Effects of Intense and Prolonged Exercise on Insulin Sensitivity and Glycogen Metabolism in Hypertensive Subjects

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Background—The information that insulin sensitivity and glycogen synthesis are reduced in hypertension arises primarily from studies using insulin infusions. Whether glycogen metabolism is actually altered in a physiological condition, such as during and after prolonged exercise, is currently unknown.

Methods and Results—To examine this issue, 9 hypertensive and 11 normotensive subjects were evaluated on a rest day and after intense and prolonged exercise on a separate day. Insulin sensitivity and hemodynamic variables were measured on both days. On the exercise day, whole-body substrate utilization was assessed and muscle biopsies were taken in the leg at baseline, immediately after exercise, and 2.5 and 4 hours after exercise. Insulin sensitivity at rest was lower in hypertensive than normotensive subjects \( (P<0.05) \) and increased after exercise in normotensive \( (P<0.01) \) but not in hypertensive \( (P=NS) \) subjects. Leg blood flow increased after exercise in both groups but to a lesser extent in hypertensive than normotensive subjects. Baseline glycogen content and maximal glycogen synthase activity were higher in hypertensive than normotensive subjects \( (P<0.001) \). Glycogen concentration decreased relatively less \( (35\% \text{ versus } 66\%) \) and returned to baseline levels faster in hypertensive subjects after exercise. Hypertensive subjects used \( =40\% \) less carbohydrates during exercise \( (P<0.001) \) at the expense of greater free fatty acid oxidation.

Conclusions—It is concluded that increased intramuscular glycogen storage and resynthesis in hypertension are independent of blood flow and may represent compensatory mechanisms for the reduced insulin sensitivity and carbohydrate metabolism in this condition. (Circulation. 2003;108:2653-2659.)

Key Words: exercise ■ insulin ■ glycogen ■ hypertension

Several epidemiological studies have indicated that hypertension is an insulin-resistant state independent of obesity.\(^1,2\) It has been shown that whole-body insulin-induced glucose uptake is reduced in hypertensive populations.\(^3,4\) The impairment of insulin-mediated glucose utilization in hypertension appears to be restricted principally to nonoxidative glucose disposal, ie, mainly glycogen synthesis in skeletal muscles.\(^5,6,7\) Defects in this pathway can alter the metabolism of glucose and contribute to insulin resistance in muscle tissue.\(^9\) Studies using intra-arterial infusions of insulin in the forearm have found smaller arteriovenous glucose differences in hypertensive than in normotensive subjects,\(^10\) suggesting that glycogen synthesis in skeletal muscles is lower in hypertensive patients, but the physiological relevance of these findings has not been clearly established.

It was proposed that the pervasive relationship between blood pressure elevation and decreased glucose extraction by skeletal muscle may be secondary to hemodynamic factors.\(^11,12\) Insulin-induced glucose uptake during a hyperinsulinemic euglycemic clamp was positively correlated to capillary density and to percent slow-twitch fiber content of different muscles.\(^13\) Slow-twitch fibers have a higher oxidative capacity, insulin binding, insulin sensitivity, basal glucose uptake, and a rich capillary supply than fast-twitch fibers.\(^14,15\) Because a reduced proportion of slow-twitch fibers was reported in hypertensive individuals,\(^16\) this alteration could contribute to the increased insulin resistance in hypertension.\(^17,18\) These observations are consistent with the concept that insulin sensitivity could be related to skeletal muscle blood flow and relative muscle fiber type.

We recently reported that changes in hemodynamics did not contribute to the increased insulin sensitivity found after 30 minutes of mild exercise in hypertensive subjects.\(^19\) In the present study, we used a more prolonged and intense exercise...
protocol to reduce intramuscular glycogen content. We also examined exercise substrate metabolism and postexercise hemodynamics, insulin sensitivity, and glycogen resynthesis in hypertensive and normotensive subjects. The primary goals of the present study were therefore to determine whether the insulin-resistant state of hypertension was associated with altered intramuscular glycogen stores and/or substrate utilization during exercise as well as slower rates of glycogen resynthesis after prolonged exercise. Secondary goals were to determine the role of skeletal muscle fiber type distribution, blood flow, and glycogen synthase activity in any alteration in glycogen synthesis in hypertension.

Methods

Patients with mild to moderate essential hypertension and age-matched normotensive subjects gave their written 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. All hypertensive subjects underwent a 4-week screening period during which they visited the Hypertension Clinic at our institution weekly, and antihypertensive medication was stopped 1 month before the study in previously treated patients. Peak oxygen uptake was measured 1 week before the laboratory evaluations.

The subjects underwent 2 evaluations on separate days at 1-week intervals in random order (Figure 1). On the control rest day and on the exercise day, insulin sensitivity and hemodynamic variables were measured in subjects fasting from midnight on. Hemodynamic variables measured were blood pressure, heart rate, forearm blood flow, and leg blood flow. On the exercise day, whole-body carbohydrate and lipid metabolisms were assessed during exercise, and muscle biopsies were taken together with hemodynamic measurements at baseline, immediately after exercise, and 2.5 and 4 hours after exercise (Figure 1). All subjects exercised on a cycle ergometer at ~70% of $V_{\text{Omax}}$ during 90 minutes. Muscle biopsies were made before exercise, immediately after exercise, and 2.5 and 4 hours after exercise. An intravenous glucose bolus was given on control rest day, 0.5 hour after end of exercise, and 3 hours after end of exercise.

Figure 1. Illustration of study protocol. Insulin sensitivity and hemodynamic variables were measured (1) on a control rest day and (2) on an exercise day in random order. On exercise day, all subjects exercised on a cycle ergometer at ~70% of $V_{\text{Omax}}$ during 90 minutes. Muscle biopsies were made before exercise, immediately after exercise, and 2.5 and 4 hours after exercise. 

Measurements

Oxygen uptake and carbon dioxide production were determined by analysis of expired gases. These values were used to calculate the respiratory exchange ratio to assess amounts of carbohydrates and fatty acids consumed during exercise. Peak oxygen uptake was measured during an increased work test. Hemodynamics, insulin sensitivity, and glycogen resynthesis were measured in specific fiber types was determined by staining transverse sections with periodic acid–Schiff reagent. Glycogen-stained sections were matched with serial sections stained for myosin ATPase for determination of exercise-induced depletion patterns in specific fiber types. Glycogen concentrations are expressed in relative units (RU) of staining intensity. Glycogen content was also measured by calculating an index that takes into account the amount of glycogen (RU) in each fiber type, the surface area (µm²) of each fiber type, and the proportion (percentage) of each fiber type with the following equation: [(glycogen type IA×surface type IA×fiber type IA)+ (glycogen type IIA×surface type IIA×fiber type IIA)+(glycogen type IIB×surface type IIB×fiber type IIB)]×10⁻⁶.

Glycogen synthase activity was measured as described by Schalin-Jantti et al., a modification of the method of Hornbrook et al. Glycogen synthase activity is expressed in micromoles of NAD formed per minute per gram wet weight of muscle tissue. Glycogen synthase activity was measured at 0.1 mmol/L of G6P substrate and at 10 mmol/L of G6P substrate. The ratio of activity determined at 0.1 mmol/L of G6P to maximal activity determined at 10 mmol/L of G6P (the fractional activity) reflects dephosphorylation and activation of glycogen synthase.

Statistical Analysis

Data are expressed as mean±SEM. Results were analyzed by ANOVA for repeated measurements considering the interaction between time (of measurement of a given variable) and group (hypertensive and normotensive). When a significant ($P<0.05$) F ratio was found, Fisher’s test was used to locate significant differences.

Results

Nine male hypertensive subjects with mild to moderate hypertension and 11 normotensive subjects participated in this study. Hypertensive subjects were similar to normotensive and hypertensive subjects.
TABLE 1. Hemodynamic Variables Before Exercise (Baseline), Immediately After Exercise, and 2.5 and 4 Hours After Exercise in Normotensive and Hypertensive Subjects During the Exercise Day

<table>
<thead>
<tr>
<th>Time/Variables</th>
<th>Baseline</th>
<th>Immediately After</th>
<th>2.5 Hours After Exercise</th>
<th>4 Hours After Exercise</th>
<th>Group</th>
<th>Time</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>NT</td>
<td>HT</td>
<td>NT</td>
<td>HT</td>
<td></td>
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<tr>
<td>SBP</td>
<td>117±3</td>
<td>142±4†††</td>
<td>109±4*</td>
<td>130±3*†††</td>
<td></td>
<td></td>
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<tr>
<td>DBP</td>
<td>75±2</td>
<td>93±3†††</td>
<td>68±4*</td>
<td>85±3†††</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>62±2</td>
<td>62±2</td>
<td>79±3***</td>
<td>78±2***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FBF</td>
<td>4.0±0.7</td>
<td>4.0±0.3</td>
<td>3.5±0.5</td>
<td>3.2±0.2†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LBF</td>
<td>2.5±0.3</td>
<td>2.8±0.1</td>
<td>3.0±0.2*</td>
<td>2.7±0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVR</td>
<td>26.9±3.1</td>
<td>28.0±1.9</td>
<td>25.6±2.3</td>
<td>33.5±3.2†</td>
<td></td>
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<tr>
<td>LVR</td>
<td>39.6±4.0</td>
<td>39.8±0.3</td>
<td>28.4±2.0*</td>
<td>38.1±2.5†††</td>
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<td></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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</tr>
<tr>
<td></td>
<td>0.001</td>
<td>0.030</td>
<td>0.01</td>
<td>0.043</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NT and HT indicate normotensive and hypertensive subjects; SBP and DBP, systolic and diastolic blood pressure (mm Hg); HR, heart rate (bpm); FBF, forearm blood flow (mL·min⁻¹·10⁻³); LBF, leg blood flow (mL·min⁻¹·10⁻³); FVR, forearm vascular resistance (units); and LVR, leg vascular resistance (units). Values are mean±SEM of 11 normotensive and 9 hypertensive subjects. ANOVA probability levels for group effect (HT, NT) and time effect (baseline, immediately after exercise, 2.5 hours, and 4 hours after exercise) are indicated at right. * *, †, and ††† indicate significant differences at P<0.05, P<0.01, and P<0.001 from respective control value. ††, †††, and †††† indicate significant differences at P<0.05, P<0.01, and P<0.001 from respective value in normotensive subjects.

178±2 cm², body surface area (2.0±0.1 and 2.0±0.1 m²), and peak oxygen uptake (45±3 and 43±2 mL/kg per minute). Clinic supine blood pressure of hypertensive subjects was higher than that of normotensive subjects (124±4/93±3 and 117±3/75±2 mm Hg, respectively, P<0.001). Four hypertensive subjects (44%) and 6 normotensive subjects (55%) had a normal glucose tolerance on the basis of a glucose disappearance rate (K₇₀) >1.5 min⁻¹, 3 hypertensive subjects (33%) and 5 normotensive subjects (45%) had an intermediate glucose tolerance (1.0<K₇₀<1.5 min⁻¹), and 2 hypertensive subjects (22%) had glucose intolerance (K₇₀<1.0 min⁻¹).

During the 90-minute exercise period, hypertensive and normotensive subjects exercised at similar workloads (135±5 and 152±9 W, respectively, P=NS), oxygen uptake (25±12 and 25±12 mL/kg per minute), and percent peak oxygen uptake (68±2 and 73±2%, P=NS). Hypertensive subjects had a significantly lower respiratory exchange ratio than normotensives (0.80±0.01 versus 0.87±0.01, respectively, P<0.001), indicating that they used ≈40% less carbohydrates over the 90-minute exercise period (102±10 versus 174±11 g, P<0.001) at the expense of greater free fatty acid oxidation (76±5 versus 49±4 g, P<0.001). Thus, 40% and 67% of the energy cost of exercise (~1250 kcal) was derived from carbohydrate metabolism in hypertensive and normotensive subjects, respectively, and 60% and 33% from free fatty acid oxidation.

Hemodynamic Results
Hemodynamic variables measured on the exercise day appear in Table 1 (baseline hemodynamic variables measured on the control rest day were similar, P=NS, data not shown). Blood pressure was higher in hypertensive than normotensive subjects (P<0.001). Systolic and diastolic blood pressures were significantly lower immediately after exercise than at baseline in both groups. Diastolic blood pressure was reduced 2.5 and 4 hours after exercise in normotensive but only in 2.5 hours in hypertensive subjects. Heart rate was similar in both groups, and the small tachycardia after exercise was similar in both groups (P=NS). Forearm and leg blood flows were respectively similar in both groups (P=NS). Forearm blood flow decreased significantly immediately after exercise and 2.5 and 4 hours after exercise in hypertensives, whereas it remained unchanged in normotensives compared with baseline (P<0.05). Leg blood flow increased only 2.5 hours after exercise (P<0.05) in hypertensives but had already done so immediately after exercise in normotensives. Reciprocal changes in vascular resistance relative to those in blood flow were found in both groups.

Metabolic Results
Insulin Sensitivity
Baseline plasma glucose was not different in hypertensive and normotensive subjects on the control rest day (5.4±0.2 and 5.2±0.2 mmol/L, respectively, P=NS) and on the exercise day (5.2±0.2 and 5.0±0.1 mmol/L, respectively, P=NS), whereas baseline plasma insulin was higher in hypertensives than normotensives on the control rest day (60±5 and 50±4 pmol/L, respectively, P<0.05) and the exercise day (70±10 and 31±5 pmol/L, respectively, P<0.01). At the end of 90 minutes of intense exercise, glycemia was unchanged in hypertensive subjects (5.4±0.3 mmol/L, P=NS) but was significantly reduced in normotensives (4.6±0.2 mmol/L, P<0.05). Insulinemia was reduced at the end of exercise in both groups, but to a lesser extent in hypertensive than normotensive subjects (42±8 and 16±2 pmol/L, respectively, both P<0.01). At the beginning of insulin sensitivity assessment (before the glucose bolus), glucose and insulin levels were not different (P=NS) from baseline values in each group (data not shown).

Insulin sensitivity (K₇₀/AUC) was significantly lower in hypertensive than normotensive subjects on the control rest day (Figure 2). Insulin sensitivity increased after exercise in normotensive subjects but not in hypertensive subjects (Figure 2). Glucose disappearance rate (K₇₀) was similar in hypertensive and normotensive subjects on the control rest day (1.6±0.3 and 1.7±0.1 min⁻¹, respectively, P=NS) but was significantly lower in hypertensive than normotensive
subjects after exercise (1.3±0.3 and 1.9±0.3 min⁻¹, respectively, P<0.05). Plasma insulin levels and IAUCs were similar in both groups during the intravenous glucose tolerance test on the control rest (IAUC values: HT, 14 578±2604 versus NT, 10 561±1348 pmol/L×min, P=NS) but were significantly higher in hypertensives than in normotensives after exercise (IAUC values: HT, 13 007±2091 and NT, 8 405±965 pmol/L×min, P<0.05).

Glucosuria measured over a period of 2 hours after the glucose bolus was not different in hypertensive and normotensive subjects (control rest day values: 2.3±0.5 and 2.1±0.2 g, respectively, P=NS) and was not affected by the previous exercise (P=NS).

Muscle Characteristics and Glycogen Content

The proportion, the surface area of different fiber types, and the number of capillaries around the different muscle fibers were similar in both groups of subjects (Table 2). Fasting muscle glycogen concentration in each fiber type (Figure 3) and the index of whole muscle glycogen content (Table 3) were higher in hypertensive than normotensive subjects (P<0.001). Glycogen content decreased immediately after exercise in both groups (P<0.05). Muscle glycogen tended to decrease less in hypertensives (−34±8 versus −46±7 RU, P=0.13), and this represented a significantly smaller proportion of muscle glycogen reserves in hypertensive than normotensive subjects (−35±8 versus −66±8%, P<0.01). Whereas glycogen remained below baseline up to 4 hours after exercise in normotensive subjects, it increased back to levels not different from baseline in hypertensive subjects 4 hours after exercise (Table 3 and Figure 3).

Glycogen Synthase

Glycogen synthase measured at 0.1 mmol/L of G6P was not different between groups (P=0.89) and increased to a similar extent after exercise in both groups (P<0.001) (Figure 4). Total glycogen synthase measured at 10 mmol/L of G6P substrate was higher in hypertensive than normotensive subjects.

### Figure 2

Line graphs illustrate individual insulin sensitivities measured on control rest day and after exercise in normotensive (NT) and hypertensive (HT) subjects. Circles lying outside individual data points represent mean±SEM. ** indicates significant differences at P<0.01 from respective control value; † and †† indicate significant differences at P<0.05 and P<0.01 from respective value in normotensive subjects.

### Figure 3

Glycogen content (RU) of type I fibers (A), type IIa fibers (B), and IIb fibers (C) at baseline (Base), immediately after exercise (0), and 2.5 and 4 hours after exercise. ††† indicates significant differences (ANOVA) at P<0.001 between hypertensive and normotensive subjects.

### Table 2. Muscle Characteristics of Hypertensive and Normotensive Subjects

<table>
<thead>
<tr>
<th>Fibers Type/Variables</th>
<th>Type I</th>
<th>Type IIA</th>
<th>Type IIB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NT</td>
<td>HT</td>
<td>NT</td>
</tr>
<tr>
<td>Proportion, %</td>
<td>44±3</td>
<td>43±4</td>
<td>40±4</td>
</tr>
<tr>
<td>Surface area, μm²×10⁷</td>
<td>5.6±0.4</td>
<td>6.8±0.4</td>
<td>6.7±0.6</td>
</tr>
<tr>
<td>Capillaries, n</td>
<td>5.1±0.3</td>
<td>5.9±0.5</td>
<td>5.0±0.3</td>
</tr>
</tbody>
</table>

Values are mean±SEM of 11 male normotensive (NT) and 9 male hypertensive (HT) subjects. All variables were similar in hypertensive and normotensive subjects (P=NS).
subjects and was not affected by exercise ($P=\text{NS}$). As a consequence, the fractional activity of glycogen synthase increased after exercise in both groups ($P<0.001$) but to a lesser extent ($P<0.001$) in hypertensive subjects (Figure 4).

**Relationships Between Hemodynamic and Metabolic Results**

Insulin sensitivity did not correlate with percent composition of muscle fiber type I in both groups ($r=0.23$, $P=0.33$). Glycogen content index did not correlate with leg blood flow in any situation (data not shown). A significant and inverse correlation coefficient was found between insulin sensitivity and maximal glycogen synthase activity after exercise ($r=0.47$, $P<0.05$) but not before exercise ($r=0.05$, $P=\text{NS}$).

**Discussion**

The results of our study clearly show, first, that whole-body carbohydrate utilization is reduced, that skeletal muscle glycogen depletion is blunted, and that its repletion is more pronounced after prolonged exercise in hypertension. Baseline and postexercise glycogen contents were higher in hypertensive subjects. Second, total glycogen synthase activity is higher in hypertensive than normotensive subjects. Third, similar muscle capillaries and muscle fiber type distributions were found in both groups. These observations will be discussed in the following paragraphs.

The present results confirm that hypertensive subjects are insulin-resistant compared with normotensive subjects.

Studies using insulin infusions have indicated that skeletal muscle was presumably the main site of insulin resistance in hypertension and that nonoxidative glucose disposal (ie, mainly glycogen synthesis) was impaired. Our hypertensive subjects had elevated baseline and postexercise glycogen concentrations and rates of resynthesis in skeletal muscles after prolonged exercise. The increased capacity for glycogen resynthesis, ie, higher maximal glycogen synthase activity, may be related to direct factors and/or represent compensatory adaptations to insulin resistance. Direct factors include higher plasma glucose and insulin levels in the postexercise period. This is supported by the fact that glycogen resynthesis occurred importantly in type I fibers, ie, those particularly sensitive to insulin. Alternatively, (1) the reduced insulin-induced glucose transport (suggested by the inverse correlation between glycogen synthase and insulin sensitivity after exercise) and/or (2) the reduced carbohydrate metabolism during exercise and/or (3) the reduced ability to mobilize the

<table>
<thead>
<tr>
<th>Variable/Time</th>
<th>Glycogen Content Index</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NT (μmol/min/g tissue)</td>
</tr>
<tr>
<td>Baseline</td>
<td>73±8</td>
</tr>
<tr>
<td>After exercise</td>
<td></td>
</tr>
<tr>
<td>0 h</td>
<td>28±9**</td>
</tr>
<tr>
<td>2.5 h</td>
<td>32±5**</td>
</tr>
<tr>
<td>4 h</td>
<td>34±5**</td>
</tr>
</tbody>
</table>

Values are mean±SEM of 11 male normotensive (NT) and 9 male hypertensive (HT) subjects. ANOVA probability levels for group effect (HT, NT) and time effect (baseline, immediately after exercise [0 h], and 2.5 and 4.0 hours after exercise) are indicated at right.

* and ** indicate significant differences at $P<0.05$ and $P<0.001$ from respective control value.

† and †† indicate significant differences at $P<0.05$ and $P<0.001$ from respective value in normotensive subjects.

Figure 4. Glycogen synthase activity measured at 0.1 mmol/L of G6P substrate (A), at 10 mmol/L of G6P substrate (B), and fractional activity (percent ratio of 2 activities, C) in muscle biopsy samples taken at baseline (Base), immediately after exercise (0), and 2.5 and 4 hours after exercise. ††† indicates significant differences (ANOVA) at $P<0.001$ between hypertensive and normotensive subjects.
active fraction of glycogen synthase may promote a compensatory increase in glycogen resynthesis capacity.

A recent study by Solini et al. reported normal levels of glycogen and glycogen synthase activity in cultured skin fibroblasts of hypertensive subjects with microalbuminuria and reduced levels in diabetic subjects with and without hypertension. Taken together, these results could indicate an early compensatory adaptation in essential hypertension, i.e., increased intramuscular glycogen synthesis and glycogen content (present study) that disappears in conditions with progressively greater insulin resistance, such as hypertension with microalbuminuria and diabetes (study by Solini et al.).

The results of our study do not support the hemodynamic hypothesis of insulin resistance in hypertension,11,12 because both groups examined were found to have similar muscle capillaries, muscle fiber type distributions, and resting muscle blood flows, whereas insulin resistance was reduced in hypertensive subjects compared with normotensives. It is possible that alterations of capillaries were undetected with the histochemical method used in the present study. Hernandez et al. did not find changes in capillaries with similar histochemical methods but found abnormal capillary endothelial cells with electron microscopy. However, vasodilatation was reduced in hypertensive subjects during the hours after prolonged exercise, whereas glycogen resynthesis occurred faster than in normotensive subjects. Furthermore, glycogen content did not correlate with leg blood flow in either group on any occasion.

Our present and previous results underline contrasting adaptations in normotensive and hypertensive subjects after exercise, depending on exercise intensity. Normotensive subjects did not demonstrate an increase in insulin sensitivity after mild-intensity exercise19 but did so after higher-intensity exercise (present study). These finding agree with other reports in the literature as discussed previously.19 In hypertensive subjects, we found an increase in insulin sensitivity after mild-intensity exercise in our previous study,19 whereas no such change was found after intense and prolonged exercise. The absence of an effect on insulin sensitivity in hypertensive patients could be secondary to the lesser glycogen depletion and/or the higher free fatty mobilization and/or the carryover of the higher adrenergic response after intense and prolonged exercise. The mechanisms underlying these contrasting adaptations in hypertension merit further investigation.

In summary, whole-body carbohydrate and skeletal muscle glycogen metabolisms are reduced during intense exercise in hypertension, and postexercise glycogen resynthesis is enhanced. Elevated intramuscular glycogen content and resynthesis in hypertension do not appear to be related to either chronic or postexercise vasodilatory changes. It is concluded that increased intramuscular glycogen storage and resynthesis in hypertension are independent of blood flow and may be related to higher plasma glucose and insulin levels in the postexercise period and/or represent compensatory mechanisms for the reduced insulin sensitivity and carbohydrate metabolism in this condition.

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References
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