Blood pressure was recorded in the opposite arm before measurement in every patient. Resting VD in the controls was measured repeatedly four times to find the intraobserver variability with a coefficient variation of 2.1%. Two other researchers evaluated the same VD separately to obtain interobserver variability with a correlation coefficient of 0.901, which was similar to that in other studies.[10]

Statistical Analysis

Statistical analysis was performed using Statistical Package for Social Sciences/PC software (SPSS for Windows, release 8.0.0—SPSS Inc., Chicago, Ill., USA) and all data are expressed as mean ± standard deviation (SD). Comparison between the two groups was performed by chi-square-test for discrete variables and by Student's *t*-test or Mann-Whitney U test for continuous variables. Correlation analysis was also performed to determine the statistical significance between two variables. Statistical significance was accepted at $p < 0.05$.

Results

Patient Characteristics

Twenty-five patients with exercise-induced hypertension (Group 1) were compared with 25 age- and gender-matched subjects as controls (Group 2). Subjects consisted of 46 men and 4 women aged 33 to 60 years (mean 45.7 ± 8.7). There was no difference in the prevalence of cardiovascular risk factors, that is, smoking history, dyslipidemia, and family history of premature cardiovascular disease in the two groups. The presence of LV hypertrophy on the ECG was observed in nine patients (36%) in Group 1 and in three subjects (12%) in Group 2 ($p < 0.05$) (Table I).

There was also no statistical difference between the two groups in the fasting glucose and lipid profile known to affect endothelial function (Table II). No LV systolic dysfunction and significant heart disease were noted on echocardiography in either group. However, LV mass index of 134.5 ± 14.2 g/m^2 was significantly higher in Group 1 than in Group 2, with 126.5 ± 11.3 g/m^2 ($p < 0.05$), despite the fact that there was no significant difference in LV wall thickness by M-mode echocardiography (Table II).

TABLE I Characteristics of subjects according to blood pressure response during exercise

	Exercise hypertension (Group 1)	Control (Group 2)
	N (%)	N (%)
Sex (M/F) (%)	23 (92)/2 (8)	23 (92)/2 (8)
Smoker (%)	10 (40)	9 (36)
Dyslipidemia (%)	3 (12)	1 (4)
Family history of premature CAD (%)	1 (4)	2 (8)
LVH on ECG (%)	9 (36) [a]	3 (12)

[a] $p < 0.05$.

Abbreviations: N = number of patients, M = male, F = female, CAD = coronary artery disease, LVH = left ventricular hypertrophy, ECG = electrocardiogram.

TABLE II Characteristics of subjects according to blood pressure response during exercise

	Exercise hypertension (Group 1)	Control (Group 2)
Age (years)	44.7 ± 8.8	46.7 ± 8.7
Height (cm)	167.9 ± 8.1	166.7 ± 7.8
Weight (kg)	70.7 ± 11.3	67.2 ± 9.2
Fasting glucose (mg/dl)	103.5 ± 13.6	98.6 ± 6.2
Total cholesterol (mg/dl)	198.7 ± 33.7	196.6 ± 24.0
Triglyceride (mg/dl)	168.1 ± 84.8	130.6 ± 68.5
HDL cholesterol (mg/dl)	44.1 ± 13.0	49.8 ± 14.0
LV mass/BSA (g/m^2)	134.5 ± 14.2 [a]	126.5 ± 11.3
Amount of exercise (mets)	9.9 ± 1.9	9.7 ± 1.3
Amount of exercise (s)	522.0 ± 104.8	514.5 ± 72.0

Data are expressed as the mean ± standard deviation.

[a] $p < 0.05$

Abbreviations: HDL = high-density lipoprotein, LV = left ventricular, BSA = body surface area.

Blood Pressure Response during Exercise

Systolic blood pressure during exercise ranging from 210 to 238 mmHg (220.2 ± 9.8) in Group 1 was significantly higher than that in Group 2, ranging from 122 to 195 mmHg (176 ± 13.5) ($p < 0.01$) (Fig. 1). No statistical difference was noticed in DBP during exercise (88.6 ± 13.8 mmHg in Group 1 vs. 86.5 ± 14.0 mmHg in Group 2) and resting blood pressure (Fig. 1). There were no differences in exercise duration (522.0 ± 104.8 s in Group 1 vs. 514.5 ± 72.0 s in Group 2) and exercise load in mets (9.9 ± 1.9 mets in Group 1 vs. 9.7 ± 1.3 mets in Group 2) (Table II).

No subject complained of angina, palpitation, or dizziness. No ST-segment change on ECG during exercise was observed.

Endothelium-Dependent Vasodilation Assessed by Ultrasound

There were no significant differences in brachial artery diameter at rest between the two groups (5.00 ± 0.48 mm in Group 1 vs. 4.96 ± 0.53 mm in Group 2), but a significant difference in endothelium-dependent vasodilation was noted by reactive hyperemia (2.81 ± 2.29 vs. 7.77 ± 5.14%, $p < 0.05$). Endothelium-independent vasodilation by sublingual nitroglycerin in Group 1 was lower than that in Group 2 but had no statistical significance (8.11 ± 3.99 vs. 10.58 ± 5.08%, $p = 0.12$) (Fig. 2).

A univariate analysis revealed that endothelium-dependent vasodilation had a negative correlation with age ($r = -0.43$, $p < 0.01$) and SBP increment during exercise (Δ SBP) ($r = -0.39$, $p < 0.01$), but not with weight, fasting serum glucose, lipid profile, or cardiac hypertrophy on echocardiography.

Multivariate analysis showed that endothelium-dependent vasodilation was significantly decreased in the patients with exercise-induced hypertension compared with those in the control group even after adjustment for factors such as gender, age, lipidemia, and LV mass index, known to affect endothelial function ($\beta = 5.375$, $p = 0.02$).

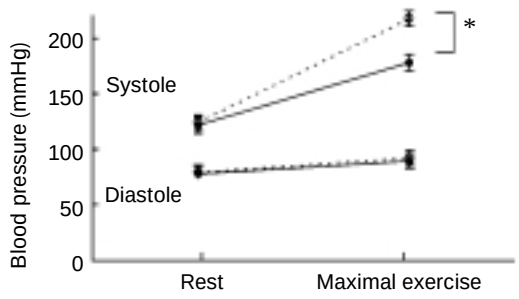

FIG. 1 Blood pressure response during exercise. Data are expressed as the mean ± standard deviation. *$p < 0.01$. - - ○ - - Exercise hypertension, —●— control.

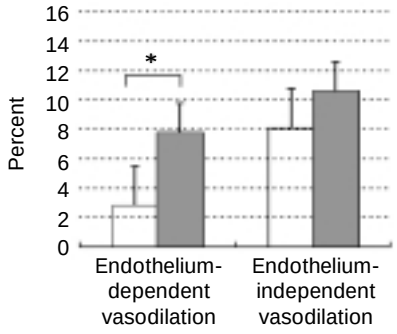

FIG. 2 Endothelium-dependent and -independent vasodilation. Data are expressed as the mean ± standard error of the mean. *$p < 0.05$. □ Exercise hypertension, ■ control.

Discussion

Our study shows that endothelium-dependent vasodilation is impaired in patients with exercise-induced hypertension. The correlation is statistically significant and clinically consistent even after adjustment for established risk factors for endothelial damage.

Exercise-induced hypertension is not an uncommon phenomenon in many exercise laboratories. Lauer *et al.*[13] reported that 9% of the normotensive healthy population has exercise-induced hypertension by the criteria of the Framingham Heart Study, that is, men ≥ 220 mmHg, women ≥ 190 mmHg.

Clinical Significance of Exercise-Induced Hypertension

So far, the clinical significance of exercise-induced hypertension is controversial and the pathophysiologic mechanism is unclear.[15] Mundal *et al.*[16] reported that an early rise of SBP during exercise added prognostic information on cardiovascular mortality. Gosse *et al.*[17] found that blood pressure measured at maximal exercise was a better prognostic indicator than resting clinic blood pressure. Recently, Filipovsky *et al.*[18] reported a similar finding in 4,907 male patients after 17 years of follow-up, indicating that peak exercise blood pressure is an independent cardiovascular risk factor among otherwise healthy middle-aged men with mildly elevated casual blood pressure.

Levy *et al.*[19] reported that an increased LV mass as a harbinger of cardiac morbidity and mortality is associated with increased SBP rather than resting blood pressure during exercise. Our results also showed that LV mass increased and that the prevalence of LV hypertrophy on ECG was higher in the patients with exercise-induced hypertension. In our study, 68% in that group, but 16% in the control group showed LV hypertrophy when using an LV mass index > 134 g/m^2, which was a finding similar to that reported by Lauer *et al.*[13] The frequent loading of high pressure on the left ventricle during exercise may have caused the positive correlation in patients with exercise-induced systolic hypertension and LV mass index.

On the basis of the current study, we suggest that exercise-induced hypertension should not be considered as a benign process but as a cardiovascular risk factor. Allison *et al.*[2] also observed that exercise-induced hypertension, including resting hypertension, was a significant predictor of future cardiovascular events after a 7-year follow-up. A "hyperactive-neurogenic" state prior to established hypertension was suggested as a mechanism for exercise-induced hypertension.[2] Our study is distinctive in that endothelial dysfunction is proven technically in patients with exercise-induced hypertension.

Hemodynamic Control during Exercise and Endothelial Dysfunction

Wilson *et al.*[20] suggested that normotensive individuals at risk for the development of hypertension showed an exaggerated blood pressure response to physical stimuli such as exercise because of poor compliance of peripheral adaptation in proportion to the increment of cardiac output.

It has been estimated that the proportion of cardiac output distributed in skeletal muscle increases from 15 to 20% of blood volume at rest to approximately 85% during dynamic exercise performed at or near maximal oxygen uptake (VO_{2max}) in humans, which stresses the importance of vascular beds in skeletal muscle as regulators of the cardiovascular system during exercise.[21]

A recent hypothesis for hyperemia during exercise is that the locus of blood flow control moves upstream from the microvessels to larger feed arteries as metabolic demand increases. This is the so-called "ascending vasodilation," which satisfies experimental observations that a delay exists between the dilation of microvessels and large arterioles at the onset of exercise. Furthermore, as a consequence of increased blood flow velocity through arterial vessels, hydrodynamic drag forces on the endothelium increase, and such increases in "shear" stress stimulate nitric oxide release from the endothelium.[22]

Endothelial cells are responsible for the continuous basal production of nitric oxide, which serves to counteract neural vasoconstrictor tone and to regulate blood flow and pressure.[23,24] Considering the acute increase of blood flow into the skeletal muscle during exercise, a vasodilatory defect due to endothelial dysfunction might be an important pathophysiologic mechanism of exercise-induced hypertension.

Gomez-Cerezo *et al.*[25] observed that flow-medicated brachial artery dilation was similarly deficient in both groups of patients with essential hypertension and white-coat hypertension, which suggested that patients with white-coat hypertension and sustained essential hypertension might have a similar level of cardiovascular risk. Furthermore, Mule *et al.*[26] reported a significant correlation between "white-coat effect" and LV mass in an analysis of 296 hypertensive patients. We postulate that a pathophysiologic process commonly involved in endothelial dysfunction may be associated with both exercise-induced hypertension and white-coat hypertension, and that the process may be a precedent to established cardiovascular events.

Conclusions

Our study shows that endothelium-dependent vasodilation is impaired in patients with exercise-induced hypertension and that the exaggerated increase of SBP in response to exercise has a negative correlation with endothelium-dependent vasodilation. It suggests that endothelial dysfunction and impaired vasodilatory capacity of peripheral vasculature may be responsible for inadequate accommodation for increased cardiac output during exercise, thus increasing blood pressure.

We propose to consider exercise-induced hypertension as an independent cardiovascular risk factor when we evaluate patients with cardiac disease.

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