

Original Article

Electrical stimulation-evoked resistance exercise therapy improves arterial health after chronic spinal cord injury

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Study design: Repeated measures training intervention.

Objectives: To evaluate the effects of neuromuscular electrical stimulation (NMES)-induced resistance exercise therapy on lower extremity arterial health in individuals with chronic, complete spinal cord injury (SCI). We define ‘arterial health’ using three surrogate markers: (a) resting diameter, (b) flow-mediated dilation (FMD), and (c) arterial range.

Setting: Department of Kinesiology, University of Georgia, USA.

Methods: We assessed five 36 ± 5-year-old male individuals with chronic, complete SCI before, during, and after 18 weeks of training. The quadriceps femoris muscle group of both legs were trained twice a week with 4 × 10 repetitions of unilateral, dynamic knee extensions. The health of the posterior tibial artery was assessed using a B-mode ultrasound unit equipped with a high-resolution video capture device. Proximal occlusion was used to evoke ischemia for 5 min and then for 10 min. FMD was calculated using the peak diameter change (above rest) following 5 min occlusion. Arterial range was calculated using minimum (during occlusion) and maximum diameters (post 10 min occlusion). Hierarchical linear modeling accounted for the nested (repeated measures) experimental design.

Results: FMD improved from 0.08 ± 0.11 mm (2.7%) to 0.18 ± 0.15 mm (6.6%) ($P = 0.004$), and arterial range improved from 0.36 ± 0.28 to 0.94 ± 0.40 mm ($P = 0.001$), after 18 weeks of training. Resting diameter did not significantly change.

Conclusions: Home-based, self-administered NMES resistance exercise therapy consisting of 80 contractions/week improved FMD and arterial range. This provides evidence that resistance exercise therapy can improve arterial health after SCI, which may reduce the risk of future cardiovascular disease.

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Keywords: spinal cord injury; arterial health; flow-mediated dilation; neuromuscular electrical stimulation; exercise; resistance training

Introduction

A prospective mortality study recently published in this journal reported diseases of the circulatory system to be the most common cause of death among persons with spinal cord injury (SCI).¹ The authors also reported that the excess mortality associated with chronic SCI is potentially related to treatable factors. For instance, increasing physical activity decreases the risk of cardiovascular disease by up to 50% in sedentary healthy non-disabled individuals.^{2–5} Similar cardiovascular benefits should be attainable for persons with SCI if physical activity can be increased.

Among paraplegic subjects, voluntary exercise is limited to the upper body. Although upper body exercise

has been demonstrated to produce cardiovascular benefits,^{6–11} it also heightens the already high prevalence of wrist and shoulder pain.¹² Therefore, many forms of electrically stimulated exercise therapy have been used to train the legs in persons with SCI, and have been shown to evoke improvements in exercise capacity,^{13,14} body composition and metabolic profiles,^{15,16} blood flow parameters,^{17–19} total peripheral conductance,²⁰ and femoral artery diameter.¹⁹ To date, most electrically stimulated exercise therapy studies have been endurance based. However, Dudley *et al*²¹ developed a resistance exercise program, using neuromuscular electrical stimulation (NMES), to evoke unilateral, dynamic knee extensions. Resistance exercise increased muscle mass by 37% in patients with complete SCI. Still, it is not clear what impact resistance training therapy might

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have on the risk of cardiovascular disease in individuals with SCI.

Cardiovascular disease is associated with reduced arterial reactivity as well as increased arterial stiffness. Arterial reactivity is typically measured as the ability of an artery to increase its size (diameter) in response to an increase in blood velocity, that is, flow-mediated dilation (FMD). Arterial stiffness has been measured in a number of ways, including as a change in the physiological operating range of an artery. In a previous study, we found that FMD and arterial range were significantly lower in the legs of patients with SCI *versus* controls, even though the arms were similar between groups.²² These findings suggest that interventions to improve SCI cardiovascular health should target the lower extremities.

The purpose of this study is to evaluate the effects of NMES-induced resistance exercise therapy on lower extremity arterial health in male individuals with chronic, complete SCI. We define arterial health using three surrogate markers: resting diameter, FMD, and arterial range. As this arterial segment does not feed the muscle mass (quadriceps femoris) activated by the NMES, any adaptations should represent generalized lower extremity adaptations. We hypothesized that 18 weeks of exercise therapy would improve our markers of arterial health. In companion studies, we evaluated the influence of NMES-induced resistance exercise therapy on muscle size, intramuscular fat, insulin resistance,²³ muscle fatigue resistance, and femoral artery size.^{23,24}

Methods

Subjects

Five individuals with chronic (13.4 ± 6.5 years) spinal cord lesions of traumatic origin at levels between C5 and T10 (American Spinal Injury Association ASIA: A) were tested. The average age was 35.6 ± 4.9 years, and height and weight were 178.8 ± 8.2 cm and 76.6 ± 21.5 kg, respectively. None of the subjects had a diagnosis of disease or disabilities other than SCI. All subjects were non-smokers and reported stable health status before study entry, that is, no reports of health complications for at least 6 months prior. Subjects were asked not to make changes to their physical activity levels or dietary habits during the course of the study. Subjects had not used NMES-induced resistance exercise training of their thighs before 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 before the start of the study.

Training

The surface NMES-induced resistance training was performed as previously described.^{21,25} After familiarization with procedures, patients were provided with an electrical stimulation unit (Richmar Theramini 2, Inola,

OK, USA) and ankle weights. Training was performed 2 days per week for 18 weeks at the patient's residence, with an investigator providing instruction by telephone for each session. Exercise consisted of four sets of 10 unilateral, dynamic knee extensions using 30 Hz trains of $450 \mu\text{s}$ biphasic pulses. The work/rest ratio was 5 second-on/5 second-off with 3 min rest between sets. Current from the stimulator was manually increased in 2–3-s intervals to evoke full knee extension and then decreased to allow the leg to return to the (relaxed) starting position. For the first 2 weeks of training, subjects used only the weight of their leg for resistance. For the remaining 16 weeks, subjects increased the load about the shin by 0.9–1.8 kg per week.

Arterial health protocols

The health of the posterior tibial artery was assessed at weeks 0, 8, 12, and 18. Subjects reported for testing after fasting for 12 h, and were asked to consume water *ad lib*. Arterial images were continuously captured using a B-mode ultrasound unit equipped with a high-resolution digital video capture device. Arterial health was assessed by measuring the size (diameter) of the artery at rest and in response to ischemia-induced reactive hyperemia. Resting measurements were recorded for 1 min following 10 min of supine rest. Ischemia was evoked using proximal cuff occlusion of the dominant limb for 5 and then for 10 min.

Flow mediated dilation (FMD) was calculated as:

$$5 \text{ min peak diameter} - \text{resting diameter}$$

where the 5 min peak diameter represents the largest diameter measurement made after 5 min of proximal ischemia. Resting diameter was also used as a covariate to adjust for between- and within-subject differences due to resting values.

Arterial range was calculated as

$$\text{maximum diameter} - \text{minimum diameter}$$

where the maximum diameter was the largest diameter after 10 min of proximal ischemia. A previous study from our laboratory found that 10 min of ischemia induces a maximal physiological diameter response.²⁶

Arterial constriction was calculated as

$$(\text{maximum diameter} - \text{resting diameter}) / \text{arterial range} \times 100$$

as has been previously reported.²⁶ The maximal diameter represents the largest diameter measurement made after 10 min of proximal ischemia.

Blood pressures and heart rates taken from the opposing arm were measured using a semi-automated device (Datascope, Montvale, NJ, USA). Recordings were taken after 10 min supine rest, at the end of occlusion, and 5 min post-occlusion.

Proximal occlusion

Briefly, a pneumatic tourniquet placed around the limb proximal to the insonated artery was rapidly inflated

(1–2 s) to a pressure of approximately 100 mmHg above the systolic blood pressure measured from the opposing arm. The use of a proximal cuff provides a larger effect size than using a distal cuff, and may be a better predictor of cardiovascular disease than FMD with a distal cuff.²⁷ The proximal cuff allowed the determination of minimal diameter when transmural pressure in the artery is near zero. Immediately post-cuff release, the hyperemic response was visualized using velocity color imaging to ensure that focus was maintained during ischemia.

Ultrasound diameter measurements

B-mode images were captured using a portable high-resolution ultrasound unit (GE Logiq book, GE Medical, Milwaukee, WI, USA) equipped with a 7–13 MHz linear probe. Measurements were made on the posterior tibial artery 3–5 cm superior to the calcaneus. The posterior tibial artery allowed for ease of proximal cuff inflation. Magnification and focal zone settings were adjusted to optimize imaging of the proximal and distal vessel walls. Image focus was maintained throughout the entire experiment by using a specialized probe-holding device. High-resolution MPEG2 recordings of the entire experiment were made using a Laptop PC equipped with video capture device (ADS technologies, Cerritos, CA, USA). Movie files collected at 30 frames per second were converted into JPEG images and subsequently used to make 30 diameter measurements per second. JPEG images provide comparable accuracy for ultrasound image measurements compared to the DICOM (Digital Imaging and Communications in Medicine) standard.²⁸

Images were analyzed offline using semi-automated edge-detection software custom written to interface with National Instruments Lab view software (see Figure 1). Reported resting diameters represent the average from 1 min of rest. Minimum diameters represent the average from the last 30 s of ischemia. Previous studies from our laboratory have shown that the minimal diameter occurs within 3–5 min after proximal cuff ischemia.²⁶ Peak (post 5 min occlusion) and maximum (post 10 min occlusion) diameters were calculated from the average of the three largest adjacent diameters post-cuff release. In our laboratory, between-day coefficients of variation for measurements of diameter ranging from rest to maximal diameters are 2–3%.²⁹

Statistical analysis

Arterial health outcomes were analyzed through hierarchical linear modeling (HLM) with the HLM6 (SSI, Lincolnwood, IL, USA) statistical package. A key application of HLM relates to the capacity to account for the repeated measures nested within each subject.³⁰ Model assumptions and graphing functions were undertaken using SPSS 13 for windows (SPSS Inc., Chicago, IL, USA).

Separate two-level hierarchical linear models were built in order to assess resting diameters, FMD, and arterial range over the course of the training study. HLM was used to account for the correlated measures by nesting the repeated measurements (level-1) within each subject (level-2). Initially, for each arterial health outcome, an unconditional model equivalent to a one-way ANOVA with random effects was fit. This

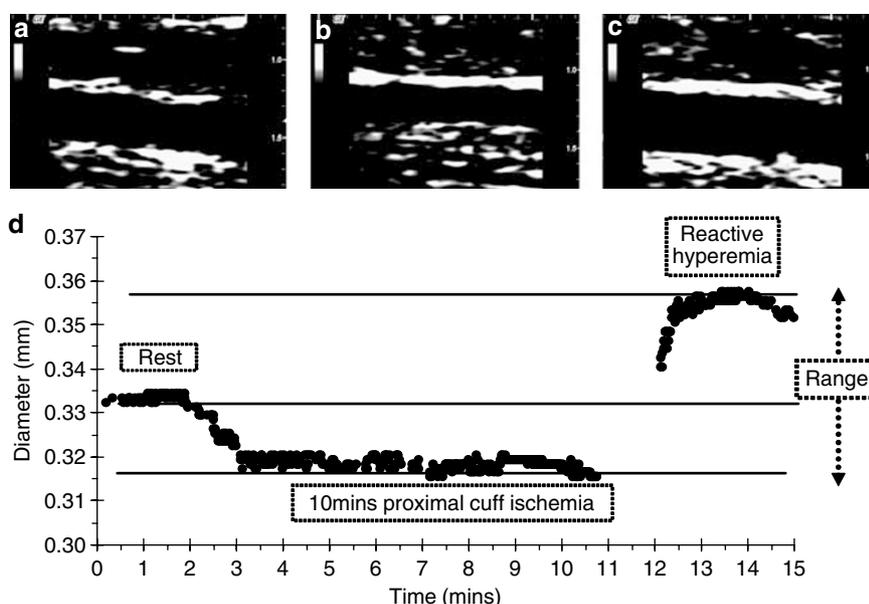


Figure 1 Examples of the image analysis for measuring arterial diameters. B-mode images of resting (a), minimum (b), and maximum (c) diameters are shown. Representative plot of arterial diameter in response to 10 min of proximal ischemia (d). Images are captured at a rate of 30 images per second. Arterial range is calculated by subtracting the minimum diameter from the maximum diameter

unconditional model included a random intercept (initial value) and slope (change per week) to determine whether random variance existed across subjects for these parameters. The intercept was subsequently 'fixed' if random variance did not exist. For the FMD model only, resting diameters were included group-centered at level-1. This served two purposes: (1) FMD is expressed as change in diameter relative to resting diameter as per convention, and (2) differences in FMD that occur over time within subject due to changes in resting diameter are controlled. The group aggregate of resting diameters was subsequently included at level-2 of the FMD model. Including a given covariate at level-1 controls for within-subject differences, whereas the aggregate of a covariate at level-2 may account for between-subjects variance. The same process was then followed for the arterial constriction covariate. The degree to which an artery is constricted relative to its operating range may change independent of any arterial remodeling that may occur. Adjusting for this variable ensures that we can assess change in arterial health independent of the level of constriction.

FMD can be represented using (a) a post-only score, (b) a change score, (c) a fraction, or (d) resting diameter as a covariate. We calculated FMD as absolute diameter change and co-varied for resting diameters. The rationale was three-fold: (a) the three measurements (resting diameters, FMD, arterial range) could be easily compared, (b) the data are less likely to become non-normally distributed, and (c) measurement variation is reduced. Although FMD is commonly presented as a fraction (the percentage change in diameter), using resting diameter as a covariate is more likely to adjust for bias due to resting values.^{31–33} Greater statistical power can be obtained by using resting diameter as a covariate.^{31–33}

Statistical significance was defined as $P < 0.05$. SCI patients were expected to have improvements in all arterial health measures; therefore hypothesis testing was directional and all P -values reported are one-tailed. All values are presented as means \pm SD.

Results

All subjects used no load during the first 2 weeks. Load was gradually increased to 6.9 ± 1.4 kg at the end of 18-weeks. No significant changes in health status were self-reported during the course of the training program.

Arterial diameters

Measurements of resting diameter as well as the minimum and maximum diameters over the 18 week duration of the study are shown in Figure 2. There was no significant change in resting diameter with the training program, based on a mean change per week of -0.005 ± 0.008 mm ($P = 0.276$ from HLM model). The minimum diameter showed a significant decrease (ie improved capacity to relax), and the maximal diameter showed a significant increase over the 18-week study.

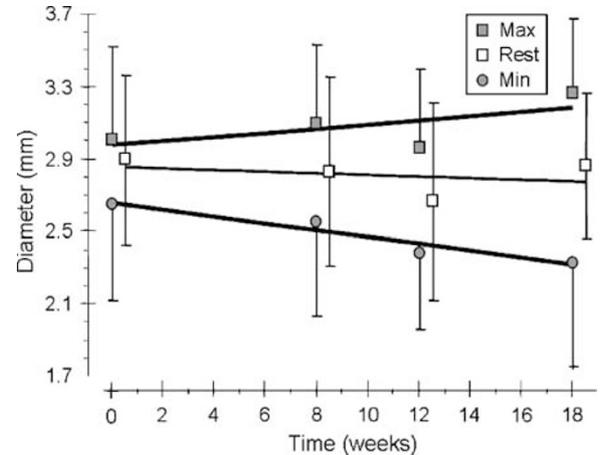


Figure 2 Baseline, minimum, and maximum diameters for weeks 0, 8, 12, and 18. Values are group means and error bars are SD. Note: resting values are positively offset on the X-axis

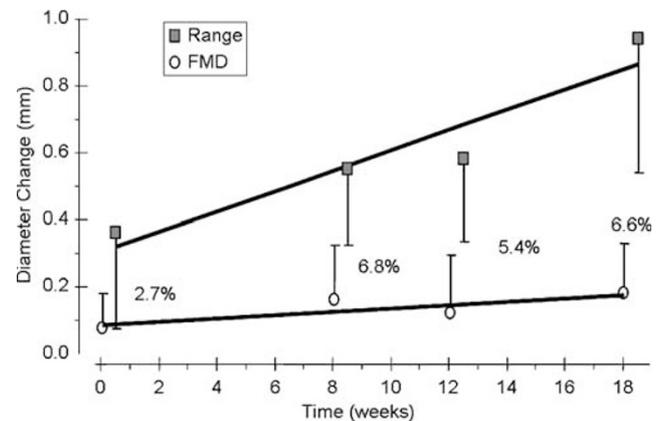


Figure 3 Arterial range and FMD for weeks 0, 8, 12, and 18. Values are group means and error bars are SD. Note: arterial range values are positively offset on the X-axis. The % values represent the group mean FMD in percentage terms for each week of measurements

Flow-mediated dilation

FMD values are shown in Figure 3. Calculated as a percentage from the raw data, FMD was $2.7 \pm 3.6\%$ at the onset of the study, and was $6.6 \pm 5.9\%$ after 18 weeks of training. Table 1 shows the results of HLM analysis for unconditional, adjusted with resting diameters, and adjusted for differences in arterial constriction models. With the unconditional model, changes in FMD did not reach significance ($P = 0.095$). However, adjusting for variance due to resting diameters meant that FMD did significantly increase with NMES training ($P = 0.028$). Adjusting FMD to arterial constriction further reduced the P -value for the change in FMD over the course of NMES training ($P = 0.004$).

Arterial range

Arterial range showed a 163% improvement after 18 weeks of training (Figure 3). Table 2 shows the results of

Table 1 HLM model fit for flow mediated dilation (FMD)

		Uncond.		Cond.		(+)AC			
		Est.	P	Est.	P	Est.	P		
<i>Fixed effects</i>									
Intercept	FMD	β_{00}	0.05	0.20	0.06	0.07	0.05	0.06	• Mean initial (pre-training) FMD
Slope P1	Week	β_{10}	0.01	0.10	0.01	0.03	0.01	<0.01	• Mean change per week
	Ave_Rest_D	β_{01}			-0.02	0.00	-0.02	0.01	• Mean change per 1 unit Rest_D
Slope P2	Rest_D	β_{20}	-0.19	0.27					• Mean change per 1 unit Rest_D
Slope P3	AC	β_{30}					0.00	0.01	• Mean change per 1 unit AC
<i>Random variance</i>									
Level 2	Between	U_0	0.01	0.22					• Between-group initial FMD random variance
	Week	U_1	0.00	0.04					• Between-group change FMD random variance
	Rest_D	U_2	0.30	0.01	0.22	0.01	0.26	0.01	• Between-group Rest_D random variance
Level 1	Within	E	0.01		0.01		0.00		• Within-group random variance

Unconditional and conditional models are shown for FMD. The final model adjusts for weekly differences in arterial constriction % (AC%)

Table 2 HLM model fit for arterial range

		Uncond.		Cond.				
		Est.	P	Est.	P			
<i>Fixed effects</i>								
Intercept	Range	β_{00}	0.33	0.02	0.33	0.03		• Mean initial (pre-training) Range
Slope P1	Week	β_{10}	0.03	0.02	0.03	<0.01		• Mean change per week
<i>Random variance</i>								
Level 2	Between	U_0	0.02	0.32	0.04	0.01		• Between-group initial Range random variance
	Week	U_1	0.00	>0.50				• Between-group change Range random variance
Level 1	Within	E	0.05		0.05			• Within-group random variance

Unconditional and conditional models are shown for arterial range

HLM analysis for arterial range unconditional (model 1) and final (model 6) models. Both the unconditional ($P=0.015$) and final models ($P=0.001$) found significant increases in arterial range. The two HLM models show that there were significant differences in range values between subjects at the onset of the study, but that the rate of increase per week was similar across individuals.

Discussion

Eighteen weeks of self-administered NMES-induced resistance exercise therapy significantly increased FMD and arterial range of the posterior tibial artery in chronically and completely injured male SCI individuals. These improvements were seen in an arterial segment that does not feed the muscle mass (quadriceps femoris) activated by NMES. Improvements in these markers of arterial health highlight the potential of this therapy for reducing the risk of cardiovascular disease after complete SCI. The fact that this therapy can

be safely self-administered in one's residence makes it especially appealing.

Flow-mediated dilation

As FMD has been used as an index of arterial health,³⁴⁻³⁶ improvements in FMD suggest that arterial health was improved as a result of 18 weeks of therapy. Interestingly, the ending values of FMD in this study were still lower than those we obtained in able-bodied subjects (6.6 ± 5.9 versus $12.0 \pm 5.2\%$, respectively) for our previous study,²² suggesting that further improvements may be possible.

A limitation of our study is that we did not measure the magnitude of the hyperemic response post-ischemia. Previous studies have stressed the importance of correcting for the hyperemic response (shear stress) when measuring FMD.^{29,37-40} The small size of the artery limited our capacity to measure blood velocities. However, in a companion study, we made measurements in the femoral artery simultaneous to the posterior tibial artery measurements for the current study. We

did not find any evidence that blood velocity was altered as a result of training.²⁴ Furthermore, in our previous studies, we found no evidence that hyperemic blood velocity after cuff ischemia was reduced in patients with SCI *versus* non-disabled controls.^{41,42} We do agree that future studies would benefit from measurement of blood velocity and calculation of shear rates.

Arterial range

In contrast to FMD, arterial range improvements brought the individuals with SCI close to those of the able-bodied individuals we previously assessed (0.940 ± 0.399 mm compared to 0.918 ± 0.266 mm, respectively).²² This notable improvement occurred despite no change in resting diameter.

The marked change in arterial range may reflect two different arterial characteristics. Arterial range is determined from both maximal and minimal diameters. Maximal diameter reflects the ability of the artery to dilate in response to increased blood velocity (shear stress). The actual mechanism(s) behind the dilation of the artery with 10 min proximal ischemia may be multifactorial. But 10 min of proximal ischemia should produce a maximal hyperemic response in both able-bodied and SCI individuals.^{38,42} The changes in minimum diameter may well reflect a completely different aspect of arterial function. The decrease in arterial size with a proximal cuff may reflect the stiffness of the artery as well as the general size of the artery. If both the dilating ability of the artery (maximal diameter) and the stiffness of the artery (minimum diameter) changed with exercise therapy, then the resulting arterial range will show even larger improvements than a variable like FMD that reflects only one factor. Although arterial range is a relatively novel measurement,^{26,43} our study suggests that it might be useful for monitoring changes in arterial function.

It is worth noting that we saw improvements in arterial range and FMD despite no change in resting diameter. These findings contrast previous studies showing functional electrical stimulation (FES) to increase resting femoral artery diameter.^{18,19} These conflicting findings may be explained by two factors: (1) the femoral artery is a large conduit, which directly supplies the quadriceps, the muscle being served during the FES training, (2) reductions in resting femoral artery diameter (~40–50%) have been closely linked to quadriceps muscle atrophy.⁴¹ The posterior tibial artery serves foot tissue, and this most likely explains why it does not see major atrophy.²² Foot tissue is not subject to major atrophy after SCI and is unlikely to hypertrophy owing to quadriceps activation. Taken together, these findings suggest that assessments solely using resting diameter to indicate arterial size may lead to erroneous conclusions. Assessments of arterial size should include measurements of the arterial 'physiological' operating range^{26,43} in addition to measurements of resting diameter.

NMES-induced arterial health improvements

Arterial adaptations associated with exercise may be induced through a *direct* shear-stress mechanism related to increased blood flow,^{44–46} or *indirectly* through reductions in cardiovascular disease risk factors, for example, blood lipids, circulating factors such as oxidants, blood pressure, blood glucose, and body fat. Although we did not measure cardiovascular disease risk factors, a recent study found that FMD improves after short-term exercise (8 weeks) without moderation of said factors.⁴⁷ The posterior tibial artery would though, as it is fed by the femoral artery, have indirectly experienced increase in blood flow. Blood flow was found to increase ~3–5 fold through the femoral artery during NMES-induced resistance exercise training (M Sabatier, personal communication). The endothelial cells of the posterior tibial artery would therefore have been repeatedly exposed to increases in shear stress.

To our knowledge, no study has investigated the potential arterial health benefits of resistance exercise for persons with SCI. Endurance exercise interventions have been shown to improve markers of arterial health in able-bodied as well as persons with SCI.^{48–51} However, it must be acknowledged that endurance exercise likely results in high blood flow conditions that are sustained for the duration of the exercise bout. One explanation for the improvements seen in our study is that the extreme inactivity associated with SCI makes the arteries especially sensitive to the changes in blood flow associated with resistance exercise. Future studies will be needed to better understand the relationship between the training stimulus and improvements in arterial health in persons with SCI.

Limitations

Although the improvements in arterial health with training were significant and were seen in all subjects, a potential limitation of our study was the small number of SCI persons recruited. Future studies are needed in order to determine how well NMES training may work for a broader range of subjects, including those with differing durations of injury, levels of injury, and characteristics such as age or gender. Further study is also needed to project the effects of this exercise modality on inactivity-related disease incidence.

Conclusions

Our findings show that home-based, self-administered NMES-induced resistance exercise therapy can improve FMD and arterial range in individuals with complete SCI. These improvements support the use of this simple and inexpensive therapy to lessen cardiovascular disease risk after complete SCI. In companion studies, the same subjects showed improved muscle mass, muscle fatigue resistance, and insulin action. Taken together, these findings suggest that meaningful health benefits are attainable through resistance-based leg exercise therapy in people with SCI.

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