Regional differences in glucose clearance: effects of insulin and resistance training on arm and leg glucose clearance in older hypertensive individuals

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Reynolds TH IV, Supiano MA, Dengel DR. Regional differences in glucose clearance: effects of insulin and resistance training on arm and leg glucose clearance in older hypertensive individuals. J Appl Physiol 102: 985–991, 2007. First published November 22, 2006; doi:10.1152/japplphysiol.00914.2006.—The purpose of this study was to compare insulin’s ability to stimulate glucose uptake in the arm and leg in a group of older hypertensive individuals (n = 13, 66 ± 2 yr old). We also examined the effect of a 4-mo whole body resistance-training (RT) program on arm and leg glucose clearance (GC) during a hyperinsulinemic-euglycemic clamp. During the hyperinsulinemic-euglycemic clamp, GC was assessed by simultaneous measurement of arm and leg blood flow (BF) and assessment of fractional glucose extraction (GE) in blood samples from the brachial artery, brachial vein, and popliteal vein. At baseline, a significant main effect (arm vs. leg) demonstrated greater GC and BF in the arm than in the leg (P = 0.006 for GC and P = 0.012 for BF). Insulin significantly increased GE, BF, and GC in the arm and leg (main effects: P = 0.0001 for GE, P = 0.0001 for BF, and P = 0.0001 for GC) at baseline. However, the effect of insulin was similar in the arm and leg. After RT, a significant main effect (baseline vs. RT) demonstrated greater GE and GC in the leg (P = 0.024 for GE and P = 0.053 for GE), but not in the arm (P = 0.31 for GE and P = 0.14 for GC). No significant main effect (baseline vs. RT) for BF in the arm or leg was observed after RT. In conclusion, the greater GC in the arm than in the leg at baseline is primarily due to enhanced arm BF. Furthermore, whole body RT appears to increase GC in the leg but not in the arm.

exercise; aging; blood flow; glucose uptake; insulin resistance

SKELETAL MUSCLE IS THE PRIMARY site for postprandial glucose disposal, and a decline in this tissue’s ability to transport glucose is believed to play a predominant role in the pathogenesis of whole body insulin resistance and Type 2 diabetes mellitus. Exercise training has proven to be an effective non-pharmacological intervention that increases insulin sensitivity by enhancing skeletal muscle glucose uptake (4, 8, 13, 18). The evidence demonstrating the importance of skeletal muscle in whole body glucose disposal is primarily based on limb balance studies measuring glucose clearance (GC) in the leg (25).

The role of the arm musculature in insulin-mediated whole body glucose disposal has not been established, despite evidence that glucose uptake is greater in the arm than in the leg (1, 23). It is quite possible that differences between arm and leg glucose uptake are due to differences in muscle fiber type (10, 12), substrate metabolism (11), and insulin-stimulated vasodilation. Furthermore, recent evidence indicates that insulin sensitivity is preserved in the arm but not in the leg in Type 2 diabetic patients (25). Since skeletal muscle glucose uptake is different between the arm and leg in Type 2 diabetic patients, it is quite possible that interventions used to improve insulin action may produce limb-specific changes. Such a finding would be quite relevant clinically and provide important mechanistic insight into the regulation of insulin-mediated glucose disposal.

Aerobic exercise training and resistance training (RT) are the two primary exercise modalities prescribed to improve health and reduce the incidence of cardiovascular and metabolic diseases. Aerobic exercise training has consistently been shown to increase insulin-mediated whole body glucose uptake (4, 8, 13, 18) and leg skeletal muscle glucose uptake (6). The increase in the ability of insulin to stimulate glucose uptake after aerobic exercise training appears to be due predominantly to an increase in the abundance of the GLUT4 glucose transporter protein (15, 16, 19). However, an increased skeletal muscle blood flow (BF) may also contribute to the elevated insulin sensitivity after aerobic exercise training (6, 7). RT also improves insulin-mediated whole body glucose disposal (14, 17, 22, 26) and skeletal muscle glucose uptake in the leg (14). However, the cellular mechanisms responsible for the enhancement in insulin action after RT are not well described.

The purpose of the present study was to compare insulin’s ability to stimulate glucose uptake in the arm and the leg. We also examined the effect of a 4-mo whole body RT program on insulin-stimulated GC in the arm and leg. Our hypothesis was that GC would be greater in the arm than in the leg and that a 4-mo RT program would increase GC by a similar magnitude in the arm and leg. We also hypothesized that any differences in GC between the arm and leg at baseline or after RT would be independent of BF.

METHODS

Subjects

Thirteen subjects (6 men and 7 women, 66 ± 2 yr old) were recruited for the study by advertisements in newspapers, from the

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University of Michigan Turner Geriatric Clinic, and from the University of Michigan Geriatric Center’s Human Subject Research Participant Core. Before participation in the study, all subjects completed a medical history, physical examination, complete blood count, routine blood chemistries, and urinalysis. Individuals were excluded from participation if they had clinically significant medical illness, were taking medications that could affect glucose metabolism, or had a recent history of smoking or drug/alcohol abuse or a clinically relevant mental disorder. All female participants were postmenopausal. Subjects were also excluded from the study if plasma glucose was \( \leq 7.8 \) mmol/l (\( \leq 140 \) mg/dl) after a 2-h 75-g oral glucose tolerance test (9a). The rationale for selecting older subjects was based on the fact that they typically exhibit hypertension and insulin resistance, two pathophysiological effects that can be reversed by aerobic exercise training. The role of RT in older hypertensive subjects is not well established but could potentially provide a nonpharmacological intervention that improves glucose metabolism without deleterious alterations in blood pressure. To this end, our results will indeed be limited to older hypertensive individuals. This study was approved by the University of Michigan Institutional Review Board.

**General Study**

After a screening visit to determine their eligibility for participation as described above, subjects signed an informed consent form approved by the University of Michigan Institutional Review Board. Hypertensive subjects who were being treated with antihypertensive medications were tapered off their medications and studied after a 4-wk period during which no antihypertensive medications were taken. Subjects then underwent a maximal graded exercise test to screen for coronary heart disease. During this test, O\(_2\) consumption (\(V\dot{O}_2\)) and CO\(_2\) production (\(V\dot{CO}_2\)) were measured continuously using a metabolic cart (model CPX/D, Medical Graphics, St. Paul, MN).

**Hyperinsulinemic-Euglycemic Clamp Studies**

Insulin sensitivity before and after 4 mo of RT was assessed by the hyperinsulinemic-euglycemic glucose clamp technique (5). The post-training clamp was performed 24 h after the last bout of RT. To reduce any potential confounding effect of diet on insulin action, a 3-day dietary record was maintained by each participant before the baseline clamp and studied after RT. Briefly, an intravenous catheter was inserted into an antecubital vein for infusion of insulin and glucose. Catheters were inserted into a brachial artery, brachial vein, and popliteal vein for blood sampling. Beginning 20 min after the insertion of intravenous lines, baseline blood samples were taken from the brachial artery, brachial vein, and popliteal vein for the assessment of plasma glucose and insulin levels. Baseline values were calculated as the mean of these three measurements for each variable. Insulin (Humulin-R, Eli Lilly, Indianapolis, IN) was administered at a primed hyperinsulinemic-euglycemic clamp, blood samples were taken every 10 min from the brachial artery, brachial vein, and popliteal vein for the assessment of plasma glucose levels (glucose oxidase method; Beckman Instruments, Fullerton, CA) and plasma insulin levels (radioimmunoassay in the Core Laboratory of the Michigan Diabetes Research and Training Center). Arterial glucose levels were maintained at basal levels with a variable infusion of 20% glucose, which was adjusted according to a computerized algorithm. For the assessment of whole body glucose disposal, mean glucose infusion rates were normalized for lean body mass (LBM) and averaged over the last 30 min of the insulin infusion. Steady-state plasma insulin levels were calculated over the same interval.

**Measurement of BF**

Forearm and calf BF were measured simultaneously using venous occlusion plethysmography according to the manufacturer’s instructions (Hokanson, Bellevue, WA). To establish a stable baseline, BF measurements were taken until three consecutive readings representing similar BF were obtained for the forearm and calf, respectively. During the hyperinsulinemic-euglycemic clamp, forearm and calf BF measurements were taken every 30 min until three consecutive readings representing similar BF were obtained for the forearm and calf, respectively.

**Fractional Glucose Extraction and GC Calculations**

Fractional glucose extraction (GE) for the arm was calculated by subtracting plasma glucose levels obtained from the brachial vein from plasma glucose levels obtained from the brachial artery, and the difference was divided by plasma glucose levels obtained from the brachial artery. The GE was multiplied by 100 and expressed as a percentage. GE for the leg was calculated as described above, except venous blood samples were obtained from the popliteal vein. GC for the arm and leg were calculated from the respective GE values and BF data as follows:

\[
\frac{[\text{Glu}_i - \text{Glu}_a]/\text{Glu}_a}{\text{BF}}
\]

where \(\text{Glu}_i\) is the plasma glucose concentration obtained from the arm (brachial vein) or the leg (popliteal vein) and \(\text{Glu}_a\) is the plasma glucose concentration obtained from the brachial artery. Because our BF values were not corrected for changes in hematocrit, our assessment of GC is potentially limited. The effect of this limitation is most likely minimal, since hematocrit does not change with RT (9).

**Measurement of Blood Pressure**

Resting blood pressure was measured in triplicate using an oscillometric technique with an automated blood pressure device (PressMate BP-8800, Colin Electronic, San Antonio, TX) on three separate days. Subjects were seated comfortably for \(>15\) min with the cuffed arm supported at heart level before measurements were taken. The mean of these blood pressure measurements is reported.

**Anthropometry**

Body weight was measured to the nearest 0.1 kg using a medical scale. Height was measured to the nearest 0.5 cm using a stadiometer. Body mass index (BMI, kg/m\(^2\)) was determined as the subject’s weight (kg) divided by the square of the subject’s height (m\(^2\)).

**Dual-Energy X-Ray Absorptiometry**

Subjects were scanned using a whole body dual-energy X-ray absorptiometry (DXA) system (model DPX-IQ, Lunar Radiation, Madison, WI; software version 4.5c) set at medium speed and medium collimation ratio. Subjects lay supine on the DXA table with their arms adequately separated from their trunk and were instructed to remain still throughout the scanning procedure.

**Measurement of Maximal \(V\dot{O}_2\)**

A maximal exercise test was performed at baseline and after 4 mo of RT. The initial treadmill speed was set to elicit 75% of the subject’s maximal \(V\dot{O}_2\) (\(V\dot{O}_{2\text{max}}\)) measured during their screening treadmill test. The treadmill elevation was increased every 2 min until the subject was exhausted and could not continue. \(V\dot{O}_2\) and \(V\dot{CO}_2\) were measured continuously, and blood pressure and a 12-lead electrocardiogram were recorded every 3 min during the test. A true \(V\dot{O}_{2\text{max}}\) was considered to be attained if two of the following criteria were achieved: 1) respiratory exchange ratio \(>1.10\), 2) maximal heart rate \(>90\%\) age-predicted maximum (220 – age), or 3) plateau in \(V\dot{O}_2\) (\(\leq 0.2\) l/min change in \(V\dot{O}_2\)) with increasing workload.

**RT**

All subjects participated in a 4-mo supervised whole body RT program on Cybex machines that consisted of the bench press, leg
press, shoulder press, lateral row, bicep curls, tricep extension, leg extensions, and leg curls. Additional exercises for the forearm included wrist extension using a free weights-pulley system and hand gripping using a grip strength dynamometer (Grip-D, Takei, Tokyo, Japan). Before the initiation of the RT program, the subject’s one repetition maximum (1-RM) was determined on the leg press and bench press exercises. This was accomplished by progressive increases in the resistance on subsequent sets until only one repetition could be completed. To allow for adequate recovery, a 2-min rest period was allowed between each set. The initial RT intensity for each exercise was progressively increased so that by the end of the 2nd wk the subjects completed two sets of 10–12 repetitions of each exercise 3 days/wk (Monday, Wednesday, and Friday). The resistance was increased by ~5 kg when the subject could complete 12 repetitions on a particular exercise. Subjects were encouraged to rest for ~2 min between exercises.

Statistical Analysis

Data were analyzed using Statview (Abacus Concepts, Berkeley, CA). An α = 0.05 was accepted for statistical significance. The differences in basal and insulin-mediated GE, BF, and GC between the arm and leg (limb effect) were assessed by ANOVA with repeated measures on time for insulin infusion (0, 60, 120, and 180 min). The differences in basal and insulin-mediated GE, BF, and GC in the arm and leg after RT (training effect: baseline vs. posttraining) were also assessed by ANOVA with repeated measures on time for insulin infusion (0, 60, 120, and 180 min). If the F ratio was significant, selected mean comparisons were conducted using the least significant difference post hoc test. The effects of RT on body composition, strength, VO₂max, and plasma glucose and insulin were assessed by paired t-tests.

RESULTS

Adherence, Strength, and Body Composition

Subject characteristics at baseline and after 4 mo of RT are shown in Table 1. All subjects who completed baseline testing completed the 4-mo RT program as well as posttesting. On average, attendance for all subjects at the RT sessions was ~87%. No adverse events were reported during the RT program. As expected, RT increased upper and lower body strength. Bench press and leg press 1-RMs increased significantly by 11% and 22%, respectively. Left and right handgrip strength increased significantly by 9%. RT did not produce any significant changes in body mass, BMI, or fat mass. However, LBM increased significantly (P = 0.015) after RT, and there was a trend for a decline in percent body fat (P = 0.07).

Whole Body Metabolism

As previously reported in these subjects, 4 mo of whole body RT produced a 16% (P = 0.013) increase in whole body glucose disposal rates (26). After RT, fasting plasma insulin levels and plasma glucose levels obtained from venous blood did not change significantly from baseline values (Table 1). During the hyperinsulinemic-euglycemic clamp, plasma insulin and glucose levels at baseline were not significantly different from plasma insulin and glucose levels after RT (Table 2). Finally, there was not a significant change in VO₂max after RT (Table 1).

Regional Glucose Metabolism

Arms vs. legs. At baseline, there was a significant (P = 0.0001) main effect for insulin to increase GE, BF, and GC in arms and legs during the hyperinsulinemic-euglycemic clamp (Fig. 1). However, the ability of insulin to increase GE and BF was similar between the arm and leg (insulin × limb: P = 0.808 for GE and P = 0.299 for BF), but there was a trend for greater insulin-mediated GC in the arm (P = 0.059). There was a significant main effect for greater BF (P = 0.011) and GC (P = 0.009) in the arm than in the leg. At all time points (0, 60, 120, and 180 min) during the clamp, BF and GC were significantly higher in the arm than in the leg (Fig. 1, B and C). A significant main effect for GE between the arm and leg was not detected (P = 0.295), indicating that a good portion of the greater GC in the arm than in the leg was due, in part, to higher BF.

Table 2. Plasma insulin and glucose levels during hyperinsulinemic-euglycemic clamp at baseline and after 4 mo of RT

<table>
<thead>
<tr>
<th>Glucose, mmol/l</th>
<th>60 min</th>
<th>120 min</th>
<th>180 min</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brachial artery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
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<td>5.9±0.3</td>
<td>5.6±0.2</td>
<td>0.794</td>
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<tr>
<td>RT</td>
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<td>5.7±0.2</td>
<td>5.8±0.2</td>
<td></td>
</tr>
<tr>
<td>Brachial vein</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Baseline</td>
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<td>4.8±0.4</td>
<td>4.5±0.2</td>
<td>0.610</td>
</tr>
<tr>
<td>RT</td>
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<td>4.5±0.2</td>
<td>4.6±0.2</td>
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<tr>
<td>Popliteal vein</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
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<td>4.9±0.3</td>
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<td>0.148</td>
</tr>
<tr>
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<td>4.5±0.2</td>
<td>4.4±0.2</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE. RT, resistance training; BMI, body mass index; LBM, lean body mass; VO₂max, maximal O₂ consumption; 1 RM, one repetition maximum; 1 kgf = force of 1 kg at standard gravity.
Effects of RT. The 4-mo whole body RT program did not produce any significant changes in GE \((P = 0.343)\), BF \((P = 0.695)\), and GC \((P = 0.182)\) in the arm during the 3-h clamp (Fig. 2). In the leg, there was significant main effect for greater

**Fig. 1.** Insulin-mediated fractional glucose extraction (A), blood flow (B), and glucose clearance (C) in the arm and leg in older hypertensive individuals. *Significantly different \((P \leq 0.05)\) from leg at specific time point during clamp.

**Fig. 2.** Insulin-mediated fractional glucose extraction (A), blood flow (B), and glucose clearance (C) in the arm before and after a 4-mo resistance-training program in older hypertensive individuals.

GE (Fig. 3A; \(P = 0.027\)) and a significant main effect for enhanced GC (Fig. 3C; \(P = 0.043\)) after RT. In the basal state (0 min) and 180 min into the clamp, leg GE was significantly greater after RT than at baseline (Fig. 3A; \(P = 0.026\) for basal and \(P = 0.029\) for 180 min). At 60 and 120 min into the clamp,
a strong trend existed for increased leg GE (P = 0.061 for 60 min and P = 0.073 for 120 min). In the basal state (0 min), leg GC was significantly greater after RT that at baseline (Fig. 3C; P = 0.011). A strong trend existed for increased leg GC at 60 min (P = 0.072) and 180 min (P = 0.056) into the clamp after RT. RT did not significantly alter BF in the leg (P = 0.961).

DISCUSSION

The present study demonstrates that, at baseline, GC is greater in the arm than in the leg. The greater GC in the arm than in the leg is primarily due to greater BF, inasmuch as no differences in GE were observed. After 4 mo of whole body RT, GC increased in the leg but not in the arm. The increase in GC in the leg after RT is primarily due to greater GE, inasmuch as no differences in leg BF were observed.

Similar to our results, Olsen et al. (25) demonstrated that basal GC was greater in the arm than in the leg in healthy individuals and type 2 diabetic patients. The greater basal GC in the arm than in the leg observed by Olsen et al. appears to be due to enhanced GE, because BF was similar between the arm and leg. In the present study, greater basal GC in the arm than in the leg appears to be due to increased arm BF, because GE is similar between the arm and leg in the basal state. During insulin infusion, we demonstrate that insulin increases GC to a similar extent in the arm and leg. Therefore, the higher insulin-mediated GC in the arm shown in Fig. 1 is primarily due to greater respective basal values. However, Olsen et al. report that insulin produces a greater increase in GC in the arm than in the leg, despite the higher basal GC in their subjects.

Although our results show that insulin increases BF in the arm and leg, the magnitude of the insulin response is similar between the arm and leg. Recently, Newcomer et al. (24) demonstrated that the nitric oxide-dependent vasodilators acetylcholine, substance P, and sodium nitroprusside produced a greater BF response in the arm than in the leg. Similar to the vasodilators used by Newcomer et al., insulin increases BF by inducing vasodilation in a nitric oxide-dependent manner (2, 3). Therefore, our results suggest that the ability of the endothelium to produce nitric oxide is similar in the arm and leg, at least in response to insulin. Newcomer et al. hypothesized that greater vasodilatory ability in the arm than in the legs may be due to the increase in blood pressure in the legs during upright posture (21). The chronically elevated leg blood pressure due to upright posture might produce deleterious changes in endothelial cells that hinder leg BF (27). Whether this mechanism would explain the higher basal nonstimulated arm BF observed in the present study remains to be established.

After our 4-mo RT program, GC was enhanced in the leg but not in the arm. The increase in leg GC is mediated by enhanced GE, because RT did not alter leg BF. The greater GE after RT indicates that the trained muscle has an enhanced ability to transport glucose, a process highly dependent on the glucose transporter protein GLUT4 (19, 20). Holten et al. (14) demonstrated that RT increased leg GC and GLUT4 content in type 2 diabetic patients. In the present study, RT increased GE and GC in the leg, but the effect of insulin on leg GE and GC was similar after RT, suggesting that increases in basal leg GE are responsible for a majority of the higher insulin-mediated GE values. In contrast to our results, Holten et al. demonstrated that a one-legged RT program did not alter basal GC but significantly increased insulin-mediated GC in the trained leg compared with the untrained control leg. Furthermore, Holten et al. observed an increase in insulin-stimulated BF in the trained leg compared with the control leg, a process that

Fig. 3. Insulin-mediated fractional glucose extraction (A), blood flow (B), and glucose clearance (C) in the leg before and after a 4-mo resistance-training program in older hypertensive individuals. *Significantly different (P ≤ 0.05) from baseline at specific time point during clamp.
mediated a good portion of the increased GC, since GE did not change in the leg subjected to RT. In contrast to the findings of Holten et al., we observed no effect of RT on leg BF in the basal or insulin-stimulated state, but we did show an increased leg GE and GC after RT. The differences between the present finding and the results of Holten et al. may be related to the different populations studied (Type 2 diabetic patients vs. hypertensive individuals) and different RT programs (6 wk of 1-legged RT vs. 4-mo of whole body RT).

One of the most novel aspects of the present study is assessment of GE, BF, and GC in the arm before and after RT. To the best of our knowledge, no other study has measured insulin action in the arm after a controlled exercise intervention, either RT or aerobic exercise training. Much to our surprise, the RT program did not alter arm GE, BF, or GC. Perhaps the training stimulus required to elicit adaptations is greater in the arm than in the leg. However, we included an equal number of upper and lower body resistance exercises that were of a similar relative intensity and demonstrated a significant increase in upper body strength (bench press 1 RM and hand-grip strength). Despite the increase in upper body strength, it is possible that insulin action in the arm is resistant to the RT stimulus. Since BF and GC were higher in the arm than in the leg at baseline, a reason for lack of adaptations after RT may possibly be that the arm is at or close to its maximal GC capacity and, therefore, requires a greater training stimulus to produce significant changes in insulin action. Although upper and lower body strength were increased significantly after RT, the percent increase was greater in the lower body (11 vs. 22%). Therefore, it is possible that an increase in insulin action in the arm might have been observed if a greater training stimulus for the upper body had been implemented. Another possible explanation for the greater effect of whole body RT on GC in the leg than in the arm is a greater increase in leg than in arm muscle mass. However, we were unable to detect changes in lean tissue in the arm or leg using DXA scans after RT (data not shown). Perhaps the DXA is not sensitive enough to detect differential changes in lean tissue between the limbs, or perhaps our RT program did not produce significant increases in lean tissue in the limbs. Since whole body RT significantly increased total LBM, the lack of detectable regional increases in arm and leg lean tissue is most likely due to the DXA’s lack of sensitivity in detecting small changes in limb lean tissue. In older hypertensive individuals, it is quite possible that a longer (>4 mo) training program is needed to produce changes in limb lean tissue mass that are detectable by DXA.

At baseline, our subjects exhibited greater GC in the arm than in the leg. Although speculative, these data suggest that the insulin sensitivity is preserved in the arm but not in the leg. This idea is supported by Olsen et al. (25), who demonstrated that Type 2 diabetic patients maintained insulin sensitivity in the arm but not in the leg. Although our data demonstrate that the greater GC in the arm than in the leg is due to increased basal GC, we show a strong trend \((P = 0.059; \text{Fig. 1C})\) for the arm being more responsive to insulin than the leg. This interpretation of our data is limited by the fact that we did not have the appropriate control group. Furthermore, it is quite possible that the increase in leg GC after RT represents a reversal of insulin resistance in the leg, but not in the arm, at baseline. However, this interpretation of our data does not support this idea, because insulin responsiveness did not change significantly after RT \((P = 0.479; \text{Fig. 3C})\), and we did not have the appropriate control group to quantify the extent of leg insulin resistance in our older hypertensive subjects at baseline. Although a control group would have enhanced our study, we are confident that the increases in strength after RT are a result of the 4-mo training program and most likely mediated the changes in insulin action.

In conclusion, we demonstrate that, in a group of older hypertensive individuals, basal GC is higher in the arm than in the leg at baseline. The higher basal GC in the arm than in the leg appears to be primarily due to greater BF, rather than a greater ability of the arm musculature to extract glucose. After 4 mo of RT, basal GC is elevated in the leg but not in the arm. The higher basal GC in the leg in the resistance-trained state appears to be primarily due to a greater ability of the leg musculature to extract glucose and independent of RT-induced changes in BF. Finally, insulin-stimulated GE, BF, and GC in the arm and leg were not altered by 4 mo of RT.

REFERENCES


