Feedback-Controlled Stimulation Enhances Human Paralyzed Muscle Performance

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Running Head: Feedback-controlled stimulation of paralyzed muscle

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Abstract

Chronically paralyzed muscle requires extensive training before it can deliver a therapeutic dose of repetitive stress to the musculoskeletal system. Neuromuscular electrical stimulation, under feedback control, may subvert the effects of fatigue, yielding more rapid and extensive adaptations to training. The purposes of this investigation were to 1) compare the effectiveness of torque feedback controlled (FDBCK) electrical stimulation with classic open loop constant-frequency (CONST) stimulation, and 2) ascertain which of three stimulation strategies best maintains soleus torque during repetitive stimulation. When torque declined by 10%, the FDBCK protocol modulated the base stimulation frequency in three ways: by a fixed increase, by a paired pulse (doublet) at the beginning of the stimulation train, and by a fixed decrease. The stimulation strategy that most effectively restored torque continued for successive contractions. This process repeated each time torque declined by 10%. In fresh muscle, FDBCK stimulation offered minimal advantage in maintaining peak torque or mean torque over CONST stimulation. As long duration fatigue developed in subsequent bouts, FDBCK stimulation became most effective (~40% higher final normalized torque than CONST). The high frequency strategy was selected ~ 90% of the time, supporting that excitation-contraction coupling compromise and not neuromuscular transmission failure contributed to fatigue of paralyzed muscle. Ideal stimulation strategies may vary according to the site of fatigue; this stimulation approach offered the advantage of online modulation of stimulation strategies in response to fatigue conditions. Based on stress-adaptation principles, FDBCK controlled stimulation may enhance training effects in chronically paralyzed muscle.

Key Words: fatigue, spinal cord injury, doublet, excitation-contraction coupling
Introduction

The loss of normal muscular activity as a result of chronic spinal cord injury (SCI) leads to a cascade of harmful physiologic changes termed musculoskeletal deterioration (29). Although muscle atrophy is the most visible early manifestation of this deterioration, rapid demineralization of long bones is more insidious and potentially more dangerous. The lifetime risk of an extremity fracture for people with SCI is nearly double that for the able-bodied population (37).

Because muscle forces, not body weight, are responsible for the majority of loads experienced by bones (18), post-SCI muscle atrophy deprives bone of its principal stimulus for maintenance of bone mineral density (BMD). The reintroduction of physiologic loads to paralyzed limbs has been postulated to be a reasonable strategy for the prevention of post-SCI osteoporosis (30, 31). Paralyzed muscle, with the aid of electrical stimulation, is an ideal delivery system for physiologic loads (30, 31). However, because paralyzed muscle atrophies and transforms to highly fatigable fibers (26), it must undergo extensive (and lengthy) training before it can deliver a therapeutic dose of repetitive stress to the musculoskeletal system. Paralyzed muscle hypertrophy and endurance are therefore both desirable outcomes of electrical stimulation training protocols for individuals with paralysis.

We have recently demonstrated that long-term constant-frequency electrical stimulation training can maintain the musculoskeletal properties of recently paralyzed individuals before the muscle transformation process (increased fatigue) occurs to the soleus muscle (30, 31, 32). However, when attempting to train chronically paralyzed muscle it becomes apparent that rapid muscle fatigue limits the amount of repetitive work
that the muscle can perform. Thus, we wished to explore whether a more sophisticated method of electrical stimulation could increase the muscle work performed during a single training session. According to the Physical Stress Theory (21) a method that enhances repetitive muscle stress within a training session would ultimately adapt musculoskeletal tissue in a more timely manner than methods that induce less stress.

Clinical neuromuscular electrical stimulators typically deliver trains of pulses at a fixed frequency. However, it is well known that the nervous system modulates the firing frequency of motor units based on changes in the force generating capacity of the muscle (fatigue) (6, 10, 35). Therefore, we developed an adaptive force feedback controlled electrical stimulation system to test if smarter patterns of stimulation could enhance the work produced by paralyzed muscle within a training session. Issues of safety, mechanisms of paralyzed muscle fatigue, and optimal overload were important considerations in the design of the feedback algorithm.

The FDBCK control system monitored isometric soleus muscle torque during repetitive electrical stimulation. When the muscle began to fatigue, the drop in torque served as feedback to the computer for the stimulator to attempt three different stimulation strategies. A high frequency strategy (H), better suited for a muscle in excitation-contraction coupling compromise (low frequency fatigue) (6), employed a fixed increase to the base stimulation frequency. A doublet strategy (D), better suited for a muscle demonstrating both low frequency fatigue and within train neuromuscular transmission compromise (high frequency fatigue) (5, 23), employed a paired pulse at the beginning of the stimulation train. A low frequency strategy (L), better suited for a muscle demonstrating high frequency fatigue (10, 20), employed a fixed decrease to the base
stimulation frequency. It is conceivable that during a bout of electrically induced exercise, one strategy that is effective early during fatigue is less effective at the end of the fatigue bout (6, 10, 20). A novel component of this investigation is the “online” ability to assess the effectiveness of three different stimulation strategies (H,L,D). In addition, it is known that the activation history may influence muscle force (22, 32), therefore, the order of the different stimulation strategies was varied.

The purposes of this investigation were to 1) determine the effectiveness of torque feedback controlled electrical stimulation of paralyzed muscle, as compared to constant-frequency stimulation, and 2) ascertain which of three FDBCK stimulation strategies were most effective in sustaining paralyzed soleus torque during repetitive stimulation. We hypothesized that feedback-controlled stimulation would be superior to constant-frequency stimulation and that the high frequency strategy, by virtue of the significant low frequency fatigue induced in paralyzed muscle (32), would be the most effective strategy to maintain torque.

Methods

Eight men with complete SCI (ASIA score “A”) (2) participated in this study (Table 1). The institution’s Human Subjects Institutional Review Board approved the protocol. All subjects provided written informed consent before participating. Inclusion criteria were complete chronic spinal cord injury (> 1 year) above T12 as determined by neurological exam, passive ankle dorsiflexion to neutral, passive knee flexion to at least 90 degrees in a seated position, and intact skin over the electrical stimulation site. Exclusion criteria were lower extremity trauma, pressure ulcers, peripheral/systemic infection, or
lower motor neuron injury below T12 (which would prevent tibial nerve electrical activation). The fatigue index was computed as 100* final contraction torque (#125) / initial contraction torque (#1). The fatigue protocol consisted of 125 contractions elicited by supra-maximal stimulation (15 Hz) of the tibial nerve every two seconds for 667 ms.

Test Apparatus and Protocol

Subjects remained in their wheelchairs during the test procedure. The ankle was stabilized in a system which measured isometric plantar flexion torque, as described previously (26-28, 30, 32, 33). The knee was positioned at ninety degrees of flexion and the ankle was in neutral joint position. Reusable self-adhesive carbon electrodes delivered electrical impulses to the gastrocnemius and soleus muscles. This test position (knee flexed) minimized the contribution of the gastrocnemius to the plantar flexor torque (24). A constant current electrical stimulator (0 to 200 milliamps at 400 volts) was triggered by digital pulses from a data-acquisition board (Metabyte DAS 16F, Keithley Instruments Inc., Cleveland, OH, USA) housed in a microcomputer under custom software control. The stimulation intensity was supra-maximal (about 1.5 times the intensity required to produce a maximum twitch).

Subjects participated in three or four stimulation sessions over a six-month study period. None of the subjects was participating in electrical stimulation training during this time. Two of the sessions utilized torque feedback-control of stimulation frequency (see descriptions below). The feedback-control (FDBCK) sessions were compared with a constant stimulation frequency session (CONST) that occurred on a separate day (mean = 5.8 wks, SE = 1.9).
For all sessions, the stimulator was programmed to deliver 10-pulse trains every two seconds. A bout of exercise consisted of 125 trains. Subjects completed four such bouts of exercise during each session. Each bout was separated by a 5-minute rest period. All four bouts during a given session employed the same stimulation strategy.

The order of the two FDBCK sessions and the CONST session(s) was randomized for each subject. The CONST protocol utilized 15 Hz stimulation. FDBCK sessions began with 15 Hz stimulation and delivered triads of 3 stimulation strategies (High (H), Low (L), and Doublet (D)) each time torque dropped by ten percent (Figure 1). In the H strategy, stimulation frequency increased by 15%. In the L strategy, the stimulation frequency decreased by 5%. In the D strategy, the first two pulses of the stimulation train comprised a doublet (10 ms interpulse interval); the remaining 8 pulses were delivered at the same frequency used in the L strategy (5% below the starting frequency). The order of H, D, and L strategies differed between the two FDBCK sessions. In the session denoted “HDL”, when torque dropped by 10%, the H strategy was first given, followed in the next successive trains by D and by L. Alternatively, in the session denoted as “LDH”, when torque dropped by 10%, the L strategy was given first, followed in the next successive trains by D and by the H. Previous muscle activation history is an important influence on muscle torque responses (22, 32). Thus, the order effect of the strategy could be determined.

The stimulator software noted whether any strategy in the triad yielded at least a 2% increase in torque from the torque value depressed by 10%. If so, the bout proceeded using the stimulation parameters of the successful strategy. Thus, if H had been selected, all subsequent trains would be elicited at 17.25 Hz (15% increase from 15 Hz). The H
strategy of the next triad would be given at 19.83 Hz (an additional 15% increase from 17.25 Hz). In some cases, more than one strategy yielded a 2% or greater increase in torque. The stimulator software selected the strategy that exceeded 2% by the greatest amount and used its stimulation parameters for subsequent stimulus trains (Figure 2). A 2% improvement assured that an increase in torque was not due to random fluctuations in transducer voltage (noise). Moreover, a 2% effect over 4 to 8 strategies would translate into a clinically meaningful 8 to 16% increase in torque.

The torque elicited by the successful strategy (be it H, D, or L) was considered the new “benchmark” torque. The next 10% decrease in torque from this benchmark would trigger the delivery of the next triad of three stimulus strategies, in the order dictated by the session (HDL or LDH).

Because of the extensive post-fatigue potentiation after one bout of 125 contractions (32), we wished to avoid setting the “benchmark” torque until the muscle reached a more potentiated state. For the second and fourth bouts in each FDBCK session, ten and fifteen potentiating contractions were given (15 Hz), respectively, prior to establishing the benchmark torque (from which a 10% decline would be measured).

Justification for Stimulation Control Parameters

We chose a 15 Hz frequency and supramaximal stimulation because this frequency generates ~ 60 % of the total torque from the paralyzed soleus muscle and lies on the linear portion of the torque-frequency curve (27). To meet therapeutic goals, the initial torque should meet the principles of muscular overload (30). However, because individuals with chronic SCI develop severe neurogenic osteoporosis (31, 34), the evoked muscle
contraction must remain below a torque level that could induce injury to the musculoskeletal system. Based on this starting frequency and our previous fatigue index studies (5, 26-28, 33), we surmised that there would be between four and eight 10% drops in torque during this protocol. Thus, we used a 10% drop in torque to trigger the feedback algorithm because this would allow several opportunities per bout to test the efficacy of the three stimulation strategies (H, D, L). We did not test acutely (within 6 weeks) paralyzed subjects because we previously established that they fatigue minimally and, therefore, are not in need of a force enhancing algorithm (5, 26-28, 33).

The high frequency strategy employed a 15 percent increase in frequency (for each 10% drop in torque). If the high frequency strategy should be selected for each of the 4 to 8 predicted feedback triads, stimulation frequency would approach 30 Hz, which is on the saturated (flattened) part of the soleus torque-frequency curve (27). The use of a percentage increase in frequency allowed for a greater incremental increase in frequency after each successful H strategy, consistent with the nonlinear relationship between torque and frequency (27). Thus, a 15% increase in frequency at 15 Hz (2.25 Hz) on the steepest part of the curve versus a 15% increase at 25 Hz (3.75 Hz), where the curve is less steep, was an important design feature of this strategy. Because of safety considerations, our goal was never to induce a frequency increment that would exceed the initial 60% of maximum torque. Pilot data assured us that these frequency increments met this design criterion.

The low frequency strategy employed a 5% decrease in frequency (for each 10% drop in torque) because physiologically this would impose an additional 4 ms between each stimulus pulse of the train from the 15 Hz initial frequency. Within or between train
neuromuscular propagation failure in the event of high frequency fatigue is sensitive to a reduction in stimulation frequency (13).

The doublet strategy employed a double pulse at the start of a train followed by a low frequency train. We based this strategy on previous studies demonstrating that high frequency doublets induce an increment in torque that is then sustained by a trailing low frequency train (11). We chose to impose the doublet on the low frequency strategy because of the inverse relationship between stimulation frequency and doublet activation (11). By design, this strategy would be most effective if neuromuscular propagation in the paralyzed muscle recovered between trains but was compromised within a train (5, 28).

Data Processing and Statistical Analysis

To determine which stimulation protocol most successfully overcame low frequency fatigue, we examined the torque generated by the soleus at contraction 125. This torque was normalized to the torque of the 1st train for each subject, to correct the across-subject and trial offset in torque generating capacity. We also obtained the mean normalized torque for each bout of 125 contractions, to provide an estimate of the ability of each protocol to sustain torque during repetitive stimulation.

Two separate Two-Way Repeated Measures Analyses of Variance were used to test for an interaction between bouts and order (HDL, LDH) and between bouts and strategy (H, D, L, and CONST). Separate One-Way Repeated Measures Analyses of Variance were used to determine if either mean or final torque differed for the H, D, L, and CONST conditions within each bout. A significant effect warranted further post hoc analysis (Tukey). Linear and nonlinear regression analysis was used to calculate the slopes of the
stimulation strategies. Dependent t-tests were used to compare the slopes. Statistical significance was set at \( p < 0.05 \) for all comparisons.

Results

Effectiveness of Feedback Protocol

The average time post injury was 7.2 years (range 1.3 to 13.9) with a mean fatigue index for the group of 41.72 (range 27.3 to 56.8) (Table 1). Examination of the data revealed that the difference in soleus torque generated by the FDBCK protocol versus the CONST protocol was greatest during bout 4 and the least during bout 1. Torque for bouts 2 and 3 did not differ considerably from each other. We therefore present data from only bouts 1, 2, and 4, to illustrate the divergent performance of the CONST and FDBCK protocols.

In bout 1, normalized CONST torque did not differ from either FDBCK protocol at any point during the 125 contractions (Figure 3, top), nor did mean (SE) peak torque across 125 contractions differ between FDBCK and CONST trials (Figure 4, top). In bout 2, both the HDL and LDH FDBCK bouts began to outperform CONST stimulation at the 20th contraction (Figure 3, middle) and all subsequent contractions (to 125) \( (p < 0.05) \). For the FDBCK bouts, both the mean torque and final torque significantly exceeded CONST torque (Figure 4, middle; \( p < 0.05 \)). In bout 4, the HDL protocol began to outperform the CONST protocol at about contraction 20 (Figure 3, bottom) and all subsequent contractions (to 125) \( (p < 0.05) \). The LDH protocol began to outperform CONST after
contraction 60 (p < 0.05). Normalized peak torque and final torque for both FDBCK protocols were higher than CONST torque (Figure 4, bottom; p < 0.05).

The HDL and LDH protocols responded similarly across all bouts, supporting that order did not influence the overall effect. A non-significant interaction indicated that the mean and final torque changes across bouts were not different regardless of which protocol (HDL or LDH) was tested (p = 0.34) (Figure 4). However, there was a difference between protocols for the specific contraction number within the bout that each protocol first influenced the peak torque (Figure 3).

**Effectiveness of High, Low, and Doublet Strategies**

A significant interaction indicated that the mean and final torque produced by the various strategies (H, D, L, or CONST) were not similar across bouts 1, 3, and 4 (p < 0.05) (Figure 4). The H strategy was selected to be the most effective the majority of the time for all bouts (~ 90% of all strategies). The doublet and low frequency strategies were selected less than 10% and 2% of the time, respectively, for all bouts in both FDBCK protocols. The H strategy demonstrated a 20 to 50% increase in normalized peak and mean torque in bouts 2 and 4 (p < 0.05), but less than 2% increase in bout 1 (Figure 4).

Figure 5 illustrates the rate of increase in frequency for bouts 1, 2, and 4 for both FDBCK protocols. Note the steepness of the slope for bouts 1 and 2 (slopes range from 0.10 to 0.13 Hz/Contraction #) as compared to bout 4 slope (0.03 Hz/Contraction #). The slopes for bouts 1 and 2 were not different from each other (p = 0.88), but both slopes were significantly greater from bout 4 slope (p < 0.05). Nonlinear regression (2nd and 3rd order) analysis did not significantly improve upon the linear regression analysis (R² = 0.65 to
This lower slope for bout 4 indicates that the muscle was more sensitive to a given change in stimulation frequency because the muscle sustained the increase in torque for a longer time without requiring an increase in stimulation frequency. It is also clear that the relative fatigue between contractions 1 and 125 was less because of decreased initial torques. As can be seen in Figure 5, torque could be maintained longer at any given stimulation frequency for bout 4 than bouts 1 and 2, yielding fewer feedback triad attempts in bout 4 (see parenthetical numbers in Figure 5 panel captions). Thus, torque declined to a lesser degree and over fewer triads in bout 4 than in bouts 1 and 2.

In some instances, none of the three stimulation strategies (H, D, or L) yielded the minimum criterion of at least a 2% increase in torque. In these cases, no change was made in the preceding stimulation parameters. A non-effective strategy occurred ~ 20% of the time.

**Discussion**

For bout 1, torque-feedback controlled stimulation offered an advantage (in terms of mean or final torque) over constant-frequency stimulation in individual cases, but when averaged across subjects did not yield a significant effect. Previous studies concur that constant and variable-frequency stimulation yield similar endpoint fatigue in fresh (no LFF) paralyzed muscle (36). The acceptance of high frequency strategies in bout one (Figure 5) supports that the high frequency was effective in increasing torque, but once accepted, the rate of fatigue increased, causing no net effect on the final torque (Figure 4). The relationship between an increased frequency of stimulation (number of stimulation pulses delivered) and increased muscle fatigue has been previously demonstrated (14, 20).
It was not until subsequent bouts (2-4), as another form of fatigue developed (low-frequency fatigue) (27, 32), that the feedback-controlled high frequency strategy had a positive net effect on final torque production. This effect was observed regardless of the order that the strategies were offered. These findings support that a smarter pattern of electrical stimulation, under force feedback control, may enhance future intervention studies designed to adapt paralyzed muscle tissue.

_Difference among Strategies_

After bout one, feedback controlled stimulation elicited ~ 40% more torque than the constant-frequency stimulation (Figure 4). However, over 90% of the strategies selected were high frequency. Previous investigators have suggested that during fatigue and associated contractile slowing, low frequency stimulation (volitionally and electrically) may be an optimal strategy for maximizing torque output (3, 4, 14). Muscle Wisdom was the term used to characterize the modulation of motor units to a lower frequency to match the slowed contractile speeds of muscle during fatigue (3, 7, 10, 20). However, Fuglevand and Keen challenged the muscle wisdom hypothesis and discovered that low frequency modulation did not restore torque when initial stimulation frequencies were in the normal physiological range for motor units (15-30 Hz) (9). Our starting frequency was 15 Hz because that frequency generated ~ 60% of the peak torque from the paralyzed soleus (27). With this initial frequency, the low frequency strategy was rarely accepted in bout 1 and was never selected during any other bouts (2 - 4) (Figure 6). The success of the high frequency strategy appears consistent with that of Fuglevand and Keen and contrary to Binder-Macleod and Guerin (4). However, Binder-Macleod and Guerin used a much
higher stimulation frequency (60 Hz) than our study (15 Hz). This high frequency may promote early compromise of the neuromuscular transmission system and, therefore set the stage for force enhancement when stimulation frequency declines. In the context of functional electrical stimulation for paralyzed muscles, high frequency stimulation is generally contraindicated during static isometric contractions because of the fracture risk to the demineralized skeletal system (12) and should be an important consideration when designing stimulation protocols to gain optimal function.

In the present study, low frequency stimulation most often yielded a drop, not an increase in torque (see inset, Figure 2B). Our findings are in accord with our previous reports (5, 28) which do not implicate neuromuscular transmission failure during medium-frequency (~15 Hz) stimulation in paralyzed muscle. On the contrary, torque in the present study could be restored via high-frequency stimulation (the H strategy or the paired pulse of the D strategy), quite the opposite from what would be expected if neurotransmitter availability were the limiting factor. As indicated in Figure 5, the high-frequency strategy was accepted even at the end of the fatigue protocol when the frequency was ~28Hz. Thus, even at these higher frequencies and after 125 contractions, the high-frequency strategy was successful and supports that neuromuscular transmission failure was negligible. These high-frequency strategies were successful even though there is significant M-wave suppression at the end of this fatigue protocol with a 15 Hz frequency (5, 26, 28). Continued acceptance of the high-frequency strategy underscores that a large safety margin must exist between M-wave depression and neuromuscular junction transmission to the sarcolemmal membrane. Accordingly, the restoration of torque with the high-frequency strategy employed in this study supports that the mechanism for fatigue
was beyond the neuromuscular transmission system and involved impairment of excitation contraction coupling leading to low frequency fatigue (LFF) (27, 32). Importantly, none of the fatigue processes could be attributed to central mechanisms (9), which play a key role during volitional fatigue tasks.

The high frequency strategy had the greatest ability to restore torque in all bouts regardless of the order of the feedback strategies. Although the doublet was selected about 10% of the time, it was not selected for every subject. In bout 1, for example, a single subject accounted for 9 of the 11 doublets that were accepted in the HDL protocol. It seems likely that the doublet strategy may have been more successful if the trailing frequency (after the paired pulse) had been higher. However, the goal was to offer a strategy that would “mix” the high and low frequency components of the three strategies in the event that within train neuromuscular transmission impairment contributed to the declining torque during the repetitive stimulation protocol. Future studies should investigate the efficacy of different doublet and or triplet train formulations with other trailing frequencies under feedback control. The order of strategies (H, D, and L or L, D and H) in the two FDBCK protocols did not influence which strategy emerged as the most successful for restoring torque (Figure 4). Pilot data also supported that the doublet strategy was accepted at a low rate when it was offered first (DLH). For this reason, we limited this study to two orders of strategies.

*Open Loop vs. Closed Loop Stimulation Control*

To our knowledge, no previous reports have used an online torque *feedback* controlled method to modulate these (HDL) stimulation strategies in human paralyzed
muscle. One previous study used online feedforward control of pulse duration to modulate quadriceps torque in subjects with SCI (1). In addition, two previous studies of paralyzed quadriceps muscle have employed single-modulation paradigms, in which stimulation parameters changed once during a bout of fatiguing contractions. Kebaetse and coauthors demonstrated that switching from 20 to 66 Hz and from 33 to 60 Hz stimulation preserved the ability of paralyzed quadriceps muscles to elicit knee extension, outperforming constant-frequency stimulation at 20, 33, or 66 Hz alone (15). Scott and colleagues employed a similar stimulation protocol that switched from 30 Hz constant frequency trains to 30 Hz doublet trains when quadriceps force fell below a single criterion value (25). Modulating stimulus parameters in this fashion allowed the paralyzed quadriceps muscles to attain a target force 14% and 18% more frequently than for either constant-frequency or doublet stimulation, respectively. The protocol described in the present study offers the advantage of continuous modulation of stimulus parameters, under closed loop feedback control, rather than a single modulation, under open loop control. As can be seen in Figure 5, the number of modulations can vary widely, depending on the fatigue state (bout #) of the paralyzed muscle. In addition, the feedback control system used in this study was capable of comparing three different strategies of stimulation. Understanding optimal activation patterns during activity appears fundamental to the needs of neuroprosthetic control for functional movement.

**Mechanisms Contributing to the High Frequency Success**

An increase in stimulation frequency is associated with a higher torque, based on the torque frequency relationship of the paralyzed soleus (27). However, repetitive high
frequency stimulation may also hasten the development of fatigue, yielding no net difference in final torque over constant-frequency stimulation, as evident in bout 1. During later bouts, however, high-frequency stimulation offered clear advantages over constant-frequency stimulation, which supports the idea that long duration fatigue (low frequency fatigue) develops following the 5 minute rest interval (27, 32).

Slow to fast skeletal muscle transformation, as occurs with chronic paralysis, predisposes muscles to long duration muscle fatigue (26, 27). Low-frequency fatigue (LFF), such as the chronically paralyzed fast soleus muscle demonstrated in this and previous reports (27), is believed to be caused by a decreased release of Ca²⁺ by the sarcoplasmic reticulum and altered receptor sensitivity (16, 17, 19, 38, 39). Fast skeletal muscle, designed for phasic activity, becomes “uncoupled” (reduced Ca²⁺ and/or reduced receptor sensitivity) after a repetitive activation protocol. As [Ca²⁺] falls during repetitive activation of paralyzed muscle, less free Ca²⁺ may be available, yielding impaired myosin regulatory light chain (RLC) phosphorylation (3, 4). Overcoming LFF with high frequency stimulation likely depends on post-translational (myosin regulatory light chains) as well as pre-translational (calcium release) mechanisms (see below).

The high frequency strategy (bouts 2 and 4) was effective even though the muscle was nearly fully potentiated within each bout before the system delivered a strategy (Figure 2). This finding suggests that the mechanism used by the higher frequency stimulation to enhance torque may only partially utilize the same mechanism that allows full potentiation of the muscle during the initial trains early during bouts 2 and 4 of the repetitive activation. Rassier and colleagues (22) induced the staircase potentiation phenomenon in paralyzed rat muscle (gastrocnemius) only after impairing the Ca²⁺ release
system with dantrolene sodium. Thus, the impaired calcium release associated with LFF appears to be a fundamental component of the potentiation process observed in fast muscle (29, 32). However, the mechanisms contributing to potentiation do not explain the success of the high frequency strategy in bouts 2 and 4 because the muscle was fully potentiated. Perhaps the high frequency strategy actively modulates the dihydropyridine and ryanodine receptors sensitivity as a function of frequency (voltage) in the t-tubules. Higher frequencies of stimulation may rapidly increase the availability of Ca\(^{2+}\) to the contractile apparatus, eliciting an increase in torque, which is over and above that induced during potentiation without high frequencies.

**Clinical Significance of Torque Optimization**

The present study illustrates that online feedback controlled stimulation can enhance the peak and mean torque produced during bouts of repetitive stimulation. Due to the profound atrophy demonstrated by paralyzed muscle, extensive training must be undertaken before functionally useful torques can be generated. This process is generally lengthy, resource-intensive, and carries substantial subject burden.

An important goal of FES research is to develop neuroprostheses that can be used for grasping, standing, and walking (8). These functional activities require that paralyzed muscles have a certain threshold of force generating capability before commencing with functional training. The process of training paralyzed muscle or the ideal pattern of stimulation for neuroprosthetic devices may be enhanced by the use of feedback-controlled stimulation strategies that subvert the effects of fatigue and elicit optimal torque output. It is theoretically possible that different stimulation strategies will be necessary to meet the
needs and context of a variety of functional tasks. The advantage of a continuous, on-line process of stimulus modulation is that stimulus parameters can be instantly customized to suit the fatigue state of the individuals’ muscles. Studies are underway to delineate if stimulation under feedback control is a more effective mode of training chronically paralyzed muscle in humans.
Grants

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References


Figure Legends

Figure 1. Representative examples of a triad of three feedback-control strategies. In each panel, the dotted line represents the train immediately preceding the feedback triad. The torque for this train was 10% below “benchmark” torque, which triggered the delivery of the triad. Solid lines indicate torque output in response to the H, D, or L strategies. Stimulus pulses appear below each torque plot. The dotted lines represent the stimulus pulses for the pre-triad train. Solid lines represent stimulus pulses given in the H, D, or L strategies. Note that in this example, only the high frequency strategy yielded a recovery of torque exceeding the 2% criterion (bouts 1 and 4).

Figure 2. Representative examples of CONST and FDBCK sessions. A) CONST session, showing torque decline over 125 contractions. Note the potentiating contractions (1 thru 10 or 1 thru 15) in bouts 2-4. B) FDBCK session (in this case, HDL). Symbols are as given in part A. When torque declined by 10% from a benchmark value, H, D, and L strategies were given. The stimulation parameters of the most successful strategy were used for subsequent trains (yielding the “jumps” in torque visible in the figure) (see inset), and the torque elicited by the most successful strategy became the new benchmark torque. Further 10% declines in torque triggered the delivery of another HDL series.

Figure 3. Mean (SE) normalized torque produced by CONST versus FDBCK stimulation strategies (HDL, and LDH) for bouts 1, 2, and 4. To improve clarity, every fifth contraction is plotted.
Figure 4. Mean torque over 125 trains (left) and final torque (right), normalized to train #1 torque. The CONST bouts accompanying the HDL and LDH protocols are combined into a single vertical bar (white) for each plot. * = significantly greater than CONST (p<0.05). For bouts 2 and 4, note that normalized torque values exceed 1.0 because post-fatigue potentiation occurred during the first several contractions after resumption of stimulation (as depicted in Figures 2 and 3.)

Figure 5. Mean frequency of stimulation used to elicit each train during the feedback control protocols (HDL, LDH).
Figure 1.
Figure 2.
Figure 3.
Figure 4.
Figure 5.
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Table 1. Subject characteristics. Fatigue index was calculated as 100 * Final torque / Peak torque during constant-frequency stimulation.
### Table 2. Group mean (SE) torque values: average over 125 trains (top) and final torque (train 125) (bottom). All torque values are in Nm.

#### Mean Torque

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<td>20.69(0.23)</td>
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#### Final Torque

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