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Resistive Training Improves Insulin Sensitivity after Stroke

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Abstract

Background—Insulin resistance is highly prevalent after stroke, contributing to comorbid cardiovascular conditions that are the leading cause of death in the stroke population. This study determined the effects of unilateral resistive training (RT) of both the paretic and nonparetic legs on insulin sensitivity in stroke survivors.

Methods—We studied 10 participants (mean age 65 ± 2 years; mean body mass index 27 ± 4 kg/m^2) with hemiparetic gait after remote (>6 months) ischemic stroke. All subjects underwent 1-repetition maximum (1-RM) strength testing, 9 had an oral glucose tolerance test (OGTT), and 7 completed a 2-hour hyperglycemic clamp (with glucose elevation targeted at 98 mg/dL above baseline fasting level) before and after 12 weeks (3×/week) of progressive, high repetition, high-intensity RT. Body composition was assessed by dual-energy x-ray absorbtiometry in all participants.

Results—Leg press and leg extension 1-RM increased in the paretic leg by 22% ($P < .05$) and 45% ($P < .01$), respectively. Fasting insulin decreased 23% ($P < .05$), with no change in fasting glucose. The 16% reduction in OGTT insulin area under the curve (AUC) across training was not statistically significant ($P = .18$). There was also no change in glucose AUC. First-phase insulin response during the hyperglycemic clamp (0–10 minutes) decreased 24% ($P < .05$), and second-phase insulin response (10–120 minutes) decreased 26% ($P < .01$). Insulin sensitivity increased by 31% after RT according to clamp calculations ($P < .05$).

Conclusions—These findings provide the first preliminary evidence that RT may reduce hyperinsulinemia and improve insulin sensitivity after disabling stroke.

Keywords

Diabetes; energy metabolism; exercise; rehabilitation; stroke recovery

Insulin resistance[1] and abnormal glucose metabolism[2] are prevalent during the subacute and chronic phases of stroke recovery, predisposing survivors to macrovascular[3,4] and microvascular complications[5] that worsen morbidity and mortality.[6] Treadmill training decreases hyperinsulinemia and improves glucose tolerance in stroke survivors with impaired glucose tolerance.[7] Although aerobic exercise rehabilitation in stroke may improve metabolic outcomes and other factors linked to cardiovascular and recurrent stroke risk,[7–10]

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no studies have assessed the effects of resistive training (RT) on glucose metabolism in chronically disabled stroke participants.

We and others have previously shown that RT improves insulin action in nonstroke populations,[12–15] with RT having recently been recognized by the American College of Sports Medicine for this purpose.[16] Quantitative[17,18] and qualitative changes[19,20] occur in skeletal muscle with RT and partially account for the observed metabolic effects. We recently reported that RT results in both paretic and nonparetic thigh skeletal muscle hypertrophy after stroke.[11] Importantly, relative adaptation in skeletal muscle quantity after stroke[11] was comparable to that observed in age-matched individuals from previous investigations.[18] Therefore, it is reasonable to hypothesize that systemic metabolic adaptations are possible after stroke with this form of intervention.

The purpose of the current study was to assess for the first time whether progressive lower-body RT reduces hyperinsulinemia and improves insulin sensitivity in chronically disabled stroke survivors.

Methods

Subjects

Participants were recruited from the University of Maryland Medical System and the Baltimore Veterans Affairs (VA) Medical Center referral networks. Chronic hemiparetic stroke patients (>6 months) had completed all conventional physical therapy and had mild to moderate hemiparetic gait deficits, defined as asymmetry of gait with reduced stance, or reduced stance and increased swing in affected limb, with preserved capacity for ambulation with assistive device (e.g., a walker or cane) or standby aid. Baseline evaluations with medical history and examination excluded those with heart failure, unstable angina, peripheral arterial occlusive disease, diabetes, and aphasia, operationally defined as the incapacity to follow 2-point commands. Patients were also excluded for dementia, untreated major depression, and orthopedic or chronic pain conditions. This study was approved by the Institutional Review Board of the University of Maryland and the Baltimore VA Research and Development committee. Written informed consent was obtained from each participant.

Testing

Of the 10 stroke subjects completing the intervention, 9 had pre- and post-oral glucose tolerance tests (OGTT), 7 completed both hyperglycemic clamp tests, and all had 1-repetition maximum (1-RM) strength, peak oxygen consumption (VO_2 peak), self-selected walking speed (SSWS), and dual-energy x-ray absorptiometry (DXA) tests before and after the intervention. One subject completed the hyperglycemic clamp testing but not OGTT testing.

Strength

A 1-RM strength test was conducted for leg press and leg extension on each leg. Two familiarization sessions were included before baseline 1-RM testing to avoid the confounding effects of learning on baseline strength measures. Strength in the paretic and nonparetic legs was tested separately using pneumatic RT equipment built for single-leg movement (Keiser, Fresno, CA).

VO_2 Peak

Exercise testing with open-circuit spirometry was conducted to measure VO_2 peak during a graded treadmill test as previously described.[21]

SSWS

The 30-foot walk test is widely recognized as a valid index of mobility recovery after stroke and simulates the distance required for many home-based activities of daily living functions. Gait velocity was determined from a self-selected pace, with participants using the same assistive device and or/orthoses as normally used to walk across a room at home. Before the test, participants were positioned several steps behind an orange cone to avoid timing the acceleration period. The tester then initiated the walks using the "ready, set, go" command. The stopwatch was started when the participant's toe crossed the first (closest) cone. The timer was stopped when the participant's heel crossed the end of the cone that was lined up with the measured distance. Participants were instructed to walk several steps beyond the second cone to avoid the confounding effects of deceleration in the timing.

DXA

Fat mass, lean tissue mass, and percentage of body fat were determined by DXA scans (Prodigy LUNAR GE, version 7.53.002; GE Healthcare, Little Chalfont, UK).

Glucose Metabolism

The OGTT was performed after a 12-hour overnight fast to measure glucose tolerance and the total glucose and insulin response to an oral glucose load. After 2 baseline venous blood samples (5 mL each) were drawn from an antecubital catheter, participants consumed 75 g of glucose. Subsequent blood samples were drawn every 30 minutes for 2 hours. All samples were analyzed for glucose (glucose oxidase method; YSI Analyzer, YSI Life Sciences, Yellow Springs, OH) and insulin by radioimmunoassay (Millipore, Billerica, MA). Plasma samples were frozen (−70°C) and analyzed in duplicate in the same assay to avoid interassay variability.

Insulin Sensitivity

Peripheral tissue sensitivity to endogenously secreted insulin and β-cell sensitivity to glucose were measured before the intervention and 24 hours after the last exercise session using the hyperglycemic clamp technique.[22] One intravenous catheter was placed in a vein in the antecubital fossa to infuse the dextrose (maintaining plasma glucose within 10% of the targeted glucose level, which was 98 mg/dL above baseline fasting level). A second catheter was inserted in a retrograde fashion into a dorsal hand or wrist vein. The hand was enclosed in an insulated chamber, warmed to "arterialize" the blood obtained. Blood samples were obtained every 2 minutes from 0 to 10 minutes and every 5 and 10 minutes thereafter for the determination of plasma glucose and insulin levels as stated above.

Glucose utilization or glucose metabolized (M) was calculated from the amount of glucose infused after correction for both glucose equivalent space and the amount of urinary glucose loss during the hyperglycemic clamp.[22] Both M (glucose utilization, 10–120 min) and insulin secretion (I; 10–120 min) were obtained to calculate M/I, which is a measure of tissue sensitivity to endogenously secreted insulin.[22] The clamp was not performed in 3 of the 10 individuals because of poor venous access.

RT

The RT exercise protocol was designed to provide a high-volume, high-intensity training stimulus for maximal adaptation in skeletal muscle mass across a 3-month period. Subjects trained 3 times per week for 12 weeks, performing 2 sets of 20 unilateral repetitions on the leg press, leg extension, and leg curl training equipment (Keiser K-300, pneumatic resistance; Keiser) at every session.[11] Generally, resistance was set at a level that would cause muscle failure somewhere between repetitions 10 and 15. Resistance was then

gradually reduced to allow completion of the full 20-repetition set. Participants trained each leg separately to account for differences in strength and progression requirements between limbs. Over time, resistance levels were gradually increased to account for strength gains and to maximize the intensity of the training. Each RT session lasted 30 to 45 minutes depending on the degree of disability.

Data Analysis

The paired *t* test was used to assess changes in outcome variables across time. Pearson correlation coefficients were used to assess the strength of relationship between body composition and metabolic variables. Results are presented as mean ± standard error (SE) with a 2-tailed *P* value of .05 required for significance.

Results

Subjects

The participants (65 ± 2 years; mean ± SE; 57–76 years; n = 10) had a mean body mass index in the overweight range, were deconditioned according to treadmill VO_2 peak testing, and had moderate disability based on walking speed (Table 1). None of these characteristics changed significantly across the intervention period. There was also no change in fat mass, fat-free mass, and percent body fat with training.

Strength

The 1-RM leg extension strength increased by 45% ($P < .01$) and 22% ($P < .05$) in the paretic and nonparetic limbs, respectively, with RT. Leg press strength increased 23% in the paretic leg ($P < .05$) and showed a 22% nonsignificant increase in the nonparetic leg (Table 1).

OGTT

At baseline, 50% of the subjects had impaired glucose tolerance. Two-hour insulin area under the curve (AUC) decreased by 16% (76,014 ± 9,243 *v* 64,141 ± 11,110 pmol/L) but failed to reach statistical significance ($P = .18$). Likewise, glucose AUC did not show a significant change during OGTT.

Hyperglycemic Clamp

Fasting plasma insulin decreased 23% ($P < .01$) with RT. Mean first-phase insulin response (0–10 min) decreased 24% ($P < .05$), and mean second-phase insulin response (10–120 min) decreased 26% ($P < .01$; Fig 1). M did not change after RT (24.2 ± 1.8 *v* 24.1 ± 1.9 $\mu mol.kg^{-1}\ min^{-1}$). However, M/I increased 31% after RT ($P < .05$), indicating an improvement in insulin sensitivity with the intervention.

Pretraining body mass index was significantly correlated with second-phase insulin response ($r = .80$; $P < .05$). However, changes in insulin action across the RT intervention could not show relationship with body composition based on the absence of change in these metrics by DXA (fat mass, fat-free mass, and percent body fat).

Discussion

Our preliminary results are the first to document improvements in insulin sensitivity with RT after stroke. We show significant reduction in fasting insulin and insulin response to glucose infusion and improvements in insulin sensitivity after 3 months of RT. This is clinically important given that insulin resistance is increasingly recognized as an

independent risk factor for stroke and cardiovascular disease,[4,23,24] a leading cause of death in stroke survivors.[25,26] Epidemiologic studies show that fasting hyperinsulinemia is related to risk of ischemic cardiac events, carotid intima-media thickening, and stroke.[27,28] In addition, a prospective investigation reports that postprandial insulin predicts risk of future stroke.[6] Our study suggests that higher intensity RT may qualify as a nonpharmacologic therapy for reducing decrements in glucose metabolism after disabling stroke.

The hyperglycemic clamp is a criterion standard assessment technique that measures β-cell sensitivity to glucose and peripheral tissue sensitivity to insulin,[29] which we have previously used to quantify hyperinsulinemia and lower insulin sensitivity in nonstroke, sedentary, older, and middle-aged women.[30,31] Our current clamp results in stroke showed much lower insulin sensitivity than either of the previously studied cohorts, reflecting an impaired metabolic status that is relevant to macrovascular complications and ongoing cardiovascular event risk.[32] In addition, our current and previous[2,7] OGTT findings in stroke reflect significant decrements in glucose metabolism and insulin sensitivity compared with sedentary adult men and women without stroke.[33] Therefore, pretraining comparisons between stroke and nonstroke groups suggest that metabolic outcomes should become a primary rehabilitation target to improve the morbidity and mortality prospects of disabled stroke survivors in the chronic phase of recovery.

There is ample precedent for using exercise and other life-style interventions to address hyperinsulinemia, insulin resistance, and associated complications that accompany normal aging,[34–36] but no other studies have examined the effects of RT on these measures after stroke. To our knowledge, our work in postmenopausal women[30] was the only previous study to use the hyperglycemic clamp across an RT intervention period. The 25% reduction in insulin response observed in the current poststroke RT study was much greater than that seen in postmenopausal women (−9%). Reasons behind the better metabolic response to RT in stroke could relate to a comparatively worsened baseline metabolic profile, resulting in an inherently higher potential for relative adaptation to the intervention. Unlike the postmenopausal women who underwent whole-body RT, stroke participants in the current investigation trained only the lower extremities.

Although we were able to show significant changes in hyperinsulinemia and insulin sensitivity with RT after stroke using the hyperglycemic clamp despite a small sample size (n = 7), we did not have adequate power to detect reductions in insulin or glucose AUC during OGTT (n = 9). Other study limitations may have resulted from heterogeneity in disability level among subjects, timing of the metabolic measurements after the last bout of training, and failure to control for the possibility of outside activity change through portable monitoring instruments. Overall, the current preliminary results in stroke are encouraging and serve as the first evidence-based rationale for extending this type of exercise rehabilitation to neurologically disabled participants with insulin resistance.

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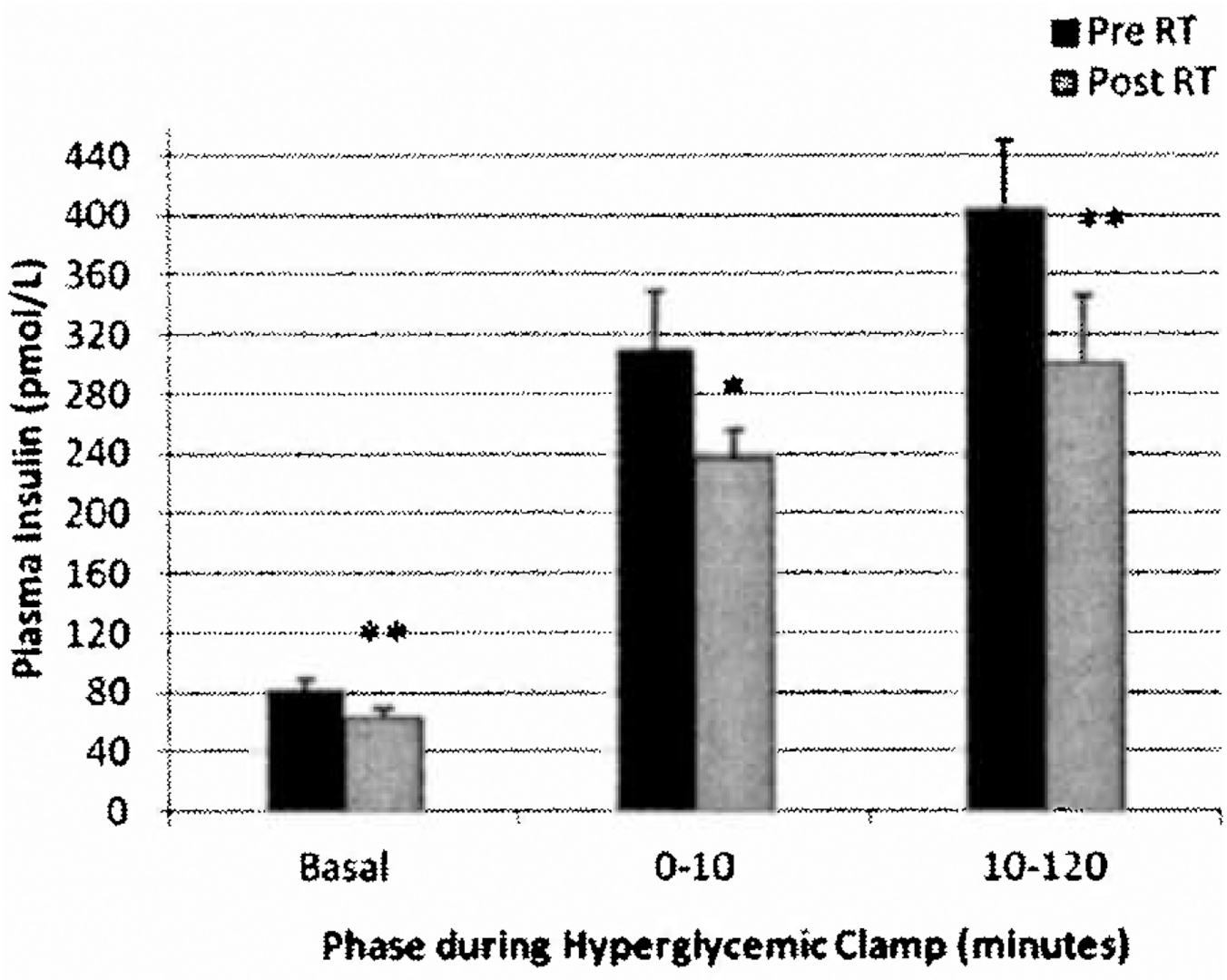

Figure 1.

Mean plasma insulin at each of 3 phases (baseline, 0–10 minutes, and 10–120 minutes) during the 2-hour hyperglycemic clamp (n = 7). There was a significant insulin reduction for each phase after 12 weeks of resistive training (RT). Values are mean ± standard error. *$P < .05$; **$P < .01$.

Table 1

Stroke participant characteristics before and after resistive training (n = 10)

	Before RT	After RT
Age (y)	65 ± 2	—
Years since stroke	9 ± 2	—
BMI (kg/m^2)	27.1 ± 1.1	—
Weight (kg)	82.1 ± 3.4	81.2 ± 3.2
Fat mass (kg)	30.4 ± 3.4	29.7 ± 3.4
Fat-free mass (kg)	54.3 ± 2.8	53.9 ± 2.5
Percent body fat	35.5 ± 2.9	35.1 ± 3.0
VO_2 peak (mL/kg/min^{-1})	18.6 ± 2.5	19.7 ± 2.5
Self-selected walking speed (mph)	1.5 ± 0.2	1.5 ± 0.3
Paretic leg extension 1-RM (lbs)	56 ± 11	81 ± 14†
Nonparetic leg extension 1-RM (lbs)	117 ± 11	142 ± 9*
Paretic leg press 1-RM (lbs)	303 ± 37	370 ± 42*
Nonparetic leg press 1-RM (lbs)	449 ± 34	547 ± 24

Abbreviations: 1-RM, 1-repetition maximum; BMI, body mass index; RT, resistive training; VO_2, oxygen uptake.

Values are shown as mean ± standard error.

$^{*}P < .05$.

$^{\dagger}P < .01$ pre-RT versus post-RT.