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Low-Force Muscle Activity Regulates Energy Expenditure after Spinal Cord Injury

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Abstract

Reduced physical activity is a primary risk factor for increased morbidity and mortality. People with spinal cord injury (SCI) have reduced activity for a lifetime, as they cannot volitionally activate affected skeletal muscles. We explored whether low force and low frequency stimulation is a viable strategy to enhance systemic energy expenditure in people with SCI.

Purpose—To determine the effects of low stimulation frequency (1 Hz, 3 Hz) and stimulation intensity (50 mA and 100 mA) on energy expenditure in people with SCI. We also examined the relationship between body mass index (BMI) and visceral adipose tissue (VAT) on energy expenditure during low frequency stimulation.

Methods—Ten individuals with complete SCI underwent oxygen consumption monitoring during electrical activation of the quadriceps and hamstrings at 1 Hz and 3 Hz and at 50 and 100 mA. We calculated the difference in energy expenditure between stimulation and rest and estimated the number of days that would be necessary to burn 1 pound of body fat (3,500 kcal) for each stimulation protocol (1 Hz versus 3 Hz).

Results—Both training frequencies induced a significant increase in oxygen consumption above a resting baseline level ($p < 0.05$). Energy expenditure positively correlated with stimulus intensity (muscle recruitment) and negatively correlated with adiposity (reflecting the insulating properties of adipose tissue). We estimated that 1 pound of body fat could be burned more quickly with 1 Hz training (58 days) as compared to 3 Hz training (87 days) if an identical number of pulses were delivered.

Conclusion—Low-frequency stimulation increased energy expenditure per pulse and may be a feasible option to subsidize physical activity to improve metabolic status after SCI.

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Conflict of Interest:

There are no conflicts of interest.

The results of this study do not constitute endorsement by the American College of Sports Medicine.

The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

Keywords

Diabetes; obesity; electrical stimulation; exercise; metabolism

INTRODUCTION

Reduced physical activity is a known primary risk factor for increased morbidity and mortality (7,17,25). The American College of Sports Medicine recommends at least 150 minutes of moderate to vigorous intensity physical activity each week to promote overall health (17). However, people with spinal cord injury (SCI) have reduced activity for a lifetime, as they lose the ability to volitionally activate the vast majority of their skeletal muscle.

Due to disuse, skeletal muscle undergoes many adverse changes soon after SCI. Within 4 months after SCI, cross sectional area of skeletal muscle decreases by as much as 55% compared to matched non-SCI controls who have not formally exercised for 6 months (9). Normally, skeletal muscle accounts for up to 75% of glucose uptake in healthy individuals (8). With SCI, physical inactivity suppresses oxidative gene expression, and mitochondrial function is halved (30). Even muscles that are predominantly composed of oxidative slow-twitch fibers, such as the soleus, transition to a glycolytic fast-twitch phenotype in people with SCI (1,37,38,40). This transformation of skeletal muscle yields a phenotype that is internally consistent among people with complete and chronic SCI. Remarkably, factors such as age, time post injury (if over 1 year) and injury level minimally impact the physiological properties of a nearly homogenous fast glycolytic paralyzed muscle (41,42). Through the combined effects of muscle atrophy and muscle phenotypic shift, people with SCI experience decreased glucose disposal by fast skeletal muscle and decreased insulin sensitivity (6,15). Overall, the metabolic changes in skeletal muscle due to SCI increase the predisposition for development of diabetes, cardiovascular disease, and other comorbidities due to altered metabolism (6,26).

One strategy to increase physical activity in people with paralysis is to induce muscle contractions using neuromuscular electrical stimulation. However, strong muscular contractions pose a fracture risk for the osteoporotic post-SCI skeletal system (13,20,40). For patients with SCI, an ideal training protocol would be to activate most of the muscle fibers without producing high force; a condition that can be accomplished with low frequency, non-tetanic contractions. When muscle is stimulated at a low frequency but high intensity, pulses are delivered with a sufficient inter-pulse interval to prevent muscle twitch summation, despite nearly complete recruitment of all muscle fibers (36). Therefore, it may be feasible to use low frequency electrical stimulation to induce safe, low-force activity in people with SCI.

Recent studies in healthy people have questioned the assumption that higher muscle forces, which contribute to “moderate to vigorous activity”, are required to improve health (5,14,23,35). Complete inactivity (like sitting) has negative health effects even for those who participate in a single bout of higher intensity daily exercise (43). Simple low intensity activities such as standing throughout the day or engaging in very light intensity activity to

interrupt periods of sitting have improved the metabolic profiles of sedentary individuals (5,14,23,35).

Recently, we demonstrated that a single bout of low frequency and low force electrical stimulation regulated key genes associated with oxidative metabolism, as measured 3 hours after training in the soleus and quadriceps of participants with chronic, complete SCI (36–38). For example, just two trains of 120 non-summating pulses were sufficient to induce expression of peroxisome-proliferator-activated-receptor-gamma-coactivator-alpha (PGC-1 α) (38). PGC-1 α gene expression is induced by physiological stress and plays a key role in initiating mitochondrial biogenesis, regulating hypertrophy, and restoring insulin sensitivity (31,32). Thus in participants with chronic, complete SCI, low frequency stimulation provided a sufficient stimulus to induce expression of genes that regulate oxidative metabolism (36,38). It therefore seems plausible that systemic adaptations observed in studies of higher-frequency stimulation (11,18,19,29) may be likewise achievable with non-summating stimulation.

A key feature of low-frequency stimulation is the relaxation of muscle force between stimulus pulses. Because relaxation is an adenosine triphosphate (ATP)-dependent process, low frequency stimulation may increase energy expenditure compared to high-frequency (tetanizing) stimulation. If this is indeed the case, people with SCI may be able to employ long-duration, low-frequency stimulation to simulate the energy expenditure of long duration, low intensity activity throughout the day (e.g. standing). By subsidizing lost activity, regular long duration, low frequency training may have the potential to improve overall systemic metabolic health. In this study, we examine whether a bout of low frequency stimulation regulates systemic energy expenditure in people with SCI. By examining two frequencies and two intensities, we put forth a “dose” effect that will be needed to implement these interventions into clinical practice.

The purpose of this study was to determine the effects of low stimulation frequency (1 Hz, 3 Hz) and low stimulation intensity (50 mA and 100 mA) on energy expenditure in people with SCI. We also examined the relationship between body mass index (BMI) and visceral adipose tissue (VAT) on energy expenditure during low frequency stimulation. We hypothesized that by distributing muscle activity over a longer time (lower frequency), energy expenditure would be greater than the energy expenditure observed when the same number of muscle contractions were elicited in a shorter time (higher frequency), despite both frequencies inducing non-tetanic contractions. We expected that the higher stimulus intensity (100 mA) would yield a greater change in energy expenditure than the lower intensity (50 mA), reflecting greater recruitment of underlying muscle tissue. We also hypothesized that because body fat may increase tissue impedance (and therefore reduce the electrical current reaching the muscle surface), BMI and VAT would negatively correlate with the change in energy expenditure.

METHODS

Subjects

Ten participants with a complete motor spinal cord injury (American Spinal Injury Association (ASIA) Impairment Scale-A) (3) participated in the study (Table 1). This study was approved by the University of Iowa Human Subjects Office institutional review board. All participants provided written informed consent prior to participation. Participants were a convenience sample from the local community and had not performed electrical stimulation training. Exclusion criteria were systemic illness, pressure ulcers, pregnancy, and inability to tolerate cutaneous electrical stimulation due to autonomic hyperreflexia. To measure components of self-perceived general health status, participants filled out the SF-36 walk-wheel (SF-36_{ww}), which includes modifications of the original SF-36 that increase responsiveness of physical function domain scores for non-ambulatory participants (27). We tabulated scores for the Physical functioning, Role limitations-physical, and General health subscales on a scale from 0 (worst function) to 100 (best function). National normative values for these subscales are anchored to a mean of 50; thus scores below 50 reflect poorer-than average function and scores above 50 indicate better-than average function for that subscale.

Instrumentation

Body Fat—Visceral adipose tissue (VAT) was measured using ultrasound imaging (LOGIQ_i, GE Healthcare, Milwaukee WI) while the subject was supine. A 4C probe was positioned transversely approximately 2.5 cm superior to the navel just to the left of the linea alba. Probe positioning was adjusted slightly until the image included the junction of the linea alba and left rectus abdominus as well as the abdominal aorta. VAT was defined as the distance in centimeters from the anterior abdominal aorta to the junction between the left rectus abdominus and linea alba.

Electrical stimulation—8 self-adhesive 7 cm × 13 cm oval carbon electrodes (Empi, Inc. St. Paul, MN) were adhered to the skin over the quadriceps and hamstring muscles (4 electrodes per leg). These muscles were selected because of their ease of access, clinical importance, and because of their large size, which we reasoned would yield the greatest potential for altering energy expenditure. The distal margin of the distal quadriceps electrode was placed over the distal-most palpable border of the vastus lateralis. The proximal quadriceps electrode was positioned as close to the inguinal crease as possible, with the medial electrode margin lateral to the adductor muscle group. The distal margin of the distal hamstrings electrode was placed over the biceps femoris and semitendinosus, proximal to the popliteal fossa. The proximal hamstrings electrode was positioned over the hamstring muscles as close to the gluteal fold as possible, with the medial electrode margin lateral to the adductor muscle group. Electrodes were connected via shielded cabling to a portable stimulator unit (Empi Infinity Plus; Empi, Inc. St. Paul, MN; maximal output: 100mA, 1–150Hz).

Heart rate (HR) and energy expenditure—To monitor heart rate during testing, each subject wore a wireless chest strap heart rate monitor (Polar Electro Inc. Woodbury, NY);

the electrodes were moistened with ultrasound gel prior to placement in order to improve electrode contact. We measured heart rate (via wireless transmission), oxygen consumption, and carbon dioxide exhalation using a metabolic cart (MEDGRAPHICS CPX Express; Medical Graphics Corporation St. Paul, MN). The participant wore a nose clip to prevent nasal inspiration/expiration and breathed through a mouthpiece connected to the metabolic cart. The metabolic cart was set to record heart rate and oxygen consumption every 30 seconds.

Experimental Protocol

Subjects lay supine on a therapy table with two pillows placed under the knees. Subject 02 reclined in his motorized wheelchair to avoid an unnecessary transfer. To measure energy expenditure resulting from electrical stimulation rather than other stimuli, we instructed each participant to lay as quietly and still as possible during testing. After affixing the quadriceps and hamstring electrodes, we covered each subject with a blanket to avoid energy expenditure from thermogenesis, and we dimmed the lighting to decrease environmental stimuli.

Baseline oxygen consumption, carbon dioxide exhalation, and heart rate were measured while participants lay quietly (Figure 1, white plots). 1 Hz stimulation to the quadriceps and hamstrings was then given at a stimulus intensity of 50 mA. Stimulation was applied simultaneously to create co-contraction, which pilot subjects indicated was more comfortable than asynchronous quadriceps/hamstrings contractions. The intensity was gradually increased over a period of 128 ± 52 seconds up to an intensity of 100 mA (the maximum output of the stimulator; thus the maximum possible muscle recruitment) (Figure 1). A gradual increase in stimulation intensity was used to prevent muscle spasm and autonomic dysreflexia. After reaching 100 mA, 1 Hz stimulation was given for 6 minutes. We selected 6 minutes of stimulation because steady state was demonstrated in this time frame and our desire to limit the experiment to one hour, to ensure participant comfort (see Figure 1). After 6 minutes of 1 Hz stimulation, the stimulator was then turned off for 8 minutes and recovery measurements were taken. (As seen in the representative subject in Figure 1, energy expenditure was typically back to baseline within 4–5 minutes. We chose 8 minutes to be assured that baseline was achieved as confirmed by visual inspection of the energy expenditure during the experiment. After full baseline was achieved, a 3 Hz stimulation was given at an intensity of 50 mA, gradually increasing over ~2 minutes to 100 mA. 6 minutes of 3 Hz stimulation were given at 100 mA, followed by another set of recovery measurements (8 minutes). Figure 1 shows a representative example of oxygen consumption during the 1 Hz, 3 Hz, and recovery intervals.

Subjects 1–7 returned on a second day (2–11 days later) to undergo measurements of the effect of stimulus intensity on energy expenditure. We used a single frequency, 3 Hz, to minimize the duration of the experiment. Using the same participant positioning and instrumentation described above, we administered 3 Hz stimulation to the quadriceps and hamstrings at a constant intensity of 50 mA for 6 minutes. After an 8 minute rest, 3 Hz stimulation was given at an intensity of 100 mA for 6 minutes. During the second bout of

stimulation, intensity was gradually increased to 100 mA in order to avoid spasms or autonomic dysreflexia.

Data Analysis

Oxygen consumption and carbon dioxide exhalation measurements were converted to energy expenditure using the Weir equation: $(\text{kcal/day} = [3.9 (\text{VO}_2) + 1.1 (\text{VCO}_2)] 1.44)$ (45). For each dependent variable (oxygen consumption, heart rate), we averaged the twelve data points captured during the 6 minutes of 1 Hz or 3 Hz stimulation at time that constituted steady state in energy expenditure. We used energy expenditure values in kcal/day to estimate the amount of time it would take to burn one pound of fat (3,500 kcal) at the two frequencies of stimulation compared to resting energy expenditure. To control for energy delivered to muscle tissues – in essence, the number of stimulus pulses delivered – calculations were made based on a daily stimulation dose of 3,600 pulses. At 1 Hz, delivering 3,600 pulses would equate to one hour of daily training, a duration chosen to reflect the likelihood that health benefits of isolated, evoked muscle exercise may require a greater time investment than the currently-recommended duration of whole-body, ambulatory physical activity (30 min/day) (17). The same dose of pulses delivered at 3 Hz would equate to 20 minutes of daily training. We took the difference between basal energy expenditure for 1 hour of rest ($3/24 \times \text{resting kcal/day}$) and for 1 hour of 1 Hz training ($3/24 \times 1 \text{ Hz kcal/day}$) to determine the energy demand of 1 Hz training that exceeds basal metabolic rate. We also calculated the energy demand of 20 minutes of 3 Hz training ($1/24 \times 3 \text{ Hz kcal/day}$) and obtained the difference from 20 minutes of rest ($1/24 \times \text{resting kcal/day}$) to determine the energy demand of 3 Hz training that exceeds basal metabolic rate. We divided the energy contained in 1 pound of fat (3,500 kcal) by these daily training-related energy costs to determine the number of days required to burn 1 pound of body fat for each training protocol.

Statistical Analysis

A repeated measures analysis of variance (ANOVA) was used to test for differences among the baseline, 1 Hz, and 3 Hz conditions for energy expenditure, HR, and days to burn 1 pound of fat ($n=10$). For each of these dependent variables, a repeated measures ANOVA was also used to test for differences between baseline, 50 mA, and 100 mA intensity conditions ($n=7$). Post-hoc analyses (Tukey) were carried out as indicated ($\alpha = 0.05$). Pearson Product Moment Correlations were calculated for oxygen consumption versus BMI/VAT for each stimulus frequency. Data are reported as mean $\pm$ standard deviation.

RESULTS

Effects of Frequency

Baseline oxygen consumption (mean 195 mL/min) increased to 311 mL/min during 1 Hz stimulation (60.8% increase) and to 367 mL/min during 3 Hz stimulation (89.8% increase) (both $p = 0.001$; Figure 2A). Oxygen consumption for the 3 Hz condition was greater than the 1 Hz condition ($p = 0.035$). 67.7% of the change in oxygen consumption at 3 Hz was achieved with 1 Hz stimulation. HR was not sensitive to the application of electrical

stimulation: HR did not differ from baseline for either 1 Hz or 3 Hz ($p = 0.071, 0.904$ respectively; Figure 2B).

When normalized across a theoretical dose of 3,600 pulses, the 1 Hz stimulation condition would require 58 days to burn 1 pound of fat (Figure 2C). The same number of daily electrical pulses at 3 Hz would require 87 days to burn 1 pound of fat ($p = 0.012$).

Effects of Intensity

The 50 mA stimulus intensity (given at 3 Hz) did not increase energy expenditure significantly from baseline ($p = 0.102$; Figure 3). Energy expenditure at 100 mA significantly differed from both baseline and the 50mA intensity (both $p < 0.001$; Figure 3).

Relationship between energy expenditure, BMI, and VAT

A negative correlation existed between BMI and the change in oxygen consumption observed at both stimulation frequencies ($r^2=0.57$ and 0.62 for 1 Hz and 3 Hz respectively; Figure 4A). Similarly, VAT was a negative correlate of energy expenditure change; r^2 was 0.47 and 0.56 for 1 Hz and 3 Hz respectively (Figure 4B). Age and time post injury were not strong predictors of energy expenditure change; r^2 was 0.06 and 0.18 for the 1 Hz condition respectively; 0.11 and 0.26 for the 3 Hz condition respectively.

The SF-36 *ww* self-reported Physical Function for the study cohort was $47(26)$, which is lower than the US mean for this subscale (50.0 ; max function = 100). The study cohort rated their General health and Role-physical function to be higher than the United States means (63 and 76 , respectively).

DISCUSSION

Our long-term goal is to develop a feasible, safe, and effective method to equip people with SCI to improve their health through regular physical activity. This goal is challenging because non-paralyzed sedentary people may watch 5 hours of television per day but still engage in some sort of physical activity by merely carrying out personal care activities, housework, or simply walking from one room to another. Conversely, people with SCI often require assistance with activities of daily life (e.g. transfers, dressing)(34) and most do not work outside of the home (34,46). These factors severely limit the potential for most people with SCI to engage in routine low-level activity. Even people with paraplegia who can manually wheel long distances cannot activate their largest, potentially most metabolically-important lower extremity muscle groups. Because people with SCI have a compromised skeletal system and minimal opportunity to exercise, we began to examine the value of distributing low force exercise across time to better understand if systemic metabolic benefits could be realized. Our previous work established that brief, low-force muscle activity initiates gene transcription changes in pathways regulating oxidative metabolism. The purpose of the present study was determine the energetic cost of low-force muscle activity and examine the effect of stimulation frequency and intensity. The major findings of this study are 1) The lowest stimulation frequency (1 Hz) most effectively increased energy expenditure in human paralyzed muscle, when normalized across a fixed number of stimulus pulses; 2) Energy expenditure during electrical stimulation is not modulated by a systemic

sympathetic response (HR), 3) The highest stimulation intensity (100 mA) most effectively increased energy expenditure, and 4) Individual factors such as increased BMI and VAT attenuate energy expenditure response to electrical stimulation.

Frequency

In this study, we determined that low frequency stimulation is an effective method to increase energy expenditure in people with SCI. The energetic cost of muscle contraction, both volitional and evoked, hinges upon the ATP-dependent processes that occur during contraction and relaxation. In addition to its critical role in the process of myofibrillar cycling, ATP is required for the re-sequestration of calcium ion after contraction. When neural activation (either volitional or evoked) ceases, sarco(endo)-plasmic calcium ATPase (SERCA), an enzyme residing on the sarcoplasmic reticulum, uses ATP to draw calcium ion away from the contractile filaments and back into “storage” in the sarcoplasmic reticulum. In the absence of calcium ion, the troponin/tropomyosin complex reconfigures and conceals myosin binding sites, preventing myosin/actin interactions and initiating muscle relaxation. The ATP-dependent action of SERCA, therefore, is a critical energy-using step in the process of muscle relaxation. When stimulus frequency is high, relaxation is incomplete between stimulus pulses and summation of force occurs. When stimulus frequency is low, the long inter-pulse interval allows SERCA to more completely re-sequester calcium ion before the arrival of a subsequent stimulus pulse. We believe it is possible that the differential in return to baseline that occurs with 3 Hz stimulation may reduce its energetic cost compared to 1 Hz stimulation. This may in part explain why 1 Hz stimulation more effectively increases energy expenditure compared to higher frequency stimulation (24). Additional support for this potential mechanism was provided by a subset of participants who performed 5 Hz stimulation (data not shown), which yields considerable summation of force. The stimulus pulse-normalized energetic cost of 5 Hz stimulation (days to burn a pound of fat) was higher than for 3 Hz stimulation, approaching over 180 days.

An alternative explanation for the reduced metabolic cost of 3 Hz stimulation may be that higher frequency stimulation may cause greater muscle fatigue. Muscle fatigue (“the decrease in force or power production in response to contractile activity (24).”) may occur due to dysfunction at any of the steps between neural propagation and excitation-contraction coupling. In this study we delivered stimulation pulses at low frequencies and separated each stimulation bout by a recovery period. It is extremely unlikely that these experimental conditions induced neuromuscular transmission failure. Another potential cause of fatigue during 3 Hz stimulation compared to 1 Hz may include impaired ryanodine receptor calcium release from the sarcoplasmic reticulum (24,28). During muscle contraction, especially in glycolytic fast-twitch muscle (the typical post-SCI phenotype), increased ATP use generates more adenosine diphosphate (ADP), which competes for ATP binding sites at the ryanodine receptor (2). As ATP availability declines and ADP accumulates, ryanodine-mediated calcium release decreases in a protective mechanism to decrease ATP consumption (2). Greater stimulation frequencies, in theory, may deplete ATP at a more rapid rate than lower frequencies, potentially causing a decline in calcium release for contractile activity. However, decreased calcium availability does not necessarily imply decreased force production (28). After initiation of contraction, myosin light chain kinase activates the

myosin regulatory light chain and increases calcium sensitivity (28). This enhanced calcium sensitivity helps to mitigate the loss of available calcium that may occur when ATP availability declines. Force production may be maintained or even increased without further increases in intracellular calcium levels.

Generally speaking, for paralyzed human muscle undergoing electrical stimulation at “physiologic” frequencies (under 30–40 Hz), our work suggests that fatigue is more dependent on the number of stimulus pulses delivered than on the force that is developed (37,41). Moreover, in a recent study we showed that the magnitude of fatigue induced after 10,000 stimulus pulses did not differ when the pulses were delivered at 5 Hz versus 20 Hz (36). It seems unlikely that the 3 Hz protocol in the present study induced a fatigue state that was meaningfully different from 1 Hz stimulation. We believe that the differential in energy cost between these two protocols is better explained by potential differences in energy required for between-pulse relaxation.

In addition to causing skeletal muscle contraction, electrical stimulation may also activate afferent sensory neurons via peripheral nociceptors (22). Sensory afferent neurons activate autonomic ganglia below the level of the SCI, triggering splanchnic outflow and autonomic activation. Autonomic responses to nociceptor input may include vasoconstriction, which increases peripheral venous return and concomitantly increases heart rate. If this combined cardiovascular response to autonomic stimulation carries an energetic cost, higher (more noxious) frequencies could create a larger energy demand than lower frequencies. However, our results indicate that heart rate did not increase significantly as a function of frequency. Neither protocol appeared to instigate a sympathetic autonomic response. Therefore, we postulate that energy expenditure during electrical stimulation at the tested frequencies is predominantly modulated by muscle metabolism and not by activation of a systemic sympathetic response.

BMI and VAT

The most effective increase in energy expenditure occurred during the highest stimulation intensity of 100 mA. A greater stimulation intensity recruits more muscle fibers for contraction (12). An increase in the number of active muscle fibers would increase oxygen demand, oxygen consumption, and energy expenditure. The relationship between energy expenditure and additional subject factors such as BMI and VAT also explain the interplay between stimulation intensity and energy expenditure.

BMI is a widely recognized value representing body fat (39). However, as BMI calculations only take into account an individual’s height and weight, body fat may be overestimated in muscular individuals or underestimated in individuals who have decreased muscle mass (39). As such, we compared our results with VAT measurements gathered with ultrasound. Both BMI and VAT negatively correlated with the energy expenditure response to stimulation. Adipose tissue increases the impedance of superficial tissues and reduces the amount of electrical energy that reaches underlying muscles, decreasing muscle fiber recruitment and energy expenditure (10). Thus body habitus is an important covariant for protocols that aim to increase energy expenditure with electrical stimulation. From an energetic standpoint, it would be most advantageous to maximize the number of active

muscle fibers by using the highest stimulus intensity that can be tolerated without discomfort or autonomic activation. Because of the highly individualized nature of SCI, finding this optimal stimulation intensity requires alert clinical observation. It is important to remember that higher stimulus frequencies that yield higher-force contractions would be suitable only for participants with adequate skeletal integrity (13,42).

Implications

Results of the SF-36 *ww* survey reveal that participants with SCI perceived their physical functioning to be lower than the U.S. normative value (Table 1). The clinical meaningfulness of this small deviation from the mean is debatable (4). However, the SCI population as a whole experiences a range of secondary health conditions that are the specific consequence of physical inactivity (1,6,9,26,30,40). Time spent engaged in physical activity markedly decreases after SCI, even for individuals with paraplegia (16).

Currently, functional electrical stimulation (FES) is a method for people with SCI to increase activity and simulate exercise (21). For example, strategic neuromuscular electrical stimulation of muscles allows people with SCI to cycle or row. However, the high cost and typical absence of insurance coverage for FES systems make them an unfeasible option for at-home use for most people with SCI. Training at a rehabilitation facility equipped with an FES system is an alternative, but engaging in routine training outside of the home adds logistical challenges with transportation and scheduling. An added difficulty with training via FES is that high muscle forces may carry a risk for fracture in individuals with post-SCI osteoporosis (20). FES approaches that generate high forces must be carefully monitored to avoid this possibility.

In contrast, training with low-frequency, low force stimulation may offer a path to mitigate the metabolic consequences of SCI without exposing participants to the risks of traditional FES. Low-frequency protocols such as the ones used in this study may be conducted at home with a portable stimulator unit, reducing the logistical challenge of engaging in daily physical activity. Participants may not even need to transfer out of their wheelchairs in order to train, further reducing the inconvenience of the protocol. These factors would likely increase participant adherence to a regular exercise regimen.

Our results indicate that low frequency (1 Hz) training may be more efficient than higher frequency (3 Hz) training for increasing daily metabolic work. After controlling for the amount of energy delivered to the muscle during stimulation, 1 Hz stimulation would burn 3,500 kcal almost a month sooner than 3 Hz stimulation despite an identical amount of energy injected into the skeletal muscle. The trade-off to reaching this milestone more rapidly is that the 1 Hz protocol would require 3 times the amount of stimulation per day (1 hour versus 20 minutes). A pilot subject in our laboratory has performed 1 Hz stimulation in this manner (3,600 contractions per day) and has indicated that he can carry out his regular home and work activities during the long duration training period with no difficulty. Current research in sedentary adults supports that this type of long-duration training may be of particular metabolic value. Regular low intensity physical activity throughout the day has been shown to have greater systemic health benefits than performing short duration, high intensity exercise (5,14). Insulin sensitivity and plasma lipid levels improved more with

frequent low intensity activity than with shorter duration exercise of high intensity (14,23,35). Ultimately, regular long-term training with low frequency electrical stimulation may prevent or reverse the development of adverse metabolic profiles and comorbidities associated with decreased activity in people with SCI. Our results underscore that the clinician must consider individual factors such as BMI and VAT to determine an adequate training intensity when prescribing low frequency electrical stimulation, in order to maximize metabolic response.

Methodological Considerations

The study cohort included a mix of participants who wheeled independently and who used power wheelchairs. Those who wheeled independently likely possessed substantially more upper extremity muscle mass than individuals with higher lesion levels, potentially yielding a higher resting energy expenditure (33). We did not contrast resting energy expenditure between these subgroups, nor did we determine whether this factor affected the change in energy expenditure during low-frequency stimulation. We did explore relationships between age, time post injury and energy expenditure because of the heterogeneity of our subjects, but found that these demographic factors did not systematically modulate energy expenditure. Future work is needed to further explore age at time of injury on metabolic flexibility in people with SCI (44).

We measured oxygen consumption during a short period of stimulation and assumed that the steady state achieved would be sustained for all 3,600 pulses. Because the energy expenditure reached a “steady state” we believe that this assumption is valid. Our metabolic measurements and calculated energy expenditure values indicate that low frequency, long duration stimulation will increase energy expenditure. Future work is needed to determine the extent to which this elevated metabolic demand may affect metabolism-related health consequences of SCI, such as diabetes and obesity. If systemic metabolic markers can be affected by this form of training, it seems likely that low frequency stimulation may be a suitable way to simulate the low intensity activity routinely performed by the general population. Studies are underway to examine the overall systemic metabolic response to this form of training in individuals with SCI.

CONCLUSIONS

The lowest stimulation frequency (1 Hz) and the highest stimulation intensity (100 mA) were most effective at increasing energy expenditure in human paralyzed muscle. During low frequency stimulation, energy expenditure was predominantly modulated by muscle metabolic demand and not by a systemic autonomic response (heart rate). Factors such as increased BMI and VAT attenuated energy expenditure during electrical stimulation. Overall, the results of this study indicate that patients with SCI may benefit from regular long duration and low force muscle stimulation to safely increase daily activity and improve health.

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Figure 1. Representative example of oxygen consumption. Baseline measurements (“No Stimulation”) were taken before, between, and after stimulation at 1 Hz and at 3 Hz. For each participant, the last 12 measurements (representing 6 minutes) of each stage were averaged.

Figure 2. Metabolic response to stimulation. A) Oxygen consumption increased as a function of stimulation frequency. * = higher than baseline ($p = 0.001$); # = higher than 1 Hz ($p < 0.05$). B) Heart rate did not change as a function of stimulation frequency (all $p > 0.05$). C) Based on measured oxygen consumption (see text for energy expenditure calculation), days to burn 1 pound of fat increased with frequency. * = higher than 1 Hz ($p < 0.05$).

Figure 3. Effect of stimulation intensity. Oxygen consumption increased as a function of stimulation intensity. * = higher than baseline and 50 mA ($p = 0.001$).

Figure 4.

Effect of body habitus: A) BMI negatively correlated with the change in oxygen consumption when applying 1 Hz stimulation ($r^2=0.57$) and 3 Hz stimulation ($r^2=0.62$). B) VAT negatively correlated with the change in oxygen consumption when applying 1 Hz stimulation ($r^2=0.47$) and 3 Hz stimulation ($r^2=0.56$).

Table 1

Subject Demographics

Subject	Sex	Age	Injury level	Years post-injury	BMI (kg·m ⁻²)	Visceral Adipose Tissue (cm)	Physical functioning	Role limitations due to physical health	General health
01	M	35	T4	13	19.4	3.9	75	100	100
02	M	49	C5-7	1	31.6	7.5	0	0	90
03	M	23	C5	4	21.6	2.8	60	100	80
04	M	44	C6	28	20.8	3.9	70	75	65
05	M	22	C4-6	2	26.4	6.0	50	50	65
06	M	36	T9-10	14	17.1	2.9	65	100	60
07	M	48	C5-6	16	25.6	7.1	30	50	90
08*	M	64	T12	5	29.9	6.8	45	50	65
09*	M	45	C5-6	27	25.2	6.9	60	100	75
10*	F	24	T3	2	22.5	3.2	10	0	65
Mean (SD)	N/A	39 (14)	N/A	11 (10)	24.0 (4.6)	5.1 (1.9)	47 (26)	63 (40)	76 (14)

* Did not perform protocol 2 (effect of stimulation intensity)