High Diastolic Blood Pressure During Exercise Is Associated With Hypercholesterolemia in Patients With Coronary Artery Disease

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SUMMARY

Evaluating blood pressure response during exercise rather than during rest might better detect a subtle impairment in relaxation of the resistance vessel in hypercholesterolemia. We examined the relation between serum cholesterol and blood pressure response during exercise in patients with coronary artery disease.

One hundred and forty-eight consecutive patients with coronary artery disease were monitored during symptom-limited incremental exercise testing with a cycle ergometer. Cuff blood pressure was measured every minute during exercise testing with an automatic indirect manometer.

Although there were no significant differences in systolic or diastolic blood pressure at rest between the patients with hypercholesterolemia (total cholesterol ≥ 220 mg/dL, n = 39) and those without it (n = 109), the former reached a higher diastolic blood pressure at peak exercise (94.8 ± 16.0 versus 87.8 ± 12.9 mmHg, P = 0.007). The increase in diastolic blood pressure at peak exercise versus the resting value in the patients with hypercholesterolemia was 20.6 ± 11.3 mmHg, and this was significantly higher than the increase in patients without hypercholesterolemia (14.8 ± 11.8 mmHg, P = 0.009). However, there were no differences in the peak exercise systolic blood pressure and the magnitude of the increase in systolic blood pressure between the two groups.

Among the patients with coronary artery disease in our study, we found that those with hypercholesterolemia had significantly higher diastolic blood pressure during exercise than those without hypercholesterolemia, strongly suggesting that patients with hyperlipidemia are at a higher risk of developing hypertensive complications. (Int Heart J 2005; 46: 79-87)

Key words: Blood pressure, Cardiac patient, Exercise, Hyperlipidemia

FOR the past several years, investigators have been trying to elucidate whether there is a causal relationship between hypercholesterolemia and hypertension.1,2)
It was recently demonstrated that both endothelium-dependent and -independent relaxation in peripheral small arteries are impaired in hypercholesterolemic patients. On the basis of this finding, we can speculate that hypercholesterolemia leads to hypertensive complications. In a review of epidemiological data on the relation between hyperlipidemia and blood pressure conducted in 1995, Goode, et al noted a significant, albeit weak, association between the level of serum cholesterol and resting blood pressure. Though the resting blood pressure may not necessarily be high when the impaired relaxation of the resistance vessel is not very severe, the vascular reactivity may be abnormal, resulting in high blood pressure during some kind of stress condition, for example, during exercise. Thus, evaluating the blood pressure response during exercise rather than during rest might better detect a subtle impairment in relaxation of the resistance vessel in hypercholesterolemia.

It is known that the risk of cardiovascular disease becomes high under the presence of endothelial dysfunction. Both hyperlipidemia and hypertension are significant risk factors of coronary artery disease and, when these factors coexist, the risk of coronary artery disease more than doubles. Thus, it is of clinical importance to investigate whether hyperlipidemia is implicated in the development of high blood pressure in patients with coronary artery disease.

Among patients with coronary artery disease, we hypothesized that the blood pressure response during exercise is more abnormal in those with hypercholesterolemia than in those without it. In order to test this hypothesis, we examined the relation between serum cholesterol and blood pressure response during incremental exercise in patients with documented coronary artery disease.

**METHODS**

**Study patients:** We studied 148 consecutive patients (125 men and 23 women) with coronary artery disease (Table 1). Coronary artery disease was diagnosed by the presence of myocardial infarction or either a current or previous history of significant coronary stenosis, defined as ≥ 75% reduction in luminal diameter of coronary vessels. Among 148 patients, 93 had a previous myocardial infarction diagnosed according to the World Health Organization (WHO) criteria. The subjects included 61 patients who received percutaneous coronary intervention and 52 patients who underwent coronary artery bypass graft surgery before the study. Patients with effort angina were excluded from the study. The protocol and procedures for the exercise testing were approved by the Human Subjects Committee of The Cardiovascular Institute. Informed consent was obtained from each patient.
Measurements: The serum levels of total cholesterol and triglycerides were measured in all subjects by an enzymatic method. HDL cholesterol was measured by a homogeneous method. Fasting blood glucose level was determined by an immobilized enzyme electrode method. LDL cholesterol was calculated by the Friedwald equation.\(^\text{10}\) Left ventricular ejection fraction (LVEF) was measured by echocardiography.

Exercise testing: An incremental symptom-limited exercise test was performed using an upright, electromagnetically braked cycle ergometer (Corival 400; Lode; Groningen, Holland). Exercise began with a 4-minute warm-up at 20 W of 60 rpm, and the load was increased incrementally by 1 W every 6 seconds (10 W/min). ECG was monitored continuously during the test (System ML-5000; Fukuda Denshi Co Ltd.; Tokyo). Cuff blood pressure was measured 4 times at rest on a cycle ergometer before the start of exercise, and then every minute during exercise testing with an automatic indirect manometer (STBP-680; Nippon Colin Co, Ltd.; Aichi, Japan).\(^\text{11}\) Resting blood pressure was defined as an average of the 4 measurements. Blood pressure at peak exercise was defined as an average of the last 2 measurements. The end point of the exercise test was leg fatigue and/or shortness of breath. No subjects experienced chest pain.
In order to measure the exercise capacity of the subjects, oxygen uptake (VO₂), carbon dioxide output (VCO₂), and minute ventilation were measured throughout the test using an AE-280 Respiromonitor (Minato Medical Science; Osaka, Japan).\textsuperscript{12,13} The VO₂ and VCO₂ at peak exercise were calculated as averages of the last 15 seconds during incremental exercise.

**Statistics:** Data are presented as the mean ± SD. Cardiopulmonary variables were compared between the patients with hypercholesterolemia (group 1, total cholesterol ≥ 220 mg/dL, \( n = 39 \)) and those without (group 2, total cholesterol < 220 mg/dL, \( n = 109 \)). Intergroup differences for variables were compared using the unpaired \( t \)-test or chi-square analysis, where appropriate. For all comparisons, \( P < 0.05 \) was considered statistically significant.

**RESULTS**

The clinical characteristics of the patients enrolled in the study are shown in Tables I and II. The mean of the total cholesterol was 243.5 ± 23.1 mg/dL in group 1 and 186.2 ± 21.8 mg/dL in group 2. The difference between the groups was significant (Table II). Group 1 also had a higher level of LDL-cholesterol than group 2 (158.3 ± 28.6 versus 106.1 ± 25.1 mg/dL, \( P < 0.0001 \)), but there were no differences between the two groups with respect to HDL-cholesterol, triglycerides, and the level of fasting glucose. Our data also showed no distinct differences in age, height, weight, body mass index, or administration of any of the prescribed medications, including lipid-lowering drugs, between the groups (Table I).

Table III shows the cardiopulmonary variables at rest and at peak exercise. The resting heart rate was significantly higher in group 1 than in group 2 (77.7 ± 12.3 versus 71.9 ± 11.7 bpm, \( P < 0.01 \)). The peak exercise heart rate was also significantly higher in group 1 (137.9 ± 17.5 bpm) than in group 2 (127.0 ± 17.2

<p>| Table II. Lipid Levels in Patients With and Without Hypercholesterolemia |
|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>All patients ( (n = 148) )</th>
<th>Patients with total cholesterol ≥ 220 mg/dL ( (Group 1, n = 39) )</th>
<th>Patients with total cholesterol &lt; 220 mg/dL ( (Group 2, n = 109) )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>201.3 ± 33.6</td>
<td>243.5 ± 23.1</td>
<td>186.2 ± 21.8</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>53.1 ± 15.5</td>
<td>55.5 ± 16.3</td>
<td>52.3 ± 15.2</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>119.7 ± 34.7</td>
<td>158.3 ± 28.6</td>
<td>106.1 ± 25.1</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>141.2 ± 81.5</td>
<td>147.1 ± 63.4</td>
<td>139.1 ± 87.2</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>110.4 ± 29.1</td>
<td>112.3 ± 26.5</td>
<td>109.7 ± 30.1</td>
</tr>
<tr>
<td>Total cholesterol / HDL cholesterol</td>
<td>4.05 ± 1.19</td>
<td>4.70 ± 1.31</td>
<td>3.82 ± 1.05</td>
</tr>
</tbody>
</table>

Data presented are the mean ± SD.
During the resting condition, there was no difference in either the systolic or diastolic blood pressure between the groups. At peak exercise, there was no difference between the groups in systolic blood pressure, but the diastolic blood pressure was significantly higher in group 1 (94.8 ± 16.0 versus 87.8 ± 12.9 mmHg, \( P = 0.007 \), Figure). The increase in diastolic blood pressure at peak exercise versus the resting value (ΔDBP) was significantly higher in group 1, both as a magnitude (20.6 ± 11.3 versus 14.8 ± 11.8 mmHg, \( P = 0.009 \)) and as a percentage (ΔDBP × 100 / resting DBP). However, there were no differences in the increase in systolic blood pressure, either as a magnitude or in percentage terms, between the two groups. There were no differences between the groups in the peak VO₂ or gas exchange ratio (VCO₂/VO₂) at peak exercise.
DISCUSSION

There is a growing body of evidence suggesting that hyperlipidemia causes an impairment in vasorelaxation in both animals and humans.3-6) These findings imply the possibility of forthcoming hypertension in hyperlipidemic patients. Quite recently, Brett, et al2) searched for an association between serum cholesterol and blood pressure response to exercise in healthy subjects. They found a significantly positive correlation between the increase in diastolic blood pressure during exercise and serum concentrations of total cholesterol, but they found no such correlation with the increase in systolic blood pressure. However, to our knowledge, no previous studies have examined this relation in patients with cardiovascular disease.

In the present study, we newly demonstrated that among patients with coronary artery disease, the increase in diastolic blood pressure during exercise was significantly higher in those with than in those without hypercholesterolemia. The greater increase in diastolic blood pressure was attributed to the higher diastolic blood pressure in the hypercholesterolemic patients during exercise.

Heart rate and blood pressure response to exercise in hypercholesterolemia:  Systemic vascular resistance during exercise normally decreases as the exercise becomes more intense in order to allow more blood to flow (cardiac output) to the exercising muscles. Thus, in normal subjects, it is known that diastolic blood pressure, a parameter determined mainly by cardiac output and peripheral vascul-
lar resistance, does not significantly change during exercise in spite of the large increase in systolic blood pressure. In the present study, the impaired vasodilator capacity in the patients with hypercholesterolemia probably resulted in a higher vascular resistance, thereby causing the high diastolic blood pressure during exercise. However, the systolic blood pressure during exercise was not associated with the level of serum cholesterol.

As described previously by Brett, et al\cite{2} brachial artery systolic blood pressure during exercise is easily influenced by the stiffness of the aorta and frequency-dependent amplification in the upper limb.\cite{14} Thus, during exercise, systolic blood pressure at the brachial artery does not accurately reflect central aortic blood pressure.\cite{2} However, diastolic blood pressure in brachial arteries predicts central aortic blood pressure during exercise fairly well.\cite{2} For these reasons, we speculated that hypercholesterolemia could lead to higher diastolic blood pressure, but not higher systolic blood pressure, during exercise.

In the present study, neither systolic nor diastolic blood pressure was influenced by the level of serum cholesterol in the resting condition. In our subjects, the level of total cholesterol was scattered within a relatively narrow range, because hyperlipidemia in most of the subjects had been controlled by medication, diet, and/or exercise therapy according to current therapeutic guidelines for hyperlipidemia. Also, most of our subjects were taking vasodilators and/or beta-adrenergic blocking agents in order to maintain blood pressure within the normal range. Due to these limitations in our population, measuring blood pressure at rest could not detect characteristics of impaired vascular relaxation in hypercholesterolemia.

In the present study, the patients with higher cholesterol had higher heart rates both at rest and at peak exercise. Since the heart rate during exercise is equal to cardiac output divided by stroke volume, the heart rate must be higher in a patient with decreased stroke volume at a given level of exercise to appropriately maintain blood flow to the exercising muscles.\cite{12} However, resting cardiac function did not significantly differ between the two groups in the present study.

Blood pressure responses to exercise can be influenced by the etiology of heart disease. Although more than half of the subjects had previous myocardial infarction, there was no difference between the two groups in the percentage of patients with previous myocardial infarction.

The patients who received lipid lowering medications in group 2 (n = 37) might have had a history of hypercholesterolemia similar to those in group 1. For this reason, we also compared diastolic pressure at peak exercise between the patients with hypercholesterolemia and/or under lipid lowering medications (n = 76) and the remaining patients in group 2 without lipid lowering medications (n = 72). However, no significant difference between these 2 groups was observed.
Endothelial dysfunction probably develops during a long-term history of hypercholesterolemia. Thus, we assume that the patients who were given lipid-lowering medications at an early stage of hypercholesterolemia could maintain normal endothelial function, thereby blunting the difference in diastolic blood pressure at peak exercise between these 2 groups.

**Study limitations:** In the present study, we used an automatic indirect manometer, the STBP 680 (Nippon Colin Co., Ltd.), to measure the blood pressure during exercise. This manometer estimates the auscultation phase IV diastolic blood pressure.\(^{11}\) The device is widely used in exercise testing in Japan, and its accuracy in measuring both systolic and diastolic blood pressure during exercise has been previously confirmed.\(^{11}\) We also averaged 4 measurements for the resting value and 2 measurements for the peak exercise value in order to minimize the random noise of the blood pressure measurements. Notwithstanding, the variability noted in diastolic blood pressure during exercise among the subjects in the present study might have been at least partly attributable to the accuracy of the manometer used in the study, in addition to the physiological variability among the subjects.

Brett, et al\(^2\) noted that impaired glucose tolerance also affects diastolic blood pressure. However, in the present investigation, there were no differences in diastolic blood pressure at peak exercise or the magnitude of its increase during exercise between the patients with fasting glucose < 110 mg/dL (\(n = 100\)) and those with glucose \(\geq 110\) mg/dL (\(n = 48\)).

Although approximately one-third of the patients were receiving lipid-lowering medications, there were no significant differences in the percentages of patients receiving these medications in the two groups. While all vasodilators of course influence the blood pressure response to exercise, vasodilators were prescribed equally in both groups. While we did not have normal controls in the present investigation, the increase in diastolic blood pressure during exercise would probably be higher in patients with coronary artery disease than in normal subjects.

**Conclusions:** The present findings strongly suggest that patients with hyperlipidemia are at a higher risk of developing hypertensive complications. A future study will have to be conducted to clarify whether any cholesterol-lowering therapies prevent high diastolic blood pressure during exercise and subsequent hypertension.

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REFERENCES