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Matching initial torque with different stimulation parameters influences skeletal muscle fatigue

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Abstract—A fundamental barrier to using electrical stimulation in the clinical setting is an inability to maintain torque production secondary to muscle fatigue. Electrical stimulation parameters are manipulated to influence muscle torque production, and they may also influence fatigability during repetitive stimulation. Our purpose was to determine the response of the quadriceps femoris to three different fatigue protocols using the same initial torque obtained by altering stimulator parameter settings. Participants underwent fatigue protocols in which either pulse frequency (lowHz), pulse duration (lowPD), or voltage (lowV) was manipulated to obtain an initial torque that equaled 25% of maximum voluntary isometric contraction. Muscle soreness was reported on a visual analog scale 48 h after each fatigue test. The lowHz protocol resulted in the least fatigue (25% +/– 14%); the lowPD (50% +/– 13%) and lowV (48% +/– 14%) protocols had similar levels of fatigue. The lowHz protocol resulted in significantly less muscle soreness than the higher frequency protocols. Stimulation protocols that use a lower frequency coupled with long pulse durations and high voltages result in lesser amounts of muscle fatigue and perceived soreness. The identification of optimal stimulation patterns to maximize muscle performance will reduce the effect of muscle fatigue and potentially improve clinical efficacy.

Key words: electrical stimulation, fatigue, frequency, NMES, pulse duration, rehabilitation, skeletal muscle, stimulation parameters, torque, voltage.

INTRODUCTION

Neuromuscular electrical stimulation (NMES) is commonly used to augment skeletal muscle output so that the muscle can generate sufficient force to facilitate functional activities. A fundamental barrier to routinely using NMES for functional activities is the high level of muscle fatigue that is associated with its use, limiting the muscles' ability to sustain appropriate output during repeated contractions. Muscle fatigue, commonly defined as a transient loss in the ability to generate force, significantly limits the therapeutic effectiveness of this modality. Moreover, the problem of muscle fatigue is exaggerated in paralyzed or paretic muscles, conditions for which the need for NMES is seemingly greatest [1–2].

Abbreviations: lowHz = low frequency (protocol), lowPD = low pulse duration (protocol), lowV = low voltage (protocol), MRI = magnetic resonance imaging, MVIC = maximum voluntary isometric contraction, NMES = neuromuscular electrical stimulation, PPI = Present Pain Intensity (scale), VA = Department of Veterans Affairs.

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Fatigue associated with the use of NMES has primarily been linked to the differences from voluntary muscle recruitment by which targeted force levels are achieved and maintained. Specifically, differences in motor unit recruitment order and activation frequencies, as well as imprecise control of muscle forces, will contribute to the increased fatigability observed with NMES [3]. Given that NMES recruits motor units in a nonselective, spatially fixed, and temporally synchronous pattern as opposed to voluntary recruitment that uses asynchronous, selective recruitment of motor units to offset fatigue during sustained or repeat contractions [4], strategies aimed at attenuating muscle fatigability are of significant interest in rehabilitation.

In an effort to reduce the effects of fatigue and gain a greater understanding of the physiological consequences associated with electrical stimulation, investigators have studied the electrical stimulation parameters known to affect external torque production, including intensity (i.e., voltage or amplitude), pulse frequency, and pulse duration [3,5–8]. Although numerous combinations of these variables can be used to generate desired force levels, systematic investigations examining the relative importance of each of these variables as contributors to muscle fatigue are limited. Kesar and Binder-Macleod and Kesar et al. have reported that lower frequency of stimulation, in combination with long pulse durations, maximizes performance during repetitive stimulation [9–10]. In addition, we recently reported that the product of pulse duration and pulse frequency, defined as total pulse charge, is a strong predictor of external torque production and that when comparing stimulation trains with equal total charge, those with lower frequencies resulted in less fatigue across a range of pulse frequencies and durations [11]. Although these studies highlight the negative consequence of higher frequencies versus pulse durations as a contributor to fatigability, none of these studies included different intensities of stimulation (i.e., voltage or amplitude) in their design.

The potential for stimulation intensity, in addition to frequency and pulse duration, to differentially affect muscle performance is suggested by Gorgey et al., who report that stimulation frequency, pulse duration, and intensity have varying effects on specific tension when muscle activation is measured with magnetic resonance imaging (MRI) [7]. Particularly, specific tension was reduced when stimulation parameters included a lower pulse duration or frequency. Given differences in specific tension, the likelihood that fatigability would be altered using various combinations of these parameters seems high. However, a more recent study by Gorgey et al. reported that longer pulse durations and higher frequencies increased specific tension but only frequency affected muscle fatigue [8].

Because of the different mechanisms by which stimulation frequency, pulse duration, and intensity affect force production, we designed this study to determine the effect each parameter would have on skeletal muscle fatigue and soreness when the initial torque was the same for each test. It has been shown that frequency of stimulation increases force production by increasing the specific tension on each individual motor unit [6–7], which may also increase the risk for contraction-induced muscle injury [12]. In fact, NMES has recently been shown to cause greater muscle damage than voluntary contractions during dynamic bouts of exercise [13]. Additionally, it is suggested that voltage increases force production by increasing the number of motor units contributing to external force production [3]. Therefore, the purpose of this study was to investigate the effect of stimulation frequency, pulse duration, and voltage on skeletal muscle fatigue during repeated contractions when starting at the same relative torque. We hypothesized that the protocol with lower frequency would show the least amount of fatigue and result in less soreness than other protocols that incorporated high frequency stimulation coupled with reduced pulse durations and voltages.

METHODS

Subjects

Thirteen subjects (28.5 ± 4.4 yr, 173.6 ± 9.6 cm, 71.2 ± 16.4 kg; 7 females) participated in this study. Criteria for participation included (1) 18–50 yr of age, (2) recreationally active, (3) no history of orthopedic or neurological injury that might affect lower-limb muscle function, and (4) no known medical conditions that would result in a contraindication to NMES.

Study Design

We used a within-subject experimental approach to determine the effects of manipulating electrical stimulation parameters on muscle fatigue. Briefly, subjects were tested on two separate occasions using three different fatigue protocols that included an initial starting force equal to 25 percent of maximum voluntary isometric force.

Isokinetic Dynamometry

Torque measurements were obtained from the quadriceps muscle group using a Biodex isokinetic dynamometer (Biodex Medical Systems, Inc; Shirley, New York). Subjects were seated in an upright chair with hips and knees flexed to ~90°. The axis of the dynamometer was aligned with the axis of rotation around the knee joint, and the leg was secured to the lever arm. Proximal stabilization was achieved with straps around the chest, waist, and thigh, as described previously [14]. Prior to data collection, subjects were allowed to perform several warm-up contractions. Next, a value for maximum voluntary isometric contraction (MVIC) was determined. MVIC was defined as the peak isometric torque achieved during three consecutive maximal efforts (~5 s contraction separated by 120 s of rest). In the event that the peak torque values differed by more than 5 percent, additional trials were conducted. Contraction intensity for subsequent NMES testing was calculated relative to each subjects' MVIC.

Electrical Stimulation

Bipolar, self-adhesive, neuromuscular stimulation electrodes (7 × 10 cm) were placed over the distal-medial and proximal-lateral portion of the quadriceps muscle group [3,15]. Stimulation pulses were delivered using a Grass S88 stimulator with a Grass Model SIU8T stimulus isolation unit (Grass Technologies; West Warwick, Rhode Island). The intensity of stimulation to elicit ~50 percent of each subjects' MVIC was determined using a 60 Hz/600 μs pulse train of 500 ms duration. We used a relatively high frequency and pulse duration to elicit initial force, knowing we were going to lower these parameters to obtain 25 percent MVIC during the fatigue protocols. Voltage was incrementally increased until 50 percent MVIC was obtained. After we determined the desired stimulation intensity, five stimulation trains (150 total pulses) were delivered at the aforementioned settings to ensure potentiation of the quadriceps muscle group, as done previously [11]. After the muscle was fully potentiated, one of the three fatigue protocols was conducted.

Fatigue Protocols

Fatigue protocols were conducted using an initial starting force equal to ~25 percent of each subjects' MVIC. This intensity was selected because it allows for recruitment of a sufficient number of motor units in the quadriceps muscle and is generally well tolerated by participants. After the voltage to elicit 50 percent MVIC ($V_{50\text{ percent}}$) was determined using 60 Hz/600 μs pulse trains, one of the three parameters (frequency, pulse duration, voltage) was decreased so that 25 percent of MVIC was elicited. Thus, there were three possible fatigue protocols: low frequency (lowHz), low pulse duration (lowPD), and low voltage (lowV). Specific parameters were held constant when they were not being manipulated: frequency = 60 Hz, pulse duration = 600 μs, and voltage = $V_{50\text{ percent}}$ using 60 Hz/600 μs train characteristics. Contractions were 1 s long with 1 s rest between contractions for 2 min (60 total contractions), as done previously [11]. A single fatigue test was conducted on the left and right legs during the first session (separated by ~15 min) and the subjects returned approximately 1 week later for the third protocol. Given our a priori hypothesis that the lowHz protocol would result in less soreness, the lowHz protocol was included during the first session in an effort to prevent the influence of a repeat-bout effect on muscle soreness [16].

Present Pain Intensity

Forty-eight hours after fatigue tests, each subject rated their quadriceps muscle soreness using the Present Pain Intensity (PPI) visual analog scale that is part of the Short-Form McGill Pain Questionnaire [17]. The scale ranges from 0 to 100 mm, with the 0 value representing "no pain" and the 100 mm value representing the "worst possible pain."

Data Analyses

Torque data were analyzed using a commercially available software package (Acknowledge v3.7.1 [Biopac System, Inc; Shirley, New York] or Chart v5.0 [ADInstruments; Bella Vista NSW, Australia]). Torque values during the fatigue tests were normalized to the initial starting force. All statistical analyses were performed using standard statistical software packages. Torque values obtained for each contraction and the relative drop in force from the initial contraction to the last contraction were calculated for each individual after each session. A repeated measures linear model was fitted to the torque data and subsequent linear contrasts were used to determine differences between the three stimulation protocols for relative drop in force. A *t*-test was used to determine whether the lowHz protocol resulted in lower PPI ratings than the protocols that used a higher frequency (lowPD and lowV combined because they had the same 60 Hz frequency). For all tests performed, the level of significance was set at $\alpha = 0.05$.

Repeated measures linear models were also used to determine the critical contraction at which the slope for the fitted linear model became not significantly different from zero. To determine the critical contraction, we fitted repeated measures linear models sequentially to the data, beginning with the last 20 contractions and sequentially adding previous contractions until the slope of the model became significantly different from zero. The significance level for the slope was corrected with a stepwise Bonferroni correction. The resulting models included contractions 28 to 60 for the lowPD protocol and contractions 24 to 60 for the lowV protocol. However, for the lowHz protocol, the initial fitted slope for the last 20 contractions was significantly different from zero; therefore, for this protocol, the initial model used to determine the critical contraction included only the last 10 contractions. The resulting model for the lowHz protocol included contractions 46 to 60 (**Figure 1**). The lines from the resulting sequential repeated measures models were used as secant lines with slopes significantly different from zero. Next, for each protocol, a curvilinear model that followed more closely the pattern of the data locally was fitted. An S-curve was fitted to the lowPD data, an inverse model curve was fitted to the lowV data, and a quadratic curve was fitted to the lowHz data. Then, using the curvilinear fitted models, we numerically determined the critical contraction, i.e., the contraction whose tangent line to the fitted curve had the slope of the secant line, for the three protocols.

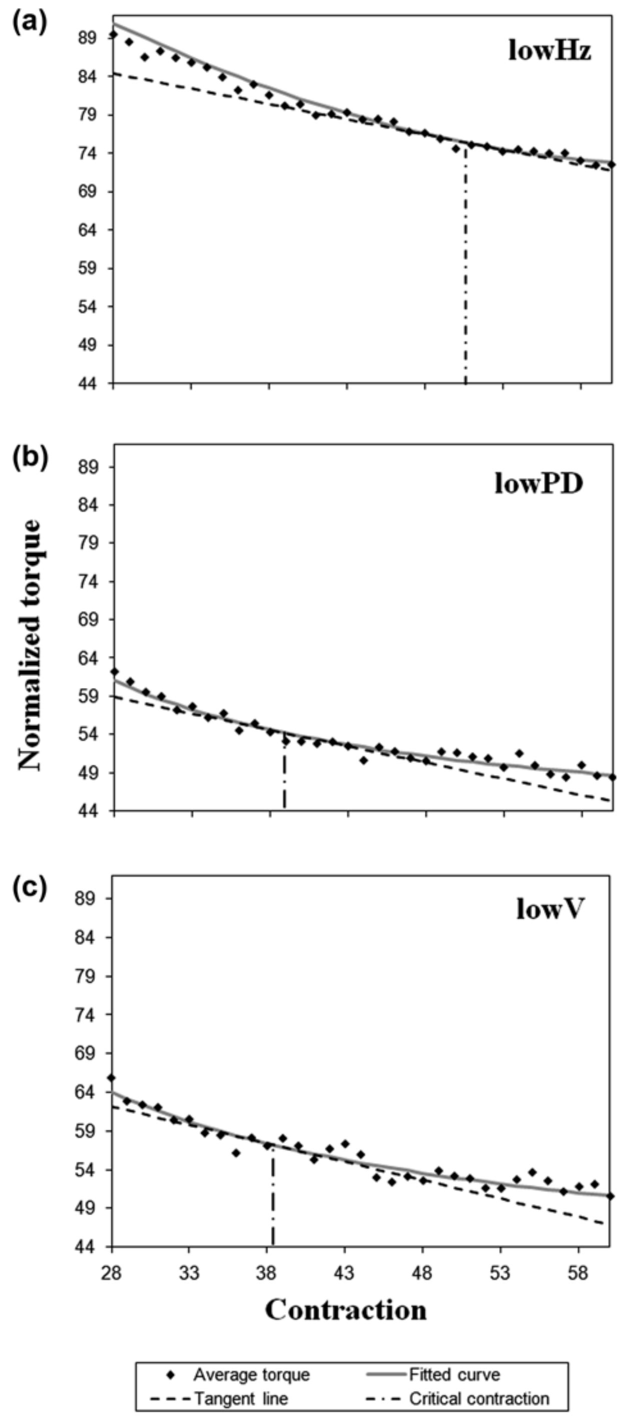

Figure 1.
Contraction by contraction analysis to determine critical contraction where slope of curve is not significantly different from zero. **(a)** Low frequency (lowHz), critical contraction = 50; **(b)** low pulse duration (lowPD), critical contraction = 39; **(c)** low voltage (lowV), critical contraction = 38.

RESULTS

The relative starting torque (mean ± standard deviation) for each fatigue protocol was lowHz = 25.7 ± 0.06, lowPD = 25.5 ± 0.06, and lowV = 25.3 ± 0.03. Average contraction by contraction torque levels for each fatigue test are presented in **Figure 2**. Values are normalized to each participant's initial torque. Significant differences

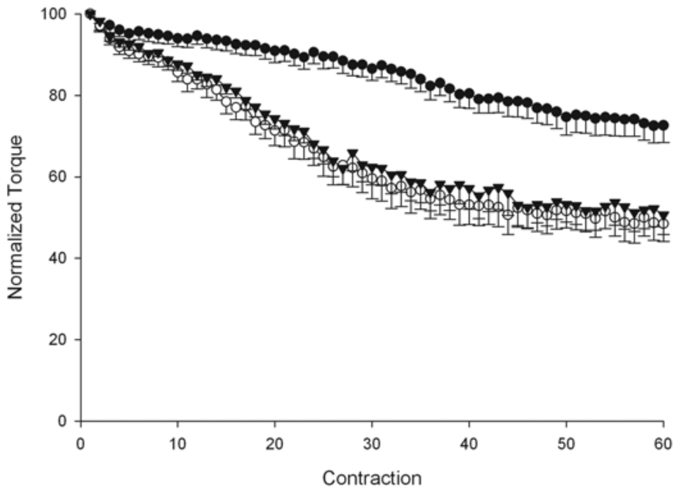

Figure 2.
Normalized torque values for each contraction obtained during fatigue test (60 contractions; 1 s on: 1 s off) under 3 different conditions: ● = low frequency (15 ± 2 Hz), ○ = low pulse duration (167 ± 29 µs), ▼ = low voltage (56 ± 12 V).

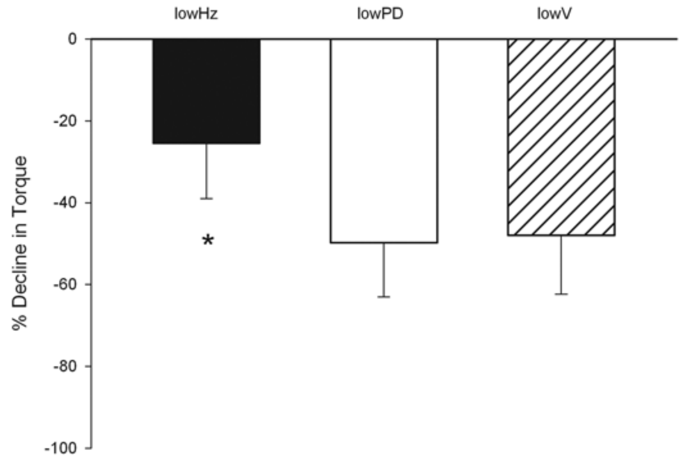

Figure 3.
Average relative decline in torque production for three different conditions. lowHz = low frequency, lowPD = low pulse duration, lowV = low voltage. *Significantly lower than other protocols.

were found between the three conditions ($p < 0.001$). Linear contrasts revealed that the lowHz protocol resulted in significantly less fatigue than the lowPD ($p < 0.001$) and lowV conditions ($p < 0.001$, **Figure 3**). The lowPD and lowV conditions were not significantly different from one another ($p = 0.82$). The lowHz protocol resulted in significantly less muscle soreness 48 h after testing than the protocols that used 60 Hz ($p = 0.006$, **Figure 4**).

Figure 2 suggests that for the lowPD and lowV protocols, the initial contractions resulted in larger decreases in torque than the final contractions and that after a certain critical contraction, the relative decrease in torque was minimal; i.e., the slope of the curve became not significantly different from zero. The critical contractions for the lowPD, lowV, and lowHz data were approximately contractions 39, 38, and 50, respectively.

DISCUSSION

The results of this study indicate that pulse frequency influences skeletal muscle fatigue and soreness to a greater degree than pulse duration and/or voltage during electrically elicited muscle contractions. We examined levels of muscle fatigue after three different protocols that used similar initial starting torques. The novel aspect of this study was that initial starting torque was obtained by three different combinations of electrical stimulation parameters. Each protocol had two standard parameters and a third parameter was altered to determine how the modification of each parameter influenced skeletal muscle fatigue. We determined that pulse duration and voltage adjustments had no effect on the degree of muscle fatigue during repeat contractions. However, pulse frequency was the primary determinant in whether a high (~50 percent drop in torque) or more modest (~25 percent drop) force loss was elicited.

This is not the first study to determine that altering pulse frequency will vary fatigue levels; however, it is the first, to our knowledge, to examine three separate parameters of stimulation at the same time. Pulse frequency has been implicated as a primary cause of muscle fatigue during electrically elicited contractions for some time [18]. Recently, Kesar and Binder-Macleod investigated differences in muscle fatigue after repeated stimulation using a low (11.5 Hz), medium (30 Hz), and high (60 Hz) frequency protocol [9]. They determined that the relative decline in peak force after repetitive electrical stimulation was related to the pulse frequency used for each protocol. Their high frequency protocol resulted in the greatest decline in peak torque followed by the medium and then low frequency trials. Our data are consistent with these findings in that our two high frequency sessions resulted in similar levels of fatigue (~50% drop

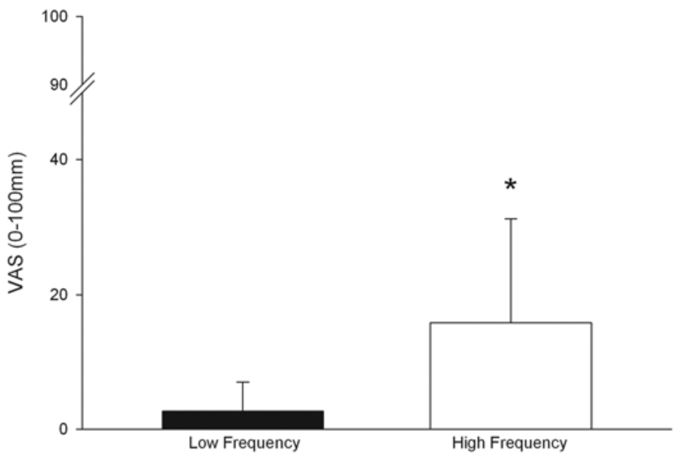

Figure 4.
Average ratings of pain on visual analog scale (VAS), 48 h after fatigue tests. Average frequency for Low Frequency condition was 15 ± 2 Hz. Low pulse duration and low voltage protocols combined in High Frequency group (60 Hz). *Significantly different from Low Frequency.

in peak torque), which were each significantly greater than our lowHz protocol.

Because pulse frequency is a primary cause of muscle fatigue during repeated electrical stimulation, we and others have spent considerable effort investigating how alterations in frequency may limit muscle fatigue without considering the other stimulation parameters that influence torque production [15,19]. Relatively little is known regarding how alterations in pulse duration influence torque production. Our recent article on the relationship between total pulse charge (product of pulse frequency and pulse duration) and torque production indicates that pulse duration may influence torque production to a similar degree as pulse frequency; however, the mechanisms remain unclear [11]. We concluded from an earlier study that optimal stimulation parameters would probably include the lowest possible frequency combined with longer pulse durations when voltage remains constant [11]. The results of the present study further support this statement. All three protocols achieved similar starting forces (~25 percent MVIC), and the protocol that used the lowest frequency resulted in the least fatigue.

As mentioned previously, little attention has been paid to how other stimulation parameters that affect muscle torque production influence muscle fatigue. Adams et al. measured muscle fatigue using 500 µs/50 Hz trains of stimulation with different stimulation amplitudes that resulted in 25, 50, and 75 percent of MVIC [3]. They determined that with greater amplitude of stimulation, more motor units were recruited, as determined by MRI. They also reported that force declines were slightly greater when using a stimulation amplitude that evoked 25 percent MVIC (20% decline in torque) compared with 75 percent MVIC (15% decline in torque) [3]. A study by Slade et al. investigated the influence of stimulation intensity on muscle fatigue and force augmentation by variable frequency stimulation [20]. They used moderate (25% MVIC) and high (50% MVIC) amplitude stimulation protocols with similar frequencies that resulted in similar torque declines between protocols (~60%–65%). Generally, stimulation amplitude is thought to primarily affect the number of motor units recruited; it is not clear whether stimulation intensity does [3] or does not [20] influence skeletal muscle fatigue to a great degree. Data from the present study indicate that pulse frequency influences muscle fatigue to a greater degree than stimulation amplitude.

A recent article by Gorgey et al. investigated the effects of different stimulation parameters on muscle specific tension [7]. They used T2-weighted MRI to quantify activated skeletal muscle using four different stimulation protocols that differed in parameter settings. When higher frequency stimulation (100 Hz) was used, the specific tension was higher in activated muscle. They also report that specific tension was reduced when pulse duration was decreased from 450 to 150 µs, while frequency remained constant at 100 Hz, suggesting that pulse duration is influencing something other than recruitment of motor units. Part of their explanation included the notion that longer pulse durations may preferentially activate fast-twitch motor units, which produce higher torque than slow-twitch motor units. Our data do not support the hypothesis that longer pulse durations preferentially activate fast-twitch motor units. If that was the case, we would expect to see differences in fatigue between our lowV and lowPD conditions that used the same 60 Hz frequency. A lowPD condition would presumably activate more slow-twitch motor units than the lowV condition and thus potentially show less fatigue. Instead, both of these conditions resulted in similar declines in torque after 60 contractions (49% and 48% for lowPD and lowV, respectively). A more recent article by Gorgey et al. further illustrated that pulse duration did not seem to affect muscle fatigue [8]. It is currently unclear what factors, other than motor unit recruitment, pulse duration may be influencing in regards to torque production.

We examined the rate of fatigue among our three protocols and observed that the lowPD and lowV protocols each had a rapid decline in force that appeared to level out in the last half of the session. This led us to statistically determine the critical contraction in which the slope of the decline was no longer different from zero. It was determined that each protocol appeared to reach a point at which declines were much smaller and force production was maintained. If resultant muscle fatigue was due to an imbalance in the ratio of energy supply to energy demand, it appears the muscle fibers reached a point at which energy supply could meet the energy demand. Simply, energy supply mechanisms were able to provide adequate ATP to meet the needs of the contracting muscle fibers. The "critical contraction" appeared after force had dropped to about 55 percent of initial values for the lowV and lowPD protocols (contractions 38 and 39 for lowV and lowPD, respectively). Interestingly, torque during the lowHz protocol was only 72 percent of initial values after 60 contractions and did not reach its critical point until contraction 50. Apparently, the lowHz protocol could have continued without ever reaching the levels of fatigue encountered by the other two protocols. Further studies need to be conducted that include longer fatigue tests and modulation of parameters (e.g., pulse waveforms, frequency, duration, or amplitude) to identify strategies that can reduce levels of fatigue. While some of this work has been done with varying degrees of success [10,21–22], electrical stimulation has great potential for rehabilitation if the degree of muscle fatigue can be reduced.

The muscle soreness data in the present study are consistent with recent reports that high frequency stimulation results in a higher specific tension (force/area of muscle activated) and may contribute to exercise-induced muscle injury [7,12]. These data are altogether not surprising because of the known differences in motor unit activation between voluntary and electrically induced motor unit recruitment. Prolonged, high-frequency activation of motor units would be a rare observation during voluntary recruitment strategies [23]. Therefore, anytime this type of activation occurred in an individual, it would be a novel activity that the neuromuscular system had not readily experienced. It has been reported for some time that delayed-onset muscle soreness often results after novel, unaccustomed muscular contractions [24]. Another advantage of lower frequency stimulation coupled with higher pulse durations and/or voltages may be reduced levels of contraction-induced muscle injury.

The idea that NMES may result in increased muscle injury is an interesting concept that has recently received attention [12–13,25]. Most of the studies that have detailed specific skeletal muscle responses to muscle injury have been performed in animal models that used electrically elicited contractions. As these studies were translated to human models, the type of activation was not; most human studies used voluntary contractions, which often yielded conflicting results. However, Crameri et al. compared voluntary and NMES-induced contractions and their resultant effect on delayed-onset muscle soreness and specific myofiber damage [25]. They found that while soreness was similar between protocols, the NMES appeared to evoke greater cytoskeletal damage as evidenced from histological analyses. Other studies have reported that NMES induced greater muscle damage than voluntary contractions [13], and NMES has even been found to cause contraction-induced muscle injury during isometric contractions [2,26]. As NMES protocols continue to be optimized, issues related to contraction-induced muscle injury should be considered.

CONCLUSIONS

One of the primary limitations to widespread use of electrical stimulation is the high degree of muscle fatigue that is often observed. We and others have shown that frequency is a key regulator of muscle fatigue, but other parameters can enhance muscle torque output without causing increased levels of fatigue. Therefore, future protocols should include low frequencies in combination with longer pulse durations and higher voltages to maximize motor unit recruitment and minimize metabolic demand of recruited motor units. Doing so may improve muscle performance during repeated contractions elicited by electrical stimulation. We recognize that this will undoubtedly still be inferior to voluntary contractions, but in conditions such as stroke and/or spinal cord injury, voluntary contractions are often not possible. Future work to improve NMES protocols for these and other populations should investigate how altering parameters during activities can attenuate the degree of muscle fatigue that will occur and improve rehabilitation programs that use NMES. We and others contend that

NMES has great potential to provide individuals with many different diagnoses the ability to perform contractions that could help maintain muscle mass, increase exercise capacity, and potentially enhance function [27–29].

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Study concept and design: C. S. Bickel, C. M. Gregory.
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