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,1–4 and it has been hypothesized that an influence of cholesterol on vascular tone may affect blood pressure.4 Reviewing recent lipid-lowering trials, Goode et al5 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.5 Hypercholesterolemia may influence vascular reactivity to a greater degree than basal tone.1–3 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.6

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 score7 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; glipizide, 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-

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TABLE 1. Characteristics of Healthy Volunteers* Participating in Study 1

<table>
<thead>
<tr>
<th>Centiles</th>
<th>10</th>
<th>25</th>
<th>50</th>
<th>75</th>
<th>90</th>
<th>Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>28</td>
<td>31</td>
<td>35</td>
<td>39</td>
<td>46</td>
<td>36±7.9</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>22</td>
<td>24</td>
<td>25</td>
<td>27</td>
<td>29</td>
<td>25±2.9</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>110</td>
<td>115</td>
<td>122</td>
<td>128</td>
<td>132</td>
<td>122±8.7</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>70</td>
<td>76</td>
<td>80</td>
<td>86</td>
<td>88</td>
<td>80±7.1</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>3.9</td>
<td>4.6</td>
<td>5.1</td>
<td>6.0</td>
<td>6.4</td>
<td>5.2±1.0</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.0</td>
<td>1.2</td>
<td>1.4</td>
<td>1.6</td>
<td>1.8</td>
<td>1.4±0.3</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>1.8</td>
<td>2.4</td>
<td>3.1</td>
<td>3.8</td>
<td>4.3</td>
<td>3.1±0.9</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>0.7</td>
<td>1.0</td>
<td>1.2</td>
<td>2.0</td>
<td>2.9</td>
<td>1.6±0.9</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>4.0</td>
<td>5.0</td>
<td>7.0</td>
<td>11.0</td>
<td>15.0</td>
<td>8.4±4.6</td>
</tr>
<tr>
<td>Homocysteine, μmol/L</td>
<td>3.9</td>
<td>6.0</td>
<td>7.9</td>
<td>9.7</td>
<td>13.3</td>
<td>8.4±3.6</td>
</tr>
</tbody>
</table>

*All subjects were treated with diet; 65 were lifelong nonsmokers, 10 were smoking 10 to 40 cigarettes per day.
†Measured in 30 subjects.
‡P<0.05, †P<0.01 vs control subjects.

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

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

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 sphygmomanometry 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 6 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 the change from resting values in blood pressure during exercise and 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
Results

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

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

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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 systolic blood pressure was significantly greater in diabetic than in nondiabetic men (11.8±1.6 versus 2.4±2.1 mm Hg at 50 W, 14.4±2.8 versus 2.0±2.3 mm Hg at 75 W, and 16.7±3.3 versus 3.6±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-
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 \(\geq 1\) 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 normocholesterolemic 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-

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**Figure 3.** Change from resting values in diastolic blood pressure (DBP) during exercise in men with type 2 diabetes (n=10, solid bars) and nondiabetic control men (n=10, open bars).
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.\textsuperscript{5} 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.\textsuperscript{24} 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 with total and LDL cholesterol results from an influence of physical fitness both because of the lack of association with fitness score and because total cholesterol shows little relation to physical fitness.\textsuperscript{7} An influence of physical fitness arising from a mismatch between workload and workload graded according to fitness is effectively excluded by our observation that the increase in diastolic blood pressure on exercise was largely independent of workload and heart rate. Thus, the diastolic pressure increase at 50 W in those subjects in the highest quartile of the cholesterol distribution was greater than that at 100 W in subjects in the lowest quartile. Similarly, in diabetic subjects, the diastolic pressure increase at 50 W was greater than the diastolic pressure rise at 100 W in nondiabetic control subjects. Thus, although cycling at fixed workloads represents different levels of maximal aerobic capacity for different individuals, the observed changes in diastolic blood pressure were similar regardless of the weight, percentage of the maximal aerobic capacity or workload for each individual.

The increase in diastolic blood pressure during mild exercise with increasing serum cholesterol or insulin resistance is likely to be of clinical relevance. The increase in diastolic blood pressure on exercise in our group of healthy active men ranged from −12 to 16 mm Hg at the lowest workload when heart rates ranged from 71 to 136 bpm. Many adults spend much of their working day exercising at heart rates within this range,\textsuperscript{25} so the change in diastolic blood pressure associated with mild increases in serum cholesterol predicted from our data could be sufficient to have an important influence on the development of hypertensive complications, such as cerebrovascular or coronary artery disease.

In conclusion, we have demonstrated a strong association between physiological regulation of diastolic blood pressure during low-workload exercise and metabolic factors, serum cholesterol and insulin resistance, which influence vascular reactivity. This may contribute to the development of hypertensive complications in dyslipidemic insulin-resistant subjects.

References

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