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Original Article

Electrically stimulated resistance training in SCI individuals increases muscle fatigue resistance but not femoral artery size or blood flow

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Study design: Longitudinal.
Objectives: The purpose of this study was to evaluate the effect of lower extremity resistance training on quadriceps fatigability, femoral artery diameter, and femoral artery blood flow.
Setting: Academic Institution.
Methods: Five male chronic spinal cord injury (SCI) individuals (American Spinal Injury Association (ASIA): A complete; C5–T10; 36 ± 5 years old) completed 18 weeks of home-based neuromuscular electrical stimulation (NMES) resistance training. Subjects trained the quadriceps muscle group twice a week with four sets of 10 dynamic knee extensions against resistance while in a seated position. All measurements were made before training and after 8, 12, and 18 weeks of training. Ultrasound was used to measure femoral artery diameter and blood flow. Blood flow was measured before and after 5 and 10 min of distal cuff occlusion, and during a 4-min isometric electrical stimulation fatigue protocol.
Results: Training resulted in significant increases in weight lifted and muscle mass, as well as a 60% reduction in muscle fatigue ($P = 0.001$). However, femoral arterial diameter did not increase. The range was 0.44 ± 0.03 to 0.46 ± 0.05 cm over the four time points ($P = 0.70$). Resting, reactive hyperemic, and exercise blood flow did not appear to change with training.
Conclusion: NMES resistance training improved muscle size and fatigue despite an absence of response in the supplying vasculature. These results suggest that the decreases in arterial caliber and blood flow seen with SCI are not tightly linked to muscle mass and fatigue resistance. In addition, muscle fatigue in SCI patients can be improved without increases in arterial diameter or blood flow capacity.
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Introduction

The spinal cord injured population has a 228% greater rate of mortality from cardiovascular disease than the able-bodied (AB) population.[1,2] In sedentary healthy individuals, physical activity significantly decreases the risk for chronic disease.[3] Therefore, there is great interest in the use of electrical stimulation training for individuals with spinal cord injury (SCI). Neuromuscular electrical stimulation (NMES) endurance training has been used to reverse the vascular changes that occur after SCI. For example, 6 weeks of NMES cycle endurance training, three times per week, decreased vascular resistance and increased femoral artery diameter and blood flow in individuals with SCI.[4,5] In contrast, low-volume high-load resistance training reverses the changes in muscle size that occurs after SCI. NMES resistance training for 8 weeks increased muscle size by 20% in individuals with SCI.[6] Short-term high-load resistance training has been shown to evoke increases in not only muscle mass, but also in capillarity, albeit in AB subjects.[7–9] The significance of these adaptations is that development of cardiovascular disease and Type II diabetes with SCI may be diminished or delayed by improving the muscles and arteries of individuals with SCI.[10] One potential limitation to NMES training for individuals with SCI is excessive muscle fatigue.[11–13]

In a recent investigation, individuals with SCI were subjected to an electrical stimulation protocol designed to evoke isometric contractions of the quadriceps muscle

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group.[11] Muscle fatigue in individuals with SCI was three times greater than that found in AB subjects. Individuals with SCI were also found to have a reduction in the rate of exercise hyperemia. A follow-up study was conducted to evaluate the effect of increased blood flow availability at the outset of exercise on muscle fatigue in individuals with SCI.[12] A delayed or reduced blood flow response at the onset of exercise appears to alter oxidative metabolism in healthy individuals[14,15] and this may exacerbate fatigue.[16] However, increasing blood flow prior to electrical stimulation had no effect on muscle fatigue of the quadriceps muscle group in individuals with SCI.[12] Therefore, it appears from these investigations that the increased muscle fatigue in individuals with SCI is not due to limitations in blood flow. However, the question of whether low-volume high-load resistance training is apt to improve these deficits has not been investigated.

The importance of muscle fatigue in SCI is that excessive fatigue may limit the ability of individuals with SCI to produce an optimal training stimulus. Training programs designed to increase muscle mass and reduce fatigue could also make 'functional' NMES more effective. The potential for physiological adaptations to exercise training is greater in people who are inactive.[17] Individuals with SCI could be more sensitive to exercise training because the lower extremities are severely detrained. Therefore, resistance training may also evoke improvements in vascular function and fatigue in individuals with SCI. In addition, lengthy travel and set-up, as well as the requirement for highly skilled staff, for NMES cycle or ambulation training can pose excessive burden on participants. This provides strong rationale for the development of simpler training protocols that individuals with SCI will likely use and maintain.

The purpose of this study was to determine whether a home-based lower-body NMES resistance training program would (1) reduce muscle fatigability, (2) reverse reduced arterial diameter, (3) increase resting blood flow, and (4) increase reactive and exercise hyperemia. Owing to the extreme disuse of the lower extremities associated with SCI, we hypothesized that lower-body NMES resistance training would (1) reduce fatigue in the quadriceps muscle group, (2) increase resting femoral artery diameter and blood flow, (3) increase peak reactive hyperemia, and (4) increase exercise hyperemia. In a companion study, we evaluated the influence of the current training program on muscle size and insulin resistance as well.[10]

Methods

Subjects

Five male subjects with complete SCI (American Spinal Injury Association (ASIA): A) were tested. Subjects had spinal cord lesions of traumatic origin at levels between C5 and T10, and at least 5 years had passed since the time of injury. The subjects' ages and physical characteristics are shown in Table 1. Subjects had no history of lower-extremity pathology and had not used NMES for training of their legs prior to inclusion in this study. This study was conducted with the approval of the Institutional Review Board at the University of Georgia, and informed consent was obtained from all subjects prior to the start of the study.

Table 1 Subject characteristics

N = 5	
Age (years)	35.6 ± 4.9
Injury time (years)	13.4 ± 6.5
Height (cm)	178.8 ± 8.2
Weight (kg)	76.6 ± 21.5

All patients were complete ASIA: A. Values are means ± SD

Training program

The NMES resistance exercise program, consisting of unilateral dynamic knee extensions, was performed twice a week for 18 weeks. Electrical current was applied to the quadriceps with surface NMES of the left and right quadriceps muscle essentially as described previously.[6,18–20] Following a complete familiarization with the training protocol, subjects were provided with an NMES unit (Richmar Theramini 2, Inola, OK, USA). Conditioning was performed by the research subjects at the subjects' residences. An investigator provided instruction by telephone for each session.

NMES was performed while the subject was sitting in a firm chair that fully supported the thighs. Stimulation consisted of 30 Hz trains of 450 μs biphasic pulses to elicit four sets of 10 dynamic knee extensions with 3 min of rest between each set. Resistance consisted of the weight of the leg and additional weight attached to the shin. Electrical current from the stimulator was manually increased in 2–3 s to evoke full knee extension and then decreased in 2–3 s to allow knee flexion to a position approximately 90° below horizontal, producing a lengthening contraction. This produced a work to rest cycle of roughly 5 s on and 5 s off. For the first 2 weeks of training, subjects used no additional weight (ie, only the weight of the leg) for resistance training. For the remaining 16 weeks, subjects attempted to increase the load of the resistance by 0.9–1.8 kg/week. Stimulation amplitudes and loads used during each set of resistance training were recorded.

Arterial diameter and blood flow measurements

Subjects were placed in a supine position on an examination table and allowed to rest quietly for 15 min prior to data collection. The diameter of the femoral artery was measured in the axial view using high-resolution B-mode imaging (General Electric LogiQ 400CL, Rainbow City, AL, USA) with a linear-array ultrasound

transducer set at 6–9 MHz. The imaging site was located distal to the femoral bifurcation and was marked to ensure replication of probe placement. The probe was held in position throughout the experiment with a custom-made probe holder. Magnification and focal zone settings were adjusted to optimize imaging of the vessel walls. Gain was held constant at a neutral setting. All artery images were saved to magneto-optical disc at the end of diastole for later offline diameter measurement using a software routine coded in LabView data acquisition software (National Instruments, Labview 6i, Austin, TX, USA).

Blood velocity was measured with pulsed Doppler ultrasound recorded in the longitudinal view using an insonation angle between 45 and 60°. The velocity gate was set to include the entire arterial diameter. Velocity measurements at the femoral artery were autocalculated every heartbeat by General Electric's advanced vascular program software for the General Electric LogiQ 400 CL. The time-averaged maximum velocities were acquired and saved directly to a computer using specially coded optical character recognition software (written with Labview 6i, Austin, TX, USA), allowing data acquisition on a beat-by-beat basis. Blood flow was calculated as the product of femoral artery cross-sectional area and the time-averaged maximum velocity. The resting vessel diameter was used for calculation of blood flow because no dilation was found in the femoral artery during exercise. The observation that the femoral artery does not dilate with exercise has been reported previously[21] and has been shown in our laboratory with exercise[11] and cuff occlusion.[22]

Resting blood flow and diameter were measured prior to cuff occlusion. Ultrasound images were recorded every 30 s during the 5-min baseline period. A pneumatic tourniquet (DT Hokanson Inc., Mahwah, NJ) placed around the right thigh proximal to the knee was then rapidly inflated (1 s) to 100 mmHg above systolic blood pressure and remained inflated for 5 min. The pressure was quickly released from the cuff (1 s) to induce reactive hyperemia and a peak blood flow response. This procedure was repeated after 5 min except that the cuff remained inflated for 10 min.

Neuromuscular electrical stimulation fatigue test

The fatigue test was used in this investigation and has been described previously.[12,23,24] In brief, subjects sat on a specially made chair with a rigid lever arm positioned 70° below horizontal. Subjects received electrical stimulation inducing isometric contraction (30-Hz train of 450-μs biphasic pulse, 50-μs phase delay) of the quadriceps at a current that would elicit 30 Nm of torque with a 1:4 duty cycle for 4 min. Blood flow was measured for 5 min prior to electrical stimulation and for 5 min of recovery. Muscle fatigue was calculated for each exercise bout as a percent decline in torque production from the first five contractions to the last five contractions.

Statistical analysis

The dependent measures evaluated in this experiment were arterial diameter, fatigue (percent torque decline during NMES fatigue test), and exercise hyperemia during the NMES fatigue test (ie, blood flow at the end of 1 min peak blood flow during exercise). A repeated measures analysis of variance (ANOVA) was used for each dependent measure with time as a within-subjects factor. The data were analyzed to verify normality and Mauchly's test was conducted to determine if sphericity was violated, in which case the repeated measures ANOVA was corrected using the Greenhouse–Geisser correction factor. Data are reported as mean $\pm$ SD. Analyses were conducted at a significance level of $P \leqslant 0.05$.

Results

Five subjects completed the 18-week NMES-induced resistance training program with 100% compliance. All subjects were able to increase weight lifted during training (group increase $= 6.9 \pm 1.4$ kg). Quadriceps femoris (QF) muscle CSA was increased in both thighs after 18 weeks of NMES-induced resistance training.[10] In the right thigh, mean QF CSA was significantly increased from 32.6 to 44.0 cm^2 ($P < 0.05$), and the left QF was increased from 34.6 to 47.9 cm^2 ($P < 0.05$), relating to a 35 and 39% increase in CSA, respectively.[10] Muscle fatigue with 4 min of electrical stimulation was 37.2 ± 14.2% before training. There was a progressive decrease in fatigue to 21.1 ± 6.9, 15.7 ± 7.0, and 14.8 ± 2.3% at 8 and 12, and after 18 weeks of training, respectively (Figure 1). The main effect for fatigue across time was significant ($F(3, 12) = 10.035$, $P = 0.008$,

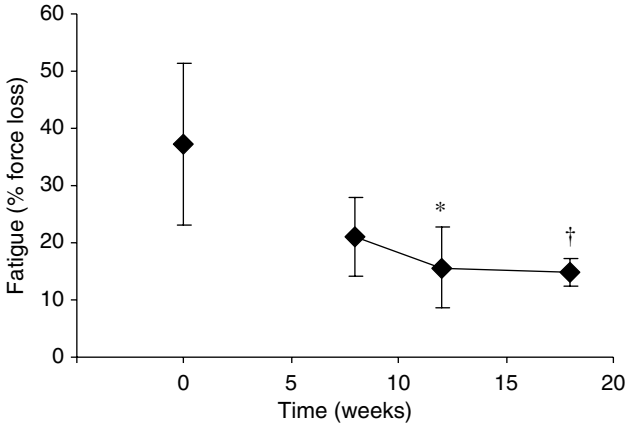

Figure 1 Fatigue before training (6–12 months prior to the initiation of this study), at 8 and 12 weeks, and post-training (18 weeks). Data are illustrated as mean $\pm$ SD. Fatigue decreased as training progressed ($P = 0.008$). Although the pretime point (ie, 0 on the graph) occurred some time before the training program began, the protocol and test administrators were identical for each test administration and subjects had not changed activity levels during the interim period. $^*P = 0.014$ for comparison with pretraining. $^\dagger P = 0.016$ for comparison with pretraining

$\eta^2 = 0.715$). *Post-hoc* comparisons were made using Fisher's LSD. There was a significant decrease from pretraining to 12 weeks ($P = 0.014$) and 18 weeks ($P = 0.016$).

Femoral artery diameter was 0.44 ± 0.03 cm at baseline (Figure 2). There was no change in femoral artery diameter with training (0.44 ± 0.04, 0.46 ± 0.05, and 0.45 ± 0.04 cm for time 8, 12, and 18 weeks, respectively; $F(3, 12) = 0.482$, $P = 0.70$). We were unable to statistically evaluate resting arterial blood flow and peak hyperemic blood flow in response to 5 and 10 min of cuff occlusion due to missing data that resulted from spasms and our small sample size. However, the group means appeared stable across time (Table 2). There was also no change in exercise hyperemia with stimulation (Table 2; exercise hyperemia; $F(3, 12) = 1.633$, $P = 0.234$).

Discussion

The primary findings of this study are that (1) resistance training that was sufficient to evoke an increase in muscle mass in individuals with SCI also reduced muscle fatigue, and (2) resistance training did not increase arterial caliber. In addition, reactive and exercise hyperemia did not appear to improve with training. A primary goal for using electrical stimulation is to recruit paralyzed muscle to increase muscle size. The resistance training protocol employed in this study has been shown to result in significant increases in muscle size.[6] With a recovery of muscle mass in paralyzed subjects, activation with NMES may be more effective as a stimulus to elicit positive cardiovascular adaptations.

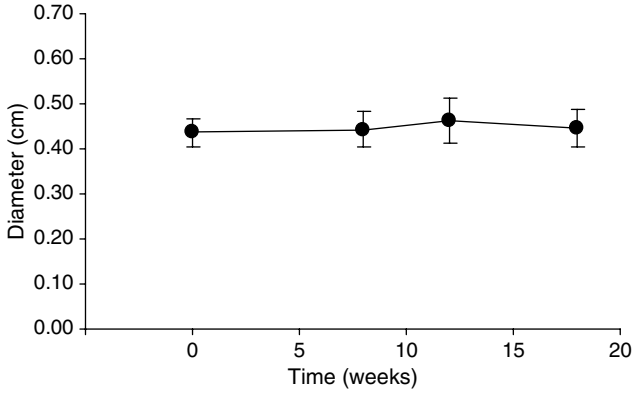

Figure 2 Femoral artery diameter before training, at 8 and 12 weeks of training, and after 18 weeks of training. There were no significant differences in diameter across the training intervention. Data are illustrated as mean $\pm$ SD

A limitation of this approach is that muscle of individuals with SCI has been shown to be extremely fatigable.[11] Increased fatigability may diminish the ability to sustain sufficient exercise intensity long enough to stimulate cardiovascular adaptations. The initial level of muscle fatigue with our stimulation protocol was 37%. This is consistent with previous data from our laboratory and is over three times greater than what was found for matched AB control subjects in this laboratory using the same protocol.[11] In the current study, muscle fatigue was reduced from 37 to 15% with training. The training protocol used in this study is not a typical endurance stimulus. It had a frequency of two times per week and a lower overall number of contractions than what would be expected from a program designed to provide a cardiovascular training stimulus for AB subjects.[25,26] However, we considered the program to have good potential to elicit improvements in vascular function for individuals with SCI due to extreme disuse of the lower body.

Although fatigue resulting from our 4-min stimulation protocol was reduced after electrical stimulation training, we are not able to determine the responsible mechanisms from our data. Previous studies from this laboratory suggested that increased fatigue in individuals with SCI is not due to reduced muscle blood flow or oxygen delivery.[11,12] Improved fatigue resistance despite an absence of improvement in arterial size and hyperemia in the current study supports this hypothesis.

A common hypothesis for the mechanism of muscle fatigue is impaired control of calcium.[27–29] It has been shown that increased fatigue is associated with an increase in half-relaxation time of torque in the QF of humans with SCI.[30] This suggests that sarcoplasmic reticulum (SR) Ca^{2+}-ATPases are not functioning optimally and/or they are reduced in SCI. In fact, SCI has been found to alter the proportions of Ca^{2+}-ATPase and myosin heavy chain isoforms such that the precision of Ca^{2+} control is reduced.[31] Therefore, the SR may be a source of adaptation in the skeletal muscle of our subjects. Future studies are needed to address the role of calcium homeostasis in muscle fatigue in subjects with SCI.

Fatigue was defined as the acute loss of torque with repeated NMES-induced contractions (ie, metabolic

Table 2 Blood flow parameters measured at time points during training program

	Pre	*8 weeks*	*12 weeks*	*18 weeks*	P
Resting blood flow (ml/min)	248 ± 125*	357 ± 202	284 ± 110	269 ± 149	—
Reactive hyperemia (5-min occlusion, ml/min)	1045 ± 196*	1169 ± 216	1034 ± 325	938 ± 188	—
Reactive hyperemia (10-min occlusion, ml/min)	1073 ± 190*	1307 ± 421	1083 ± 349	1032 ± 194	—
Exercise hyperemia (%)	74.9 ± 8.6	83.8 ± 10.4	66.6 ± 19.1	84.4 ± 14	0.234

Values are means $\pm$ SD. *$n = 4$ for the statistic

alterations that reduce force). Alternatively, the loss of torque may have resulted from acute muscle injury (ie, structural alterations that reduce muscle force production). We recently showed that excessive muscle injury occurs with a bout of NMES-induced isometric contractions in humans with SCI.[23] Fatigue with an acute bout of electrical stimulation was 66% (compared to 37% for controls) and area of damage was 25% (compared to 2% for controls) after 3 days. The repeated bout effect of muscle contraction on muscle damage may help explain the decrease in 'fatigue' seen in our study.[24,32] The repeated bout effect refers to the increased resistance to acute muscle damage with exercise that is thought to result from improvements in integrity of muscle cells, muscle connective tissue, and/or motor unit activation.[32] The residence-based NMES-induced resistance training program used in this study evoked dynamic knee extensions where eccentric actions constituted approximately half of each repetition. Repeated eccentric actions over weeks of resistance training may have allowed the newly hypertrophied skeletal muscle to express a protective effect.

In previous studies, it was suggested that artery size and magnitude of hyperemic blood flow were matched with the muscle size in individuals with SCI.[22] The results of this study do not support this relationship since electrical stimulation training resulted in an increase in muscle size with no change in either of these parameters. Previous studies have reported that electrical stimulation training increases arterial diameter.[5,33] For instance, 6 weeks of functional electrical stimulation (FES) cycle training three times per week for 30 min per bout increased resting femoral artery blood flow by 29%.[5] We reasoned that due to the extreme state of disuse of the lower extremities in our SCI group, NMES resistance training program would provide sufficient stimulus for femoral artery remodeling. However, analysis of our data did not reveal changes in artery size. Resting blood flow and reactive hyperemic blood flow also did not appear to change.

The resistance training program used in this study was a low-volume protocol. It consisted of a time-under-tension of only 8 min/week (6 s per repetition $\times$ 10 repetitions $\times$ 4 sets $\times$ 2 training bouts/week) throughout the study. A total of 90 min of recurrent repetitive muscle contractions per week (ie, 1025% more than in our experiment) and 2250 contractions per week (ie, 2713% more than in our experiment) was used in the previous experiment.[5] Therefore, it is plausible that the volume of training in the present experiment was insufficient to evoke an increase in conduit artery size. Similarly, it is also plausible that the absence of nontraining recruitment of skeletal muscle in SCI subjects may have obviated any subsequent adaptation of blood flow at rest and during reactive and exercise hyperemia. In addition, only the quadriceps muscle group was stimulated in the current experiment. In the previous experiment, the hamstring muscle group was also stimulated in order to produce the cycling motion of the leg. The smaller amount of activated muscle mass in this study may have reduced the stimulus for arteriogenesis.

The absence of an observed change in exercise hyperemia and peak reactive hyperemia also suggests that endothelial function was not improved with the current NMES-induced resistance training program. Exercise hyperemia is controlled by several endothelial-derived factors, including adenosine, nitric oxide, prostacyclin, and endothelial-derived hyperpolarization factor.[34,35] The availability of all these dilators may be affected by endothelial function. Although it is clear from previous research that blood flow increases acutely during NMES-induced contractions of the quadriceps,[36] a stimulus that was more aerobic or voluminous might have evoked improved blood flow kinetics.

Endurance training increases reactive hyperemic flow in AB subjects.[37] Individuals with SCI have reduced reactive hyperemic blood flow in comparison to AB controls[22] and training has been found to improve on this deficit by 78%.[33] In this study, reactive hyperemia did not appear to change throughout the training intervention. This might be explained by several previous findings with respect to muscle capillarization with SCI. SCI results in a reduction of muscle capillarization concomitant with an increased proportion of fast-twitch muscle fiber composition below the level of injury.[38,39] Hind-limb unloading models in rats have demonstrated that arterioles also reduce in size with disuse.[40] Although one study showed that electrical stimulation training increased muscle capillarization in SCI subjects,[38] the 24-week protocol that was used progressed to a final 6 weeks of 8-h-long stimulation sessions. The program parameters used in that study are in stark contrast to those used in the current study. Although the ability of arterioles to dilate may be increased with endurance training in paraplegic subjects,[41] our results suggest an absence of these adaptations and angiogenesis with NMES-induced resistance training.

In conclusion, muscle size increased and muscle fatigue improved in subjects with SCI after an NMES-induced resistance training protocol. However, artery size and blood flow did not increase. This suggests that the relationship between muscle size and blood flow in humans with SCI[22] is limited to those who are untrained and that our training program did not improve vascular function. These data also support previous findings that increased fatigue in SCI patients is not related to inadequate blood flow.[12] Future studies are needed to (1) evaluate the mechanisms for muscle fatigue and (2) determine the threshold stimulus to evoke vascular improvements in subjects with SCI.

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