Effects of Mild Exercise on Insulin Sensitivity in Hypertensive Subjects

Caroline Rhéaume, Paulo H. Waib, Yves Lacourcière, André Nadeau, Jean Cléroux

Abstract—Physical exercise increases insulin sensitivity in conditions associated with insulin resistance, such as obesity and diabetes, but little is known in this regard in hypertension. Whether postexercise changes in hemodynamics and/or changes in insulin-induced vasodilatation could contribute to a postexercise increase in insulin sensitivity in hypertensive subjects is unknown. We investigated the effects of acute physical exercise on insulin sensitivity in 10 hypertensive and 10 normotensive subjects during a control evaluation (CTRL), during lower body negative pressure (LBNP), after 30 minutes of mild bicycle exercise (POSTEX), and during LBNP after exercise (POSTEX + LBNP). Insulin-induced vasodilatation was assessed from peak forearm blood flow during the intravenous glucose tolerance test. Cardiac output (4.9±0.3 versus 5.3±0.4 L/min, mean±SEM) and insulin sensitivity (the glucose disappearance rate over insulin area under the curve: 0.91±0.07 versus 1.38±0.25 min⁻¹[pmol · L⁻¹]·minute) were lower (both \( P<0.05 \)) in hypertensive than in normotensive subjects, respectively. Cardiac output decreased during LBNP, increased during POSTEX, and was similar to control during POSTEX+LBNP in both groups. Insulin sensitivity was unchanged during LBNP, increased during POSTEX, and remained elevated during POSTEX+LBNP in hypertensive subjects, whereas it remained unchanged in normotensives. Peak forearm blood flow was significantly lower in hypertensive than in normotensives, despite higher insulin levels in hypertensives, and was not modified by LBNP or exercise. In conclusion, insulin sensitivity increases after exercise in hypertensive subjects, and the increase in cardiac output does not contribute to this effect. Endogenous insulin-induced vasodilatation is reduced in hypertensive subjects, and this insulin action is not affected by physical exercise. (Hypertension. 2002;39:989-995.)

Key Words: exercise ■ hypertension, essential ■ insulin ■ vasodilatation ■ blood flow ■ cardiac output

Physical exercise increases insulin sensitivity in subjects with insulin resistance as occurs in cases of obesity and diabetes. However, little is known of the effects of a single bout of exercise on insulin sensitivity in hypertensive subjects. It has been proposed that vascular changes associated with hypertension contribute to insulin resistance. As a consequence, the postexercise increase in cardiac output could favorably modify insulin sensitivity in hypertensive subjects. Therefore, the first goal of this study was to assess the effects of exercise on insulin sensitivity in hypertension and to determine the role, or lack thereof, of postexercise changes in hemodynamics on insulin sensitivity. For this reason we examined the relationship between hemodynamics and insulin sensitivity after exercise, both with and without the application of lower body negative pressure (LBNP), which decreases cardiac output. Thus, after exercise, application of LBNP reduced the postexercise vasodilatation in hypertensive and normotensive subjects.

From another perspective, it has been suggested that the vascular actions of insulin may increase glucose supply to the cell via a rise in blood flow. An increase in insulin-induced vasodilatation in skeletal muscles after exercise could therefore contribute to increased insulin sensitivity. Although insulin-induced vasodilatation has been reported to be reduced in hypertension, this issue remains controversial. Previous studies have mainly examined insulin-induced vasodilatation by infusing insulin over several hours, the physiological relevance of which has been questioned. The second goal of this study was to assess the effects of exercise on insulin-induced vasodilatation by using an approach involving the homeostatic release of endogenous insulin. We therefore used an intravenous glucose tolerance test to assess insulin sensitivity and to study the vascular actions of insulin on skeletal muscle blood flow after exercise in hypertension.

Methods

Patients with mild-to-moderate essential hypertension and control normotensive subjects gave their informed consent to participate in this study. The procedures followed were in accordance with our institutional guidelines and the protocol approved by Laval University Hospital Research Center’s ethics committee on human research. Antihypertensive medication was withdrawn 1 month before the study when appropriate. All subjects were evaluated in a randomized crossover design with 4 situations, 1 week apart: (1) control (CTRL),
Results

Ten hypertensive subjects (2 women, 8 men; clinic seated blood pressure 154±6/97±3 mm Hg) and 10 normotensive subjects (3 women, 7 men; clinic seated blood pressure 124±2/77±2 mm Hg) were evaluated in the present study. Hypertensive subjects tended to be older than normotensives (45±3 and 39±2 years, respectively, P=0.08) but body weight (80±3 and 78±4 kg), height (172±3 and 172±10 cm), body surface area (1.93±0.05 and 1.95±0.07 m²), and peak oxygen uptake (39±4 and 47±4 mL/kg per minute) were not different (all P=NS) between groups, respectively.

During the 30-minute exercise period, hypertensive and normotensive subjects exercised at a similar exercise intensity (50±1% and 51±1% of peak oxygen uptake), heart rate (112±5 and 122±3 b/min), and workload (93±15 and 114±11 Watts, P=NS).

Statistical Analysis

Data are expressed as means±SEM. Two-way analysis of variance (ANOVA) for repeated measurements was used for comparisons between normotensive and hypertensive subjects during the 4 evaluations. When a significant (P<0.05) F ratio was found, the Fisher exact test was used to locate significant differences.

An expanded Methods section can be found in an online data supplement available at http://www.hypertensionaha.org.

Hemodynamic Results

Hemodynamic variables were stable during 60 minutes of sham insulin sensitivity assessment. For illustrative purposes, during CTRL, forearm blood flow 20-minute averages were 3.6±0.4, 3.5±0.5, and 3.7±0.5 mL/(dL·min⁻¹), and cardiac output duplicate averages every 20 minutes were 6.3±0.7, 6.0±0.5, and 6.4±0.8 L/min (P=NS for time effect). During LBNP, values were lower than during CTRL (P<0.05) and similarly stable (data not shown).

Supine blood pressure and heart rate during the evaluations appear in Table 1. Systolic blood pressure did not change during the different evaluations compared with CTRL, whereas diastolic blood pressure and heart rate increased significantly during LBNP and POSTEX+LBNP in both groups of subjects. Cardiac output (Figure 2) and forearm blood flow (Figure 3) were lower in hypertensive than in normotensive subjects (P<0.05). Cardiac output was reduced during LBNP, increased during POSTEX, and unchanged during POSTEX+LBNP compared with CTRL in both groups. Forearm blood flow was reduced during LBNP and POSTEX+LBNP in both groups. Forearm blood flow increased POSTEX compared with CTRL in normotensive, but not in hypertensive subjects.

During all evaluations, forearm blood flow increased significantly 2 minutes after the glucose bolus, but consistently to a lesser extent in hypertensive than in normotensive subjects (Figure 3). The highest single blood flow, or peak blood flow, was also smaller in hypertensives (Table 2, Figure 4). Similarly, peak forearm vascular conductance was significantly lower in hypertensive than in normotensive subjects (Table 2). At peak blood flow, heart rate increased by ∼5 to 10 b/min (P<0.05), systolic blood pressure remained stable (P=NS), and diastolic pressure was reduced by ∼5 to 10 mm Hg (P<0.05) (Table 2, Figure 4). Blood flow returned

Figure 1. Illustration of study protocol. The subjects were evaluated on 4 occasions in random order: (1) during a control study after 30 minutes of seated rest (CTRL), (2) during lower body negative pressure after seated rest (LBNP), (3) after 30 minutes of exercise (POSTEX), and (4) after exercise during lower body negative pressure (POSTEX+LBNP). Blood pressure was measured continuously beat by beat. Forearm blood flow was measured 1.5 minutes out of every 2 minutes throughout the evaluation. CO indicates cardiac output.
faster to baseline in hypertensive than in normotensive subjects (within 4 versus 6 minutes, respectively, \( P<0.05 \)). This was accompanied by a reduction in forearm vascular conductance and a rise in systolic blood pressure of \( \pm 15 \) to \( 25 \) mm Hg (\( P<0.05 \)) that started \( \pm 1.5 \) minutes after the glucose bolus, during which diastolic pressure and heart rate returned to baseline (Table 2, Figure 4). Blood pressure remained elevated longer in hypertensive than in normotensive subjects. However, the duration of this pressor response was reduced in both groups after exercise (Table 2).

**Metabolic Results**

Baseline plasma glucose was higher in hypertensives than in normotensives (mean of 4 evaluations: \( 5.3\pm0.1 \) versus \( 5.1\pm0.1 \) mmol/L, respectively, \( P<0.05 \)), whereas baseline insulin was not significantly different (\( 55\pm4 \) and \( 49\pm3 \) pmol/L, respectively, \( P=NS \)). Between 2 and 8 minutes after the glucose bolus, plasma glucose increased to higher levels in hypertensive than in normotensive subjects (\( P<0.05 \)), but similar levels were found thereafter in both groups (Figure 5). The glucose disappearance rate (\( K_g \)) was unchanged in the different situations and was similar in hypertensive and normotensive subjects (mean values: \( 1.7\pm0.2 \) and \( 1.5\pm0.2 \) \( \text{min}^{-1} \), \( P=NS \)) (Figure 5). Plasma insulin levels and insulin areas under the curves (\( I_{\text{AUC}} \)) were significantly higher in hypertensives than in normotensives during the intravenous glucose tolerance test (mean \( I_{\text{AUC}} \) values: \( 17\,894\pm2479 \) versus \( 12\,399\pm1586 \) pmol/L · minute, \( P<0.001 \)) (Figure 6).

The index of insulin sensitivity (\( K_g/I_{\text{AUC}} \)) was significantly lower in hypertensive than in normotensive subjects during

**TABLE 1. Supine Blood Pressure and Heart Rate in Normotensive and Hypertensive Subjects During the Different Evaluations**

<table>
<thead>
<tr>
<th>Evaluation/Variables</th>
<th>CTRL</th>
<th>LBNP</th>
<th>POSTEX</th>
<th>POSTEX+LBNP</th>
<th>Group Situation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NT</td>
<td>HT</td>
<td>NT</td>
<td>HT</td>
<td>NT</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>112±2</td>
<td>133±4†††</td>
<td>112±3</td>
<td>137±8†††</td>
<td>112±2</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>73±2</td>
<td>85±3†††</td>
<td>77±1*</td>
<td>93±4*†††</td>
<td>78±1</td>
</tr>
<tr>
<td>HR (b/min)</td>
<td>59±3</td>
<td>63±4</td>
<td>64±4*</td>
<td>67±4*</td>
<td>63±3</td>
</tr>
</tbody>
</table>

Values are mean ± SEM of measurements between 1 minute and 20 minutes before glucose bolus and between 20 and 50 minutes after the glucose bolus. Blood pressure and heart rate were similar during these two periods (\( P=NS \), data not shown). These values were taken to exclude measurements during the glucose bolus and up to 20 minutes thereafter when blood pressure and heart rate were found to change. Data shown therefore represent mean blood pressure and heart rate over 1.5 hours after exercise or the control rest period, with or without LBNP. ANOVA probability levels for group effect (HT, NT) and situation effect (CTRL, LBNP, POSTEX, POSTEX+LBNP) are indicated at right. CTRL indicates control evaluation; LBNP, lower body negative pressure; POSTEX, postexercise; POSTEX+LBNP, application of lower body negative pressure after exercise; NT and HT, normotensive and hypertensive subjects; SBP and DBP, systolic and diastolic blood pressure (mm Hg); HR, heart rate (b/min).

*Significant differences at \( P<0.05 \) from respective control value.
†††Significant differences at \( P<0.001 \) from respective value in normotensive subjects.

**Figure 2.** Cardiac output before the glucose bolus and 40 to 50 minutes after the glucose bolus during CTRL, LBNP, POSTEX, and POSTEX+LBNP evaluations in normotensive (NT, top) and hypertensive subjects (HT, bottom). Cardiac output was significantly lower in HT than in NT subjects (ANOVA, \( P<0.05 \)). \( *P<0.05 \) and \( **P<0.01 \) indicate significant differences versus CTRL.

**Figure 3.** Lines graphs illustrate forearm blood flow (FBF) at baseline (B) and during the intravenous glucose tolerance test in normotensive (NT, top) and hypertensive subjects (HT, bottom) during CTRL, LBNP, POSTEX, and POSTEX+LBNP evaluations. FBF was significantly lower in HT than in NT subjects (ANOVA, \( P<0.05 \)). Insets: bar graphs illustrate areas under the curves of FBF x time (FBF\(_{\text{AUC}}\)). *Significant differences versus CTRL at \( P<0.05 \). Statistical analysis of data in line graphs yielded the same conclusions as analysis of areas under the curves, and these data are therefore not indicated.
Insulin Sensitivity and Postexercise Hemodynamics

According to the hemodynamic hypothesis of insulin resistance in hypertension, vascular changes associated with hypertension modify skeletal muscle circulation and reduce glucose access to the muscle to contribute to the insulin resistance.6,7 A corollary of this theory is that an increase in skeletal muscle blood flow could increase insulin sensitivity, an assumption that is supported by some studies but not by others.9,10 In the present study, several observations indicate that the increase in insulin sensitivity in hypertensive subjects after exercise was not related to changes in hemodynamics: (1) cardiac output and forearm blood flow (mainly to skeletal muscle) were reduced by application of LBNP, but insulin sensitivity remained unaffected; (2) cardiac output was increased after exercise but superimposition of LBNP during the postexercise period canceled this effect without altering the positive effects of exercise on insulin sensitivity; (3) forearm blood flow was not increased in hypertensive subjects after exercise but was reduced by superimposition of LBNP during the postexercise period, whereas insulin sensitivity remained elevated in both conditions. Postexercise changes in hemodynamics are therefore not likely to contribute importantly to the observed increase in insulin sensitivity in hypertensive subjects. Other mechanisms, such as skeletal muscle contraction-induced increase in glucose transport proteins (GLUT 4) together with exercise-induced increase in insulin-stimulated GLUT4 translocation to the membrane, are more likely to be involved in this observation.14 Our findings therefore do not support the hemodynamic hypothesis of insulin resistance in hypertension.

Insulin sensitivity did not increase after exercise in normotensive subjects in the present study, in agreement with the CTRL evaluation (Figure 7). In hypertensive subjects, insulin sensitivity increased significantly POSTEX and POSTEX+LBNP but remained unchanged during LBNP compared with CTRL (Figure 7). In normotensive subjects, insulin sensitivity did not change significantly during the various maneuvers. Thus, during POSTEX and POSTEX+LBNP, insulin sensitivity was no longer different between the 2 groups of subjects (Figure 7).

Relationships Between Hemodynamic and Metabolic Results

In normotensive subjects, the increase in forearm blood flow at peak value correlated positively with the increase in insulin measured 2 minutes after the end of the glucose bolus during CTRL (r=0.75, P=0.013), LBNP (r=0.85, P=0.002), but not during POSTEX (r=0.51, P=0.1) or POSTEX+LBNP (r=0.36, P=0.31). These correlation coefficients were not significant in hypertensive subjects (range 0.14 to 0.43, P=NS).

Discussion

The results of the present study indicate firstly that a single bout of mild physical exercise normalized the reduced insulin sensitivity in hypertensive subjects and that the change in insulin sensitivity was not related to postexercise hemodynamics. Secondly, our results suggest that endogenous insulin-induced vasodilatation in skeletal muscle is reduced in hypertensive compared with normotensive subjects and that exercise does not modify this response. These findings will be addressed in turn in the following sections.
several,1,20–22 but not all, earlier reports.2,23,24 These different findings may be related to several factors including exercise protocols and, specifically, exercise intensity. A mild exercise intensity was used in the present study and in those that did not report a change in insulin sensitivity,1,20–22 whereas a higher intensity, ie, above 70% VO2 max, was typically used in the studies that reported an increase in insulin sensitivity.2,23,24 Thus, exercise intensity may be involved in these discrepancies.

Endogenous Insulin and Forearm Vasodilatation

A brief vasodilatation occurred in the forearm shortly after glucose injection when insulin peaked. This appears to be the first report of an acute short-lived vasodilatation associated with an increase in insulin concentration. Vasodilatation has previously been reported to occur only after 1 to 2 hours of insulin perfusion, a phenomenon whose physiological relevance has been questioned,14 or between 1 and 2 hours after an oral glucose tolerance test.25 In the study of Egan and Stepniakowski,25 forearm blood flow was either unchanged or reduced during the first hour after oral glucose, although plasma insulin increased. Changes in blood flow at this time could reflect a changing balance between splanchnic and peripheral blood flow during glucose absorption. In the present study, insulin levels at peak blood flow are comparable to those associated with vasodilatation during systemic insulin infusion (=600 pmol/L) (Capaldo and Saccà26). In addition, changes in forearm blood flow correlated with those in insulin levels in normotensive subjects. We therefore interpret these findings as evidence of endogenous insulin-induced vasodilatation in skeletal muscle.

In our hypertensive subjects, peak blood flow was reduced compared with normotensives although insulin levels were greater. Furthermore, insulin levels did not correlate with peak blood flow in these subjects. This suggests that the hemodynamic effects of insulin are altered in hypertension. These results agree with those of Baron and colleagues27 who reported a reduced insulin-induced vasodilatation in insulin-resistant (obese) subjects compared with insulin-sensitive subjects. Nevertheless, studies in hypertensive patients could not find a reduced insulin-induced vasodilatation13 apart from one notable exception.12 However, these studies used exogenous insulin infusion to assess the effects of insulin. The results of our study appear to be the first to demonstrate that the effects of endogenous insulin on skeletal muscle blood flow is attenuated in hypertensive, compared with normotensive, subjects. Insulin-induced vasodilatation was not changed during the different evaluations in either group, indicating that a change in this action of insulin is not involved in the postexercise increase in insulin sensitivity in hypertensive subjects.

A vasoconstriction that was greater and longer in hypertensive subjects was observed within the minute following the brief vasodilatation. The extent to which this vasoconstriction is mediated by a central action of insulin and/or arterial and cardiopulmonary baroreflexes, which are altered

![Figure 4. Representative tracing showing forearm blood flow, heart rate, and blood pressure in one normotensive subject (top) and one hypertensive subject (bottom) before the glucose bolus (Baseline), at peak forearm blood flow, peak blood pressure, and 5 minutes after the end of the glucose bolus (Recovery) during CTRL.](http://hyper.ahajournals.org/doi/fig/10.1161/HYP.0b013e3181c1a9a0)
in hypertension,\textsuperscript{28} cannot be assessed by the present study. Prior exercise reduced the duration of the increase in blood pressure in both groups. Thus, our results suggest (1) that insulin-induced vasodilatation is reduced in hypertensive subjects, (2) that this vasodilatation triggers a reflex increase in blood pressure that lasts longer in hypertensive subjects, and (3) that exercise does not affect insulin-induced vasodilatation but reduces the duration of the subsequent vasoconstriction in both groups of subjects.

Relationships With Other Studies

Several studies, including our own,\textsuperscript{8} have indicated that physical exercise induced a significant antihypertensive effect for several hours.\textsuperscript{29} We earlier found that blood pressure decreased and that forearm blood flow increased only in hypertensive subjects after exercise,\textsuperscript{8} whereas blood pressure was unchanged after exercise in both groups (NT: 112±2/73±2 mm Hg at rest versus 112±3/78±1 mm Hg after exercise; HT: 133±4/85±3 at rest versus 131±5/84±3 mm Hg after exercise, P=NS) and blood flow increased in normotensive subjects in the present study. This discrepancy could be related to the intravenous glucose tolerance test in the present study although hemodynamic variables were stable and similar to baseline values outside of acute events surrounding glucose infusion. It should be noted that forearm blood flow increased by a similar amount in both studies in normotensive subjects (0.2 mL/dL per minute, significantly so only in the present study probably because of more frequent measurements) and that changes in blood pressure and in forearm blood flow are consistent in hypertensive subjects in both studies.

Jamerson et al\textsuperscript{30} reported that thigh cuff inflation at 40 mm Hg, resulting in blood pooling in the legs similar to the effects of LBNP in the present study, produced insulin resistance. In the present study, LBNP-induced reductions in blood flow did not affect insulin sensitivity. We used an intravenous glucose tolerance test algorithm that relies on compensatory hyperinsulinemia to assess insulin sensitivity. In this setting, the reduction in blood flow during LBNP will be offset by the increased arterio-venous glucose difference as the Fick principle would predict for freely diffusible molecules. Jamerson et al\textsuperscript{30} used an intra-arterial insulin infusion in the forearm, which increased baseline blood flow and could have disrupted this homeostatic relationship.

In conclusion, a single bout of mild exercise increases insulin sensitivity in hypertensive subjects, and increases in cardiac output or in forearm blood flow do not contribute importantly to this effect. Our results further indicate that endogenous insulin-induced vasodilatation is reduced in hypertensive subjects but is not affected by physical exercise.
suggested that it does not contribute to the increase in insulin sensitivity after exercise. These findings therefore do not support the hemodynamic hypothesis of insulin resistance in hypertension.

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References
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