Case Reports in Clinical Medicine, 2024, 13, 544-557
https://www.scirp.org/journal/crcm
ISSN Online: 2325-7083
ISSN Print: 2325-7075

High-Voltage Electrical Stimulation Can Restore Mitochondrial Capacity Following Denervation by Cauda Equina Injury

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How to cite this paper: McCully, K.K., Reynolds, M.A., Erickson, M.L. and Tansey, K.E. (2024) High-Voltage Electrical Stimulation Can Restore Mitochondrial Capacity Following Denervation by Cauda Equina Injury. *Case Reports in Clinical Medicine*, **13**, 544-557.
https://doi.org/10.4236/crcm.2024.1312064

Received: October 31, 2024
Accepted: December 9, 2024
Published: December 12, 2024

Abstract

High-voltage functional electrical stimulation (HVFES) training of denervated, degenerated muscle (DDM) increases muscle mass and force output, regenerates muscle fibers and restores muscle ultrastructure. However, the effects of this training on the metabolic capacity of DDM have not been reported. **Objective:** Describe the effects of a novel HVFES exercise protocol on lean muscle, adipose tissue thickness (ATT), and mitochondrial capacity in DDM. **Design:** Single subject proof of principle investigation, pre/post-intervention. **Methods:** This study measured changes in muscle thickness, ATT, and mitochondrial capacity in the DDM of a chronically spinal cord injured (SCI) 33-year-old man before and after 20 months of HVFES training. Muscle thickness and ATT were measured with ultrasound. Mitochondrial capacity, measured as the rate of recovery of muscle oxygen consumption using near-infrared spectroscopy, was the metabolic outcome measure. **Results:** HVFES increased muscle tissue thickness of the right vastus medialis and lateralis from 1.65 cm (SD 0.26 cm) and 1.25 cm (SD 0.24 cm) at six weeks to 1.94 cm (SD 0.47 cm) and 1.68 cm (SD 0.07 cm) at 20 months, respectively. Mitochondrial capacity increased from *no detectable metabolic response* at 1.3 months of training to 0.30 min^{-1} at 14 months, 0.91 at 15 months, and 0.99 min^{-1} at 20 months. Rates were slower than able-bodied values but within the range observed in paralyzed muscle from complete SCI with intact lower motor neurons (LMN). **Limitations/Conclusions:** HVFES training restored DDM's mitochondrial capacity in a case study to levels exceeding paralyzed muscle from untrained, complete SCI with intact LMNs; however, more research is needed to replicate this response and determine if increased mitochondrial capacity results in additional metabolic benefits for patients.

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Keywords

Skeletal Muscle, Training, Near Infrared Spectroscopy

1. Introduction

Severe injuries to the lower thoracic or lumbar spine, at or just caudal to the terminus of the spinal cord, may result in the loss of sensory and lower motor neurons (LMNs) responsible for innervating muscles of the lower limbs. Injuries occurring at T_{11}-L_1 account for 14.2% of total SCIs in the United States [1] and can present as different levels of vertebral neurological injury: upper motor neuron (UMN) syndrome, a mix of upper and lower motor neuron syndromes, or predominantly a LMN/peripheral nerve injury. LMN/peripheral nerve injuries manifest as conus medullaris syndrome (CMS) and/or cauda equina syndrome (CES), with CES being the most prevalent [2]-[6].

Injuries involving LMNs result in muscles innervated by these spinal levels to show severe muscular atrophy, leading to subsequent disorganization of the contractile apparatus and inability to sustain tension, as well as increased fatty and connective tissue infiltration within the muscle and local vascular dysfunction. [7]-[10]. To combat the ultrastructural and functional changes that occur in denervated, degenerated muscle (DDM), European Project RISE researchers developed a novel therapeutic tool for people with complete conus or cauda equina injury [11]-[17], namely a commercially available, high-voltage functional electrical stimulator (HVFES) capable of eliciting contractions in DDM using high-intensity, long-duration impulses (Stimulette den2X, Medizintechnik, Mödling, Austria). Studies using this FES system in DDM have reported increased muscle mass and force output, as well as regeneration of muscle fibers and the return of normalized muscle ultrastructure following training with this FES [16] [17]. However, there is no information available on the recovery of metabolic capacity in denervated, degenerated muscles after high-voltage FES.

Emerging evidence suggests that chronic resistance and endurance training with lower-voltage neuromuscular electrical stimulation (commonly used FES) can enhance mitochondrial function in LMN and UMN SCI [18]-[20], but no study to date has assessed the effect of HVFES on the restoration of muscle metabolism and mitochondrial function in people with LMN injuries. This is the first study to evaluate the effects of HVFES on muscle metabolism in a human subject with chronic cauda equina syndrome. This study specifically measures muscle mitochondrial capacity in DDM of completely and permanently denervated muscle before and after 20 months of HVFES training.

2. Methods

Subject Profile

The subject was a 33-year-old white male who, at the time of enrollment, was three years and three months status-post a motor vehicle crash resulting in T_{12} American Spinal Injury Association (ASIA) Impairment Scale (AIS) A (sensory and motor complete) cauda equina injury [21]. Prior to screening for this study, the subject received information about the training protocol developed by the European Project RISE [12] and provided informed consent approved by the primary Institutional Review Board (IRB) at Shepherd Center, as well as the secondary IRB at the University of Georgia. The inclusion criteria for this study were based on the criteria outlined in the European Project RISE: complete conus, cauda equina, or lumbar plexus lesion with chronic denervation of the quadriceps muscle; time since denervation $\geq$ 9 months and $\leq$ 9 years; absent sensation in the thighs; flaccid paralysis without spasticity or segmental reflexes; and intact skin. Exclusion criteria were implants at or near the sites of stimulation (e.g., orthopedic hardware, defibrillators, Brindley stimulators, pumps, pain stimulators), hazardous infections (e.g., hepatitis B or C or HIV/AIDS), and pregnancy. At enrollment, poly-EMG testing confirmed this subject had a complete cauda equina lesion with chronic denervation of his lower extremities (no motor unit action potentials recorded during attempts at voluntary or reflex muscle activation and no spontaneous motor unit potentials recorded). Clinical examination also confirmed the absence of spasticity and segmental reflexes throughout both of his lower extremities. The subject satisfied all study inclusion/exclusion criteria except for having passive hardware in his left femur (plate and screws) following open reduction and internal fixation of a femur fracture in 2011. This hardware was later removed in the spring of 2012. The subject also had fixation hardware in his thoracolumbar region, which was incompatible with magnetic resonance imaging (MRI) of his spinal injury. Once the subject consented, he underwent repeated clinical and functional assessments, including reflex testing, stimulation-response testing, and ultrasound testing, which were performed at Shepherd Center's Hulse Spinal Cord Injury Laboratory, Atlanta, GA (USA). Due to the necessity for muscle contractions for the near-infrared spectroscopy (NIRS) mitochondrial assessment, NIRS measurement was not conducted until visible contractions were observed (40 days of training). The first NIRS test was conducted at the University of Georgia's Department of Kinesiology, Athens, GA (USA). Subsequent NIRS testing was conducted at the University of Georgia, Athens, GA (USA) and Shepherd Center, Atlanta, GA (USA).

HVFES Training and Testing

For this study, a Stimulette den2X FES device (Schuhfried GMBH, Mödling, Austria) was used for training and testing. The trained muscles included the quadriceps, hamstrings, tibialis anterior, triceps surae, and gluteals. Testing occurred on the quadriceps muscle of the right leg. The Stimulette den2X is capable of delivering high-intensity and long-duration impulses sufficient to directly depolarize and elicit contraction of denervated skeletal muscle fibers [11]. In the first two months of training and testing, the subject used FES gel and large (180 cm^2) electrodes (Schuhfried GmbH, Modling, Austria) made of conductive polyurethane.

The subject secured the electrodes over the muscle bulk of his lower extremities and gluteal muscles using elasticized wraps (**Figure 1**). Despite the subject using appropriate amounts of conductive gel, he developed superficial and partial-thickness burns at some sites at about the eighth week of training. With temporary suspension of the stimulation (eight weeks), these wounds healed, and future burns were avoided by switching from gel-coated electrodes to sponge cloth bag-type covers for the electrodes. The electrodes were sufficiently flexible to allow improved distribution of pressure to the subject's skin, and care was taken to prevent the electrodes from contacting each other during testing and training.

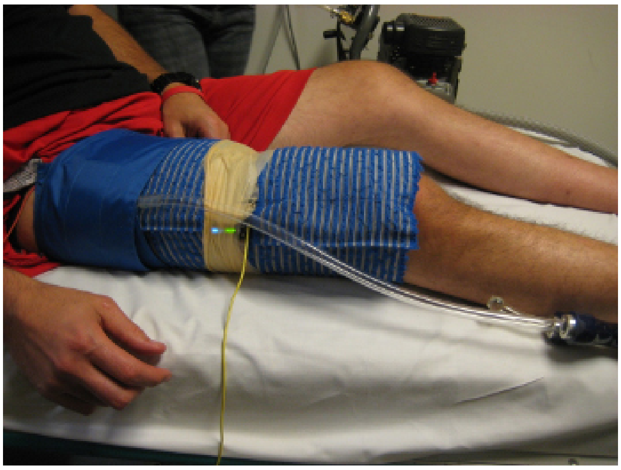

Figure 1. Set-up of den2X for stimulation of the right quadriceps during NIRS testing. The subject used sponge cloth bags and carbon electrodes for stimulation. These electrodes were secured with elasticized bandages (white arrows). A blood pressure cuff (striped arrow) was placed as high on the thigh as anatomically possible. This cuff was used to perform intermittent arterial occlusions as part of the NIRS testing. The NIRS optode (cross-hatched arrow) was secured in place with a pre-wrap between the stimulating electrodes and over the bulk of the subject's right vastus lateralis muscle.

The training protocol (as per the European Project RISE) and testing schedule used for this study are outlined in **Table 1**. All trained muscles followed the same protocol as in the table except the left leg. The left hamstrings and quadriceps were not trained until the subject had his femur fixation hardware electively removed. The HVFES strategy consisted of three stimulation programs that were introduced in phases as the subject's responsiveness to and tolerance of the stimulation progressed. Stimulation phases were advanced based on the muscular responsiveness of the quadriceps muscle groups to the stimulation as assessed by twitch or sustained muscular contraction in response to the stimulation. At the beginning of the HVFES training, bi-phasic stimulation impulses of long duration (150 msec) and high intensities (up to 220 mA) were applied. Each of these parameters was adjusted as the protocol was advanced. The subject underwent clinical assessment every six to eight weeks by the research physical therapist, who progressively modified the stimulation parameters and protocol to maximize the subject's responses.

Phase I consisted of eliciting twitch contractions only for up to 15 minutes per muscle group trained. Phases II and III combined twitch and tetanic contractions in sessions lasting up to 25 minutes per muscle group trained. At the beginning of the stimulation protocol, the subject's muscles could only produce single twitches. By 14 months of training, it was possible to reduce the impulse durations used and produce tetanic contractions, which were initially weak, but subjectively improved in strength by 20 months of training. The training of the subject's left leg was delayed due to his fixation hardware; however, he was able to achieve phase three of training bilaterally by 14 months.

Table 1. High-voltage electrical stimulation training and testing protocol. Trained muscles included the quadriceps, hamstrings, gluteals, tibialis anterior, and triceps surae. Training of the left thigh was delayed for six months due to the presence of fixation hardware in the subject's left thigh. NIRS and ultrasound testing were conducted on the right quadriceps only (vastus lateralis for NIRS and vastus medialis/lateralis for ultrasound).

	Phase I	**6 Weeks**	**7 Weeks Phase II**	**6 Months Phase III Right; Phase II Left**		**10 Months Phase III-Advancing**	**14- and 20-Months Phase III continued**
Impulse Duration (msec)	120 - 150 (Bilateral Except Left Thigh)	Metabolic Tests (NIRS) Ultrasound	70 - 100 (Bilateral Except Left Thigh)	30 - 50 (Right Side)	70 - 100 (Left Side Including Thigh)	30 - 50 (Bilateral)	Metabolic Tests (NIRS) Ultrasound
Interpulse Interval (msec)	400		400	10 - 15	400	10	
Surge Duration (sec)	4		5	2	5	2	
Surge Interval (sec)	4		5	3	5	2	
Repetitions	3 - 4 × 3 min		4 - 5 × 3 min	4 - 5 × 3 min	4 - 5 × 3 min	4 - 5 × 20 repetitions	
Pause (min)	1 - 2 min		1 - 2 min	1 - 2 min	1 - 2 min	1 - 2 min	
Days/Week	5 - 6		5 - 6	5 - 6	5 - 6	5 - 6	

The stimulation provided by the den2X consisted of balanced bi-phasic square waves that were of much longer impulse duration (30 - 150 msec vs. 1 - 400 µsec, respectively) than traditional neuromuscular electrical stimulation, thus allowing for the direct depolarization of denervated muscle rather than reliance upon intact peripheral nerve terminals to conduct action potentials to the muscles via motor endplates. The surge durations were also much longer, allowing for more total energy to be passed into the tissue during each stimulated contraction. With every change in the impulse parameters, the adjustment of the signal frequency was calculated and displayed on the device. Pulses were delivered in surges lasting several seconds, followed by intervals/pauses between surges. Surge durations were ≥ 5 × (impulse duration + inter-pulse interval). The mVO_2max measurements require muscle activation. Because of this, the first NIRS measurement occurred after six weeks of training once visible muscle contractions were observed. Measurements were also taken at 14, 15, and 20 months of training.

Ultrasound Testing of Tissue Thickness

Subcutaneous adipose tissue thickness (ATT) and muscle thickness were measured in seven locations along the lengths of the vastus medialis and lateralis muscles of the subject's right thigh using B-mode ultrasound (LOGIQ e, GE Healthcare, USA). Bony landmarks and length measurements were used to gauge the location of each measurement to try to ensure consistency of the ultrasound testing between sessions. The tissue of the left thigh was not measured due to the fixation hardware initially present in the subject's left femur. Adipose tissue thickness and muscle thickness measurements from multiple sites were averaged for reporting.

Near-Infrared Spectroscopy (*NIRS*): *Measurement of Mitochondrial Capacity*

Skeletal muscle mitochondrial capacity (mVO_2max) was evaluated using near-infrared spectroscopy (NIRS) to measure the rate of recovery of oxidative muscle metabolism from exercise levels to resting [22]-[25]. The NIRS device (PortaMon, Artinis Medical Systems, Zetten, Netherlands) used in this study measured the absorption properties of hemoglobin and myoglobin at 760 and 850 nm, and the difference signal between these two wavelengths used to measure relative changes in oxygen levels within the tissue over time [24] [26]-[29]. The device had optode distances of 20, 30, and 40 mm and a sampling rate of 10 Hz. No differences were seen in the data from the different optode distances, and the data from the 40 mm separation distance was used to calculate mVO_2max. The depth of penetration of the light was approximately half of the inter-optode distance [30].

For the NIRS testing, the subject was positioned semi-recumbent on an adjustable mat table with his lower extremities fully extended. The NIRS device was secured with an elasticized wrap and bi-adhesive tape between the stimulating electrodes and over the right vastus lateralis (**Figure 1**). A blood pressure cuff (used for intermittent arterial occlusions) was placed proximal to the NIRS device over the proximal stimulating electrode. Testing began with resting oxygen consumption (mVO_2) measurements, which was the slope of the change in the oxygen signal with five seconds of arterial occlusion. Following resting measurements, one minute of electrical stimulation set at the subject's training parameters was applied to the right quadriceps to stimulate skeletal muscle metabolism. Repeated arterial occlusions were performed after stimulation and at increasing time intervals to measure the rate of recovery of mVO_2 post-exercise [22] [23] [25] [31]. Metabolic recovery data were recorded for up to ten minutes during these tests. NIRS data were scaled as a percentage of the maximal physiological range in mVO_2 as described in previous studies [23] [25] [32]. The physiological range of the muscle was obtained with a 5 - 8 minute arterial occlusion that completely oxygen-depleted the muscle tissue distal of the cuff. The release of the arterial occlusion then elicited reactive hyperemia. The physiological range was calculated as the difference between the minimum and maximum NIRS values during the ischemia/hyperemia test, which allowed us to control for adipose tissue thickness in our testing [23] [33] sessions with no adverse events.

The mVO_2 was calculated as the rate of change in the NIRS signal during the intermittent arterial occlusions using simple linear regression and was expressed as a percentage of the physiological range per unit of time. The post-exercise repeated measurements of mVO_2 were fit to a mono-exponential curve according to the formula below (Equation (1)) where y is relative mVO_2 during the arterial occlusions, *End* is the mVO_2 immediately after the end of exercise, *Delta* is the change in mVO_2 from rest to end of exercise, k is the fitting rate constant (proportional to the mitochondria's oxidative capacity), and t is the time.

$$y = End - Delta \times e^{-k \cdot t} \tag{1}$$

Analysis

Data for adipose tissue thickness (ATT) and lean muscle thickness are presented as means (SD). NIRS data analysis was performed using custom-written routines (Department of Kinesiology, University of Georgia, Athens, GA) for Matlab version 7.13.0.564 (The Mathworks, Natick, MA). An individualized blood volume correction factor for each arterial occlusion was applied to all data [23].

3. Results

Lean Muscle Thickness and Adipose Tissue Thickness

Ultrasound measurements of the right vastus medialis and lateralis muscle were taken after six weeks of training and after 20 months of total HVFES training. ATT over the vastus lateralis was 1.14 cm at 6 weeks and 0.954 cm at 20 months. ATT over the vastus medialis was 1.23 cm at 6 weeks and 1.25 cm at 20 months. The vastus lateralis muscle thickness increased from 1.65 cm at 6 weeks to 1.94 cm at 20 months. The vastus medialis muscle thickness increased from 1.41 cm at 6 weeks to 1.68 cm at 20 months. This indicated increases in muscle thickness of 18% and 19% for the vastus lateralis and vastus medialis muscles, respectively.

Near-Infrared Spectroscopy (*NIRS*): *Mitochondrial Capacity*

Following the first 1.3 months of HVFES training (twitch contractions only), no muscle metabolism at rest or with electrical stimulation was observed (**Figure 2(A)**). Muscle metabolism was seen both at rest and with electrical stimulation at the other time points (**Figure 2(B)**). The recovery curves used to calculate mVO_2max are shown in **Figure 3**. At 1.3 months, there were no measurable changes in mVO_2, and recovery kinetics could not be calculated. Recovery kinetics could be calculated for the rest of the time points.

mVO_2max appeared to increase at the 15 and 20-month time points from the first detectable appearance of mVO_2 observed at 14 months (**Figure 4**). Results for LMN intact participants taken from a previous study are plotted in **Figure 3** for comparison.

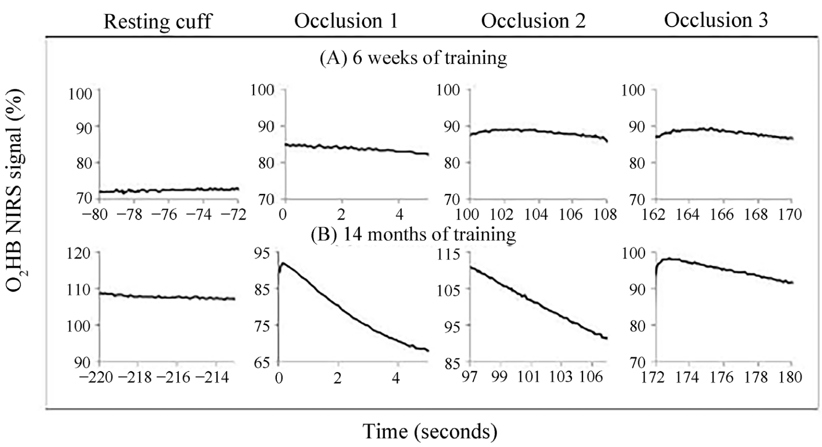

Figure 2. NIRS O_2Hb signals during arterial occlusions at rest and at three representative time points during a mVO_2max test. Time zero is prior to electrical stimulation and represents resting muscle oxygen consumption. Occlusion 1 is an arterial occlusion at 5 seconds into the kinetic recovery test; Occlusion 2 is at 100 seconds; and Occlusion 3 is at 160 seconds in the test. Panel A shows testing after 6 weeks of training, where there was little change in metabolic rate (mVO_2) post-exercise. Panel B shows testing after 15 months of training, where there was a noticeable change from resting to exercise mVO_2.

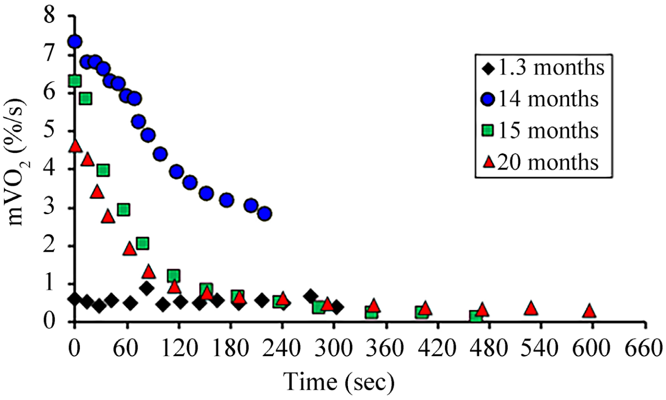

Figure 3. Graph of NIRS oxidative recovery curves of the vastus lateralis after 1 minute of electrically stimulated exercise. At 1.5 months (black diamonds), mVO_2max could not be calculated. At the 13.8, 15.4, and 20.5-month time points, muscle metabolism had increased with electrical stimulation enough to allow measurement of recovery rates. Thus, mVO_2max could be calculated for these time points. For the 13.8, 15.4, and 20.5-month time points, the data shown are averages of two stimulation and recovery time course measurements.

4. Discussion

The present study provides the first proof of principle report that HVFES of sufficient strength and duration is not only capable of producing muscular contractions but also improvements in the mitochondrial capacity of denervated and degenerated human muscle, even after a prolonged period of denervation. The subject in this study began stimulating his muscles when he was more than three years post-SCI, suggesting that muscle tissue degeneration had likely occurred as a result of injury, prior to the initiation of HVFES training [14] [17] [34] [35]. In spite of the chronicity of his denervation, the time course of the increases in visible contraction strength in his muscles was consistent with the European Project RISE results, where twitch contractions eventually converted to tetanic contractions that could move limb segments against gravity [12] [14]-[17]. The subject was evaluated at regular intervals by the research physical therapist, who progressed the stimulation parameters and protocol from twitch contractions in the first four months to longer duration and even tetanic contractions against gravity using the weight of the limb for resistance [7] [12] [16]. In previous research conducted for the European Project RISE, long-duration and high-intensity stimulation training have led to recovery of human muscle contractility, muscle cross-sectional area, fiber size, and ultrastructural features [14] [17]. In the present study, MRI confirmation of changes in muscle ultrastructure and cross-section was not possible due to the subject's metal implants. Ultrasound testing showed an increase in quadriceps muscle thickness, consistent with the changes in muscle morphology seen in the RISE project.

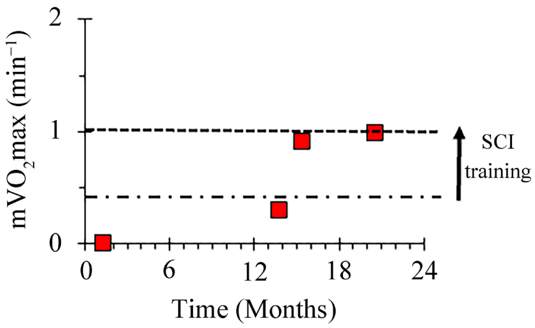

Figure 4. mVO$_2$max during training in the subject with a lower motor neuron (LMN) injury. Values for untrained subjects with complete SCI with intact LMNs before and after endurance training are shown for comparison [38]. Also, for comparison, untrained, able-bodied subjects have mVO$_2$max values of 1.9 min^{-1} [31].

The major new finding of the present study was the increase in mitochondrial capacity measured with NIRS, which had not been reported in previous studies of HVFES training in human DDM. The present study shows that after supervised, progressive HVFES training, a measurable improvement in mitochondrial capacity can be obtained in chronically denervated human skeletal muscle. Consistent with European Project RISE, the time course for this subject's muscle improvement was greater than one year to achieve substantial recovery in muscle metabolic functioning. After more than 14 months of stimulation training, mVO$_2$max in this subject with chronic DDM was amongst the lowest values known to the authors [36], and similar to mitochondrial capacity values in people with SCI who are untrained but have intact LMNs [37] [38]. With additional months of training, the subject's muscles showed increasing improvements in mitochondrial capacity.

The mVO_2max values at 15 and 20 months were similar to those seen in motor-complete SCI after endurance training [38]. Still, at the end of the study, the mVO_2max was ~1.0 min^{-1}, which is much less than the ~1.9 min^{-1} for able-bodied individuals [31]. It is interesting to note that there was no measurable change in muscle metabolic rate or mitochondrial capacity at six weeks of training, despite the visible muscle contractions elicited by the HVFES. This suggests that contractility and its resulting energetic demands may precede mitochondrial recovery and could, perhaps, be causal.

One of the questions raised by this study pertains to the magnitude of improvement in mVO_2max that was observed. mVO_2max appears to have leveled off in this subject by 20 months of HVFES training. A previous study showed that endurance training of a person with complete SCI with intact LMN improved mVO_2max to a similar level with 4 months of endurance training and that this mVO_2max also appeared to have leveled off [32]. These levels are not only lower than untrained able-bodied people, but much lower than the values seen in endurance athletes (~1.0 compared to ~3.5 min^{-1}) [31]. To further enhance mitochondrial capacity in people with DDM, more endurance-oriented training might be necessary; however, the total stimulation duration in this study was already two hours per day (30 minutes per muscle). It might take more advanced technology to allow more endurance-trained stimulus protocols to become practical for a person with DDM. In addition, patients and clinicians contemplating the use of HVFES for the restoration of DDM should consider the costs/benefits of training relative to their goals (*i.e.*, improved metabolism, increased muscle bulk to prevent pressure ulcers, or to prepare muscle for future re-innervation strategies). The benefits of HVFES based on the changes in skeletal muscle seen in this and other studies remain to be quantified.

5. Limitation

The present study had several limitations. First, we do not know whether the training dosage was optimal for improving mitochondrial capacity in the subject's muscles. The number of training sessions, the duration of each training session, the parameters selected, and the training frequency were modeled after the European Project RISE research. The protocol and dosages were selected based on the subject's muscular responses and his skin tolerance to the stimulation. Subsequently, the training dosage was based in part on clinical judgment in the absence of experimental evidence related to the optimal training dosage needed to restore muscle metabolism in DDM. Second, due to the incompatibility of the subject's spinal hardware with magnetic resonance imaging, we were unable to confirm muscle cross-sectional and ultrastructural changes that may have been produced by the training, although the ultrasound findings suggest that these training effects may have been present in our subject. A final drawback was that this study was limited to one participant. The stimulator used for this research is not readily available for purchase in the United States, meaning that access here to such devices for research or training purposes is limited. Further study is necessary to determine if HVFES training is able to consistently restore mitochondrial capacity in people with DDM following conus or cauda equina injury. Care needs to be taken to watch for skin lesions, however, especially with the gel electrodes. It is not recommended to perform this kind of stimulation without close medical supervision.

6. Conclusion

This single-subject case study showed that with adequate stimulation training, mitochondrial capacity can be at least partially restored in denervated, degenerated human skeletal muscle. After more than a year of training, the subject developed an enhanced metabolic rate in response to the use of electrical stimulation, which allowed for the measurement of mitochondrial capacity. HVFES training improved the subject's mitochondrial capacity similar to that of untrained muscle in people with SCI who have intact LMNs, but remained less than what would be expected for someone without injury. This study helps to confirm the findings of the European Project RISE, showing that training of long-term denervated muscles is possible. In addition, this study provides the first proof of principle evidence that mitochondrial capacity in trained muscle can be recovered in chronic DDM.

Acknowledgements

This study is dedicated to Joy A. Bruce, DPT from the Hulse SCI Lab at the Shepherd Center, who led the study but passed away before the study could be published. We would like to acknowledge Katie Fitzgerald, DPT with Shepherd Center, Atlanta, GA, for monitoring the subject's skin care and Winfried Mayr, PhD, for his insights about the HVFES and the subject's passive implants.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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