Diastolic Blood Pressure Changes During Exercise Positively Correlate With Serum Cholesterol and Insulin Resistance

Sally E. Brett, BN; James M. Ritter, FRCP; Philip J. Chowienczyk, FRCP

Background—Metabolic factors, including plasma concentrations of cholesterol and insulin resistance, may influence blood pressure through effects on vascular reactivity. Such effects might influence blood pressure during exercise more strongly than at rest.

Methods and Results—We examined whether there is an association between serum cholesterol or insulin resistance and change in blood pressure during mild exercise. Blood pressure was measured at rest and during fixed low-workload bicycle ergometry (50, 75, and 100 W, each for 3 minutes) in 75 healthy active men (age, 18 to 66 years). Blood pressure at rest was not significantly correlated with serum cholesterol or insulin resistance (estimated from the fasting glucose–insulin product). The change from resting values in diastolic but not systolic blood pressure during exercise was correlated with serum cholesterol ($R>0.47$, $P<0.0001$ for each workload) and insulin resistance ($R>0.38$, $P<0.01$ for each workload). Serum cholesterol and insulin resistance were the only independent predictors of the change in diastolic blood pressure during exercise in a stepwise regression model incorporating age, body mass index, serum cholesterol, triglycerides, HDL cholesterol, insulin resistance, and heart rate during exercise. In a further study, the change in diastolic blood pressure during exercise was greater in men with uncomplicated type 2 diabetes (13.6 mm Hg [95% CI, 8.5 to 18.8]; n = 10) than in nondiabetic control men (2.7 mm Hg [95% CI, −2.0 to 7.3]; n = 10; $P=0.002$).

Conclusions—Changes in diastolic blood pressure during gentle exercise are strongly associated with serum concentrations of total cholesterol and insulin resistance. This may contribute to development of hypertensive complications in dyslipidemic and/or insulin-resistant patients. (Circulation. 2000;101:611-615.)

Key Words: blood pressure ■ diabetes mellitus ■ exercise ■ hypercholesterolemia

Endothelium-dependent relaxation of resistance vessels by such agonists as acetylcholine is impaired in hypercholesterolemia, and it has been hypothesized that an influence of cholesterol on vascular tone may affect blood pressure. Reviewing recent lipid-lowering trials, Goode et al have provided evidence for an association between plasma concentrations of cholesterol and resting blood pressure. The association, however, is relatively weak, and cholesterol-lowering therapy results in only a modest reduction in blood pressure. Hypercholesterolemia may influence vascular reactivity to a greater degree than basal tone. Such an effect might influence blood pressure during exercise more strongly than blood pressure at rest. In this present investigation, we therefore examined the relation between changes in blood pressure during exercise and serum cholesterol. This additionally revealed a relationship between changes in blood pressure during exercise and insulin resistance (assessed from the fasting glucose–insulin product). In a second study, we compared changes in blood pressure during exercise in severely insulin-resistant normotensive men with uncomplicated type 2 diabetes mellitus with those in age-matched, nondiabetic control men. We also compared changes in blood pressure during exercise with serum total homocysteine, a factor known to influence vascular reactivity.

Methods

Subjects

In study 1, healthy active men were recruited consecutively in response to an advertisement for cardiovascular screening. All were asymptomatic with no past history of cardiovascular disease, and no subject was on drug therapy. Diabetes was excluded by measurement of fasting plasma glucose concentrations. A physical activity score based on the frequency and type (intensity) of regular activity was determined for each subject. Subject characteristics are shown in Table 1. In study 2, men with type 2 diabetes were recruited from the diabetic clinic at St Thomas’ Hospital. None had evidence of macrovascular or microvascular complications other than mild background retinopathy. All had urinary albumin-to-creatinine ratios within the normal range. None was taking drugs other than oral hypoglycemic agents. Five subjects received sulfonylureas (glibenclamide, n = 3; glimepiride, n = 1) and/or metformin (n = 2). These drugs were omitted on the morning of the study. The mean duration of diabetes from diagnosis was 3 years. Nondiabetic control men age matched to within 2 years were recruited concurrently. These control subjects were included in the analysis for study 1. Characteristics of diabetic and control men are shown in Table 2. Additional healthy volunteers were recruited to examine the reproducibility and accu-
TABLE 1. Characteristics of Healthy Volunteers* Participating in Study 1

<table>
<thead>
<tr>
<th></th>
<th>Centiles</th>
<th>Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>Age, y</td>
<td>28</td>
<td>31</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>22</td>
<td>24</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>110</td>
<td>115</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>70</td>
<td>76</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>3.9</td>
<td>4.6</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.0</td>
<td>1.2</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>1.8</td>
<td>2.4</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>0.7</td>
<td>1.0</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>3.9</td>
<td>4.2</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>4.3</td>
<td>4.6</td>
</tr>
<tr>
<td>Insulin, μU/mL</td>
<td>4.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Homocysteine, μmol/L†</td>
<td>3.9</td>
<td>6.0</td>
</tr>
</tbody>
</table>

*All subjects (n=75) were asymptomatic men on no medication; 65 were lifelong nonsmokers, 10 were smoking 10 to 40 cigarettes per day.
†Measured in 30 subjects.

TABLE 2. Characteristics of Men With Type 2 Diabetes and Nondiabetic Control Subjects Participating in Study 2

<table>
<thead>
<tr>
<th></th>
<th>Type 2 Diabetes (n=10)</th>
<th>Nondiabetic Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>44.5±15.3</td>
<td>42.1±8.0</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.6±4.8</td>
<td>23.5±2.3</td>
</tr>
<tr>
<td>Treatment, M/S*</td>
<td>2/4</td>
<td>...</td>
</tr>
<tr>
<td>Smoking/nonsmoking</td>
<td>1/9</td>
<td>1/9</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>127.8±13.2</td>
<td>123.6±6.3</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>81.4±5.3‡</td>
<td>75.6±5.7</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.6±1.0‡</td>
<td>5.6±1.0</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.0±0.2‡</td>
<td>1.4±0.5</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>2.6±0.9</td>
<td>3.4±0.9</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>2.2±1.3</td>
<td>1.7±1.0</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>11.3±4.8‡</td>
<td>4.8±0.5</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>8.9±2.5‡</td>
<td>5.0±0.7</td>
</tr>
<tr>
<td>Insulin, μU/mL</td>
<td>22.5±6.6‡</td>
<td>16.3±3.5</td>
</tr>
</tbody>
</table>

Values are means±SD when appropriate.
*All subjects were treated with diet; some patients also were treated with metformin (M) and sulfonylureas (S).
†P<0.05, ‡P<0.01 vs control subjects.

The accuracy of diastolic blood pressure measurements during exercise. Approval for each protocol was obtained from St Thomas’ Hospital Research Ethics Committee, and written informed consent was obtained from all subjects.

Metabolic Measurements
Subjects attended a quiet, temperature-controlled clinical laboratory in the morning after an overnight fast. A fasting blood sample was taken for measurement of serum concentrations of total cholesterol, HDL cholesterol, triglycerides, glucose, glycosylated hemoglobin (HbA1c), and insulin. LDL cholesterol was calculated from the Friedewald equation. Insulin resistance was estimated by homeostasis model assessment from fasting glucose and insulin values. Serum total homocysteine was measured by high-performance liquid chromatography according to the method of Fiskerstrand et al in 30 healthy volunteers.

Exercise Blood Pressure Responses
After resting for 30 minutes, subjects performed a submaximal exercise test on a bicycle ergometer (Seca Cardiotest 100, Cardiokinetics). Subjects rested seated for 9 minutes to establish baseline readings and then cycled for 9 minutes (3 minutes at 50 W, 3 minutes at 75 W, and 3 minutes at 100 W). Subjects then rested for a 9-minute recovery period. Pulse and blood pressure were recorded at 3-minute intervals before, during, and after exercise. Blood pressure was measured by mercury sphygmomanometer with an appropriately sized cuff by a single trained observer who had no knowledge of the biochemical data at the time of the exercise study. Diastolic blood pressure was measured at Korotkoff phase IV according to American Heart Association guidelines for measurement during exercise.

Mercury sphygmomanometry was used in preference to automated methods or intra-arterial monitoring following preliminary studies that demonstrated sphygmomanometry to be more reproducible. Provided measurements were made by the same trained observer. Agreement between sphygmomanometric (obtained by the same trained observer) and intra-arterial diastolic blood pressure measurements was assessed in healthy men. A 22-gauge cannula was inserted into the left radial artery and attached to a pressure transducer (Baxter BV). The mean difference between diastolic blood pressure measured by the 2 methods was 5.3 (95% CI, −1.7 to 12.4), 4.2 (95% CI, −6.1 to 14.5), and 2.7 mm Hg (95% CI, −7.3 to 12.6) at 50, 75, and 100 W, respectively.

The reproducibility of sphygmomanometric blood pressure measurements during exercise was assessed in 8 healthy volunteers who exercised on 3 occasions separated by ≥24 hours. The mean within-subject SD values of diastolic blood pressures were 4.1, 2.7, and 3.6 mm Hg at 50, 75, and 100 W, respectively.

Statistical Analysis
Results are presented as mean±SEM or means with 95% CIs. Univariate and multivariate stepwise regression analyses were used to examine the association between blood pressure and the following potential cardiovascular risk factors: age, body mass index (BMI), smoking status, fitness score, serum cholesterol, triglycerides, HDL cholesterol, and insulin resistance. This analysis was performed for absolute values of blood pressure at rest and during exercise. Because homocysteine was measured in a subset of subjects, the association of blood pressure changes with homocysteine was
examined only by univariate analysis. ANOVA for repeated measures was used to test for differences in blood pressures between diabetic and control subjects. $P<0.05$ was considered significant.

**Results**

**Study 1: Relation Between Blood Pressure and Metabolic Characteristics in Healthy Nondiabetic Men**

During exercise, heart rate increased from $69 \pm 1.3$ bpm at rest to $93 \pm 1.4$, $106 \pm 1.5$, and $118 \pm 1.62$ bpm at 50, 75, and 100 W, respectively. Blood pressure increased from $122 \pm 1.0/80 \pm 0.2$ mm Hg at rest to $139 \pm 1.4/81 \pm 1.0$, $151 \pm 1.8/81 \pm 1.0$, and $164 \pm 1.9/81 \pm 1.0$ mm Hg at 50, 75, and 100 W. Resting values of systolic and diastolic blood pressures were not significantly correlated with serum cholesterol. Changes from resting values in systolic blood pressure during exercise were not significantly correlated with any of the risk factors examined.

Changes from resting values in diastolic blood pressure at all workloads were positively correlated with serum total cholesterol ($R=0.47$, $P<0.0001$ for each workload; Figure 1) and LDL cholesterol ($R=0.37$, $P<0.002$ for each workload). For each subject, the change from baseline in diastolic blood pressure remained approximately constant over the range of workloads studied, so values at 50 and 100 W were similar for subjects in both the highest and lowest quartiles of the distribution of serum cholesterol ($6.0 \pm 1.4$ and $5.5 \pm 2.0$ mm Hg at 50 and 100 W, respectively, for subjects in the top quartile versus $1.4 \pm 1.1$ and $2.8 \pm 1.5$ mm Hg at 50 and 100 W for subjects in the bottom quartile; Figure 2). The mean increase in diastolic blood pressure on exercise for all workloads was 2.9 mm Hg (95% CI, 1.8 to 4.1) per 1-mmol/L increase in total cholesterol. Univariate analysis also demonstrated a significant correlation between the change in diastolic blood pressure on exercise and serum total homocysteine at 50 W ($R=0.47$, $P<0.01$) and 75 W ($R=0.38$, $P<0.05$) but not at 100 W ($R=0.33$, $P<0.08$). Overall, across all workloads, the association with homocysteine was significant ($R=0.40$, $P<0.05$).

Stepwise multiple regression analysis demonstrated changes in diastolic blood pressure at all workloads to be independently correlated with serum cholesterol and insulin resistance but not with age, BMI, heart rate, fitness score, triglycerides, or HDL cholesterol. The correlation coefficient for the final model incorporating total cholesterol and insulin resistance was $R=0.58$ ($P<0.0001$) for the mean change in diastolic blood pressure from resting values at all workloads, with partial correlation coefficients of 0.43 and 0.37 for the correlations with serum cholesterol and insulin resistance, respectively. Absolute values of diastolic blood pressure at all workloads were also significantly correlated with serum cholesterol ($R=0.36$, $P<0.01$).

**Study 2: Comparison of Blood Pressure Responses in Men With Type 2 Diabetes and Nondiabetic Control Men**

Absolute values of systolic blood pressure at rest and the change from resting values in systolic blood pressure (at all workloads) did not differ significantly between diabetic and nondiabetic men. At all levels of exercise, the change from resting values in diastolic blood pressure was significantly greater in diabetic than in nondiabetic men ($11.8 \pm 1.6$ versus $2.4 \pm 2.1$ mm Hg at 50 W, $14.4 \pm 2.8$ versus $2.0 \pm 2.3$ mm Hg at 75 W, and $16.7 \pm 3.3$ versus $3.6 \pm 2.1$ mm Hg at 100 W; $P=0.002$ by ANOVA; Figure 3). The change from resting values in diastolic blood pressure was similar in the diabetic subjects treated with diet alone and those treated by diet plus oral hypoglycemic drugs. There was no significant correlation between the change in diastolic blood pressure and total cholesterol in the diabetic group.

**Discussion**

Most studies on blood pressure during exercise have focused on systolic blood pressure. An exaggerated increase in systolic blood pressure predicts development of future hyper-

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**Figure 1.** Relationship between serum total cholesterol and change from resting values in diastolic blood pressure (DBP) during exercise (mean change for all workloads) in 75 healthy active men ($R=0.5$, $P<0.0001$).

**Figure 2.** Change from resting values in diastolic blood pressure during exercise for men with serum total cholesterol in highest ($n=18$, solid bars) and lowest ($n=18$, open bars) quartiles of cholesterol distribution.
 tăng12 và là một phong kiến dự đoán của tử vong.13

Interpretation of systolic blood pressure measured at the brachial artery during exercise is complex because during exercise systolic pressure is greater than central aortic blood pressure by ≤80 mm Hg.14 This occurs as a result of the frequency-dependent transmission characteristics of the upper limb.15 The main findings in the present study relate to diastolic blood pressure during exercise. Unlike systolic blood pressure, diastolic pressure remains similar in brachial and central arteries during exercise. Diastolic blood pressure measurements during exercise, however, are rarely reported, perhaps because of concern about the accuracy of such measurements. Our verification studies demonstrate that diastolic blood pressure measurements taken at Korotkoff phase IV (as recommended by AHA guidelines11) by a trained observer are reproducible and in acceptable agreement with intra-arterial measurements.

Resting diastolic (or systolic) blood pressure in the healthy active men participating in this study was not significantly correlated to serum concentrations of total cholesterol or other lipids. This finding does not conflict with previous reports of a weak association between resting blood pressure and cholesterol, because our study had insufficient power to detect such an association. In contrast, the change in diastolic blood pressure on exercise was closely related to serum total cholesterol (and to LDL cholesterol), with diastolic blood pressure increasing during exercise in subjects with the highest concentrations of cholesterol and decreasing in those with the lowest concentrations. The strength of the association is striking considering the limited range of cholesterol values (3.0 to 7.7 mmol/L) in the subjects under study and the limited accuracy with which diastolic blood pressure can be determined during exercise. There is no possibility that observer bias was responsible for the observed association, because the observer was unaware of cholesterol values at the time of blood pressure measurement.

Diastolic blood pressure is determined mainly by cardiac output and peripheral vascular resistance.16 During exercise, cardiac output increases and peripheral vascular resistance decreases in response to vasodilation of resistance vessels within exercising skeletal muscle.16 An increase in diastolic blood pressure during exercise could therefore result from an inappropriately high cardiac output or impaired vasodilation of resistance vessels within skeletal musculature. Hypercholesterolemia is strongly associated with impaired reactivity to endothelium-dependent and, to a lesser extent, endothelium-independent vasodilators.1–4 Vasodilation of resistance vessels in muscle during exercise is influenced by several endothelium-derived and endothelium-independent mediators, including nitric oxide, prostaglandins, adenosine, and other metabolically linked vasodilators, such as potassium and hydrogen ions.17–20 Hypercholesterolemia may inhibit ≥1 of these vasodilator mechanisms and thus result in elevated diastolic blood pressure during exercise in hypercholesterolemic subjects. Effects of hypercholesterolemia on vascular reactivity have been demonstrated in small groups of subjects in whom basal vascular tone has not been elevated compared with normcholesterolemic control subjects.1–3 Thus, effects of hypercholesterolemia on basal tone, if any, may be less than those on vascular reactivity. This is consistent with the association we observed between serum cholesterol and the change in diastolic blood pressure during exercise rather than resting blood pressure.

Serum concentrations of triglycerides and HDL cholesterol were not associated with blood pressure changes during exercise. Insulin resistance, as measured simply by the fasting glucose–insulin product, was the only other factor besides total cholesterol that was independently associated with the change in diastolic blood pressure during exercise in the healthy nondiabetic men. Associations with BMI and age, which may be surrogates for insulin resistance, were nonsignificant when insulin resistance was included in the regression model. Although the correlation of the change in diastolic blood pressure on exercise with the fasting insulin–glucose product was not as strong as that with cholesterol, this may reflect the limited accuracy of the fasting glucose–insulin product as an estimate of insulin resistance. In patients with type 2 diabetes who were normotensive at rest, diastolic blood pressure increased to a greater extent during exercise than in nondiabetic control subjects. These patients were markedly insulin resistant compared with control subjects. Although an effect of sulfonylurea treatment on vasodilation mediated by ATP-dependent potassium channels is possible, it is unlikely in the present study, because sulfonylurea treatment was stopped 24 hours before the exercise study and blood pressure responses were similar in patients treated with and without sulfonylureas. It is also possible that physical changes in resistance arteries produced, for example, by advanced glycosylation end products could contribute to exercise diastolic hypertension in the diabetic patients. However, insulin resistance and the presence of type 2 diabetes are, like hypercholesterolemia, associated with markedly impaired vascular reactivity.21–23 which alone could account for the abnormal exercise blood pressure response we observed in these conditions. Hyperhomocysteinemia is also associated with impaired vascular reactivity,6 and it is notable that in a subset of 30 healthy volunteers, we found a significant association between the increase in diastolic blood pressure on exercise and serum total homocysteine. This association occurred despite the fact that most subjects had homocysteine levels within the accepted normal range. Thus, the association of exercise diastolic hyper-
tension with conditions in which vascular reactivity is impaired supports the concept that impaired vascular reactivity influences changes in systemic vascular resistance and hence diastolic blood pressure during exercise. Brachial artery systolic blood pressure during exercise is likely to be influenced primarily by stiffness of the aorta and frequency-dependent amplification in the upper limb. It will therefore be affected by changes in peripheral vascular resistance to a much lesser extent than diastolic pressure, consistent with the relative lack of association between changes in systolic blood pressure and metabolic factors influencing vascular reactivity observed in this study.

Insulin resistance is influenced by physical training and fitness. A difference in physical fitness between subjects could therefore be postulated to explain some or all of the associations we observed between changes in diastolic blood pressure during exercise and insulin resistance. However, we did not observe a significant association between changes in diastolic blood pressure and physical fitness score. Furthermore, the positive associations were observed at low workloads (mean heart rate at the lowest load, 93 ± 1.4 bpm) and were not explained by differences in heart rate between subjects. It is unlikely that the association of the increase in diastolic blood pressure on exercise in our group of healthy active men ranged from 71 to 136 bpm. Many adults spend much of their 10. Fiskerstrand T, Refsum H, Kvalheim G, Ueland PM. Homocysteine and 18. Wilson JR, Kapoor SC. Contribution of prostaglandins to exercise-induced vasodilation in humans. J Physiol. 1993;265:H171–H175.


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