Feedback-controlled stimulation enhances human paralyzed muscle performance

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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.

Keywords

fatigue; spinal cord injury; doublet; excitation-contraction coupling

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The loss of normal muscular activity as a result of chronic spinal cord injury (SCI) leads to a cascade of harmful physiological 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. The reintroduction of physiological 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 physiological 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 (CONST) electrical stimulation training can maintain the musculoskeletal properties of recently paralyzed individuals before the muscle transformation process (increased fatigue) occurs to the soleus muscle (30–32). 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 (FDBCK) electrical stimulation system to test whether 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 (H) strategy, better suited for a muscle in excitation-contraction coupling compromise [low-frequency fatigue (LFF)] (6), employed a fixed increase to the base stimulation frequency. A doublet (D) strategy, better suited for a muscle demonstrating both LFF 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 (L) strategy, 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, and 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 FDBCK electrical stimulation of paralyzed muscle, compared with CONST stimulation; and *2*) ascertain which of three FDBCK stimulation strategies was most effective in sustaining paralyzed soleus torque during repetitive stimulation. We hypothesized that FDBCK stimulation would be superior to CONST stimulation and that the H strategy, by virtue of the significant LFF induced in paralyzed muscle (32), would be the most effective strategy to maintain torque.

METHODS

Eight men with complete SCI (American Spinal Injury Association 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 SCI (>1 yr) above T_{12}, as determined by neurological examination; passive ankle dorsiflexion to neutral; passive knee flexion to at least 90° 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 motoneuron injury below T_{12} (which would prevent tibial nerve electrical activation). The fatigue index was computed as 100 * final contraction torque (no. 125)/initial contraction torque (no. 1). The fatigue protocol consisted of 125 contractions elicited by supramaximal stimulation (15 Hz) of the tibial nerve every 2 s for 667 ms.

Test apparatus and protocol

Subjects remained in their wheelchairs during the test procedure. The ankle was stabilized in a system that measured isometric plantar flexion torque, as described previously (26–28, 30, 32, 33). The knee was positioned at 90° 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 (0–200 mA at 400 V) was triggered by digital pulses from a data-acquisition board (Metrabyte DAS 16F, Keithley Instruments, Cleveland, OH) housed in a microcomputer under custom software control. The stimulation intensity was supramaximal (about 1.5 times the intensity required to produce a maximum twitch).

Subjects participated in three or four stimulation sessions over a 6-mo 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 FDBCK sessions were compared with a CONST session that occurred on a separate day (mean = 5.8 wk, SE = 1.9).

For all sessions, the stimulator was programmed to deliver 10-pulse trains every 2 s. 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-min 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 three stimulation strategies (H, L, and D) each time torque dropped by 10% (Fig. 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 eight 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 (Fig. 2). A 2% improvement ensured that an increase in torque was not due to random fluctuations in transducer voltage (noise). Moreover, a 2% effect over four to eight strategies would translate into a clinically meaningful 8–16% 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 postfatigue 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, 10 and 15 potentiating contractions were given (15 Hz), respectively, before 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, and L). We did not test acutely (within 6 wk) 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 H strategy employed a 15% increase in frequency (for each 10% drop in torque). If the H strategy should be selected for each of the four to eight 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 vs. 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 ensured us that these frequency increments met this design criterion.

The L 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 D 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 L 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 LFF, we examined the torque generated by the soleus at *contraction 125*. This torque was normalized to the torque of the first 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 whether 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 postinjury was 7.2 yr (range 1.3–13.9 yr), with a mean fatigue index for the group of 41.72 (range 27.3–56.8) (Table 1). Examination of the data revealed that the difference in soleus torque generated by the FDBCK protocol vs. 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 (Fig. 3, *top*), nor did mean (SE) peak torque across 125 contractions differ between FDBCK and CONST trials (Fig. 4, *top*). In *bout 2*, both the HDL and LDH FDBCK bouts began to outperform CONST stimulation at the 20th contraction (Fig. 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 (Fig. 4, *middle; P < 0.05*). In *bout 4*, the HDL protocol began to outperform the CONST protocol at about *contraction 20* (Fig. 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 (Fig. 4, *bottom; P < 0.05*). See Table 2.

The HDL and LDH protocols responded similarly across all bouts, supporting that order did not influence the overall effect. A nonsignificant interaction indicated that the mean and final torque changes across bouts were not different, regardless of which protocol (HDL or

LDH) was tested ($P = 0.34$) (Fig. 4). However, there was a difference between protocols for the specific contraction number within the bout in which each protocol first influenced the peak torque (Fig. 3).

Effectiveness of H, L, and D 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* ($P < 0.05$) (Fig. 4). The H strategy was selected to be the most effective the majority of the time for all bouts (~90% of all strategies). The D and L strategies were selected <10% and 2% of the time, respectively, for all bouts in both FDBCK protocols. The H strategy demonstrated a 20–50% increase in normalized peak and mean torque in *bouts 2* and *4* ($P < 0.05$) but a <2% increase in *bout 1* (Fig. 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 number) compared with *bout 4* slope (0.03 Hz/contraction number). 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 ($R^2 = 0.65$–0.67). 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 Fig. 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*. 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 noneffective strategy occurred ~20% of the time.

DISCUSSION

For *bout 1*, torque FDBCK stimulation offered an advantage (in terms of mean or final torque) over CONST stimulation in individual cases, but, when averaged across subjects, it did not yield a significant effect. Previous studies concur that constant and variable-frequency stimulation yield similar end point fatigue in fresh (no LFF) paralyzed muscle (36). The acceptance of high-frequency strategies in *bout 1* (Fig. 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 (Fig. 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 (*bouts 2– 4*), as another form of fatigue developed (LFF) (27, 32), that the FDBCK H 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 1*, FDBCK stimulation elicited ~40% more torque than the CONST stimulation (Fig. 4). However, >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 (9) 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). 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 L strategy was rarely accepted in *bout 1* and was never selected during any other bouts (*bouts 2– 4*). The success of the H 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*, Fig. 2*B*). Our findings are in accord with our laboratory's 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 Fig. 5, the H strategy was accepted, even at the end of the fatigue protocol when the frequency was ~28 Hz. Thus, even at these higher frequencies and after 125 contractions, the H strategy was successful and supports that neuromuscular transmission failure was negligible. These H 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 H 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 H 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 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 H strategy had the greatest ability to restore torque in all bouts, regardless of the order of the feedback strategies. Although the doublet was selected ~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 D 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 (Fig. 4). Pilot data also supported that the D 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 (15) 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 CONST stimulation at 20, 33, or 66 Hz alone. Scott and colleagues (25) 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. Modulating stimulus parameters in this fashion allowed the paralyzed quadriceps muscles to attain a target force 14% and 18% more frequently than for either CONST 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 Fig. 5, the number of modulations can vary widely, depending on the fatigue state (bout number) of the paralyzed muscle. In addition, the FDBCK 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 CONST stimulation, as evident in *bout 1*. During later bouts, however, high-frequency stimulation offered clear advantages over CONST stimulation, which supports the idea that long-duration fatigue (LFF) develops following the 5-min rest interval (27, 32).

Slow-to-fast skeletal muscle transformation, as occurs with chronic paralysis, predisposes muscles to long-duration muscle fatigue (26, 27). 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 Ca^{2+} by the sarcoplasmic reticulum and altered receptor sensitivity (16, 17, 19, 38, 39). Fast skeletal muscle, designed for phasic activity, becomes "uncoupled" (reduced Ca^{2+} and/or reduced receptor sensitivity) after a repetitive activation protocol. As Ca^{2+} concentration falls during repetitive activation of paralyzed muscle, less free Ca^{2+} may be available, yielding impaired myosin regulatory light chain phosphorylation (3, 4). Overcoming LFF with high-frequency stimulation likely depends on posttranslational (myosin regulatory light chains) as well as pretranslational (calcium release) mechanisms (see below).

The H strategy (*bouts 2* and *4*) was effective, even though the muscle was nearly fully potentiated within each bout before the system delivered a strategy (Fig. 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 Ca^{2+} 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 H strategy in *bouts 2* and *4*

because the muscle was fully potentiated. Perhaps the H strategy actively modulates the dihydropyridine and ryanodine receptor 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 FDBCK 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 FDBCK 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, online 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.

Acknowledgments

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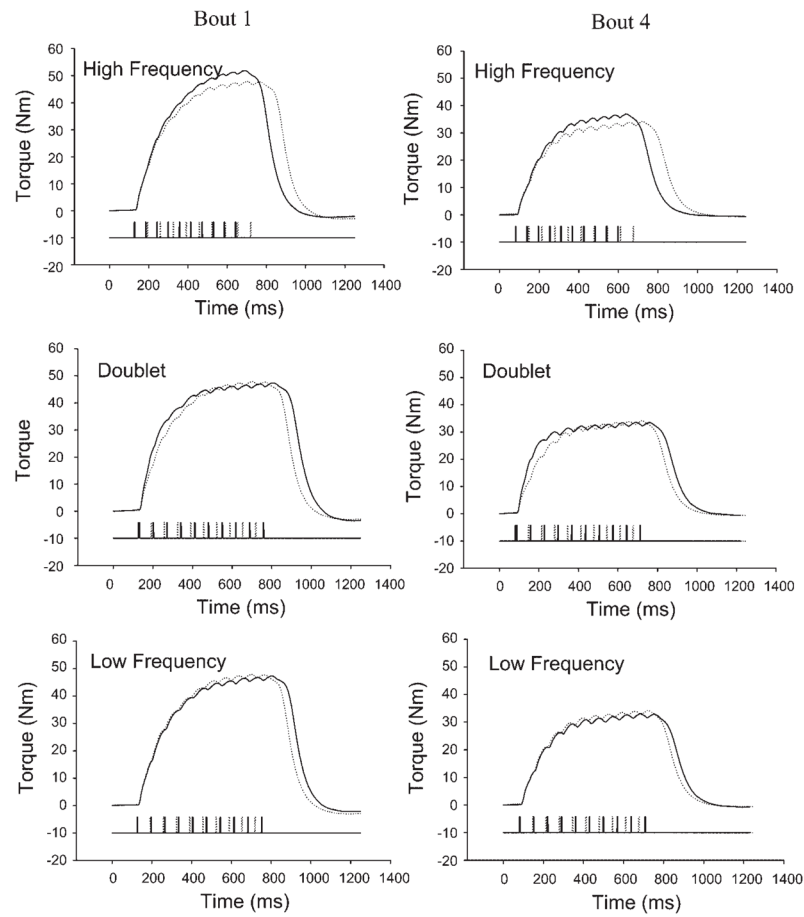
Fig. 1.
Representative examples of a triad of three feedback-control strategies. In each panel, the dotted line represents the train immediately preceding the feedback triad. The torque for this train was 10% below "benchmark" torque, which triggered the delivery of the triad. Solid lines indicate torque output in response to the high-frequency (H), doublet (D), or low-frequency (L) strategies. Stimulus pulses appear below each torque plot. The dotted lines represent the stimulus pulses for the pretriad train. Solid lines represent stimulus pulses given in the H, D, or L strategies. Note that, in this example, only the H strategy yielded a recovery of torque exceeding the 2% criterion (*bouts 1* and *4*).
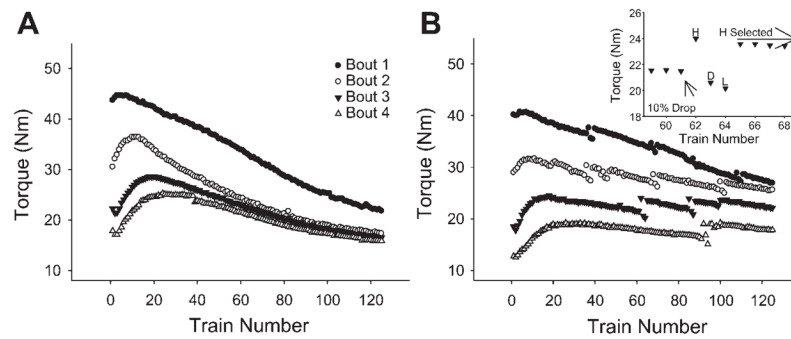
Fig. 2.
Representative examples of constant-frequency (CONST) and feedback-controlled (FDBCK) sessions. *A*: CONST session, showing torque decline over 125 contractions. Note the potentiating contractions (1–10 or 1–15) in *bouts 2– 4. B*: FDBCK session (in this case, HDL). Symbols are as given in *A*. 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.
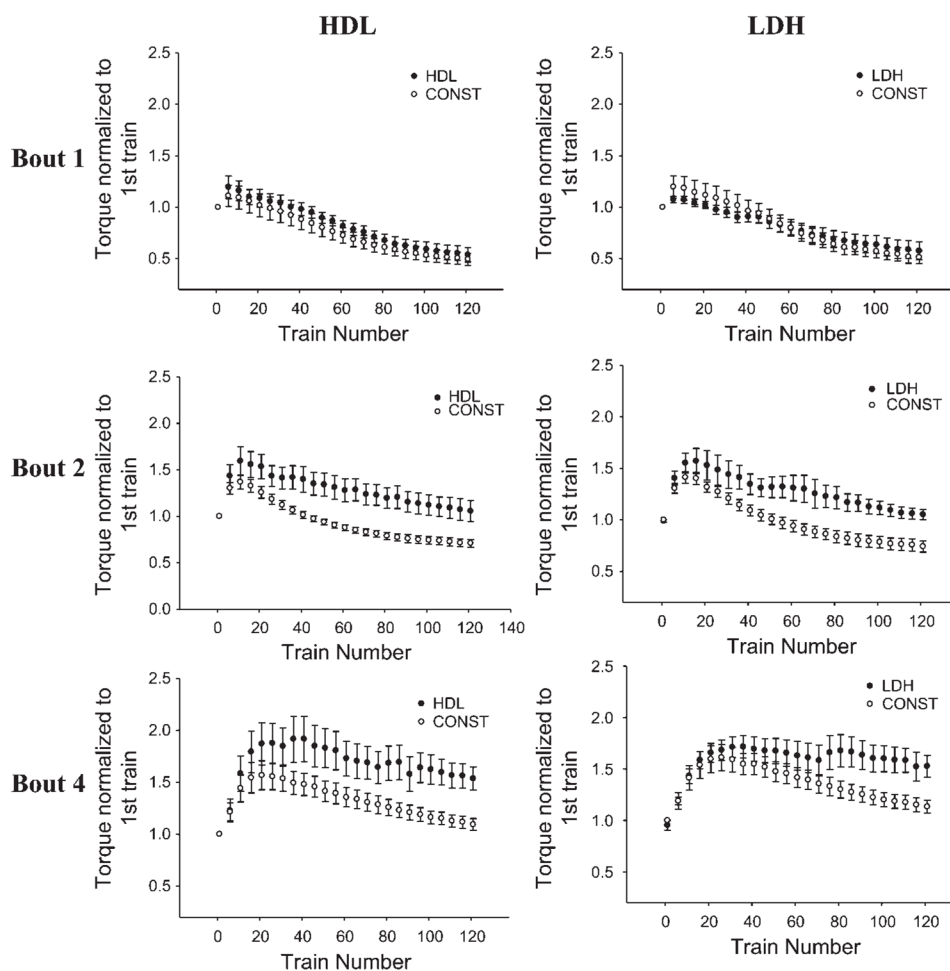
HDL **LDH**

Fig. 3.
Mean (SE) normalized torque produced by CONST vs. FDBCK stimulation strategies (HDL and LDH) for *bouts 1*, *2*, and *4*. To improve clarity, every 5th contraction is plotted.
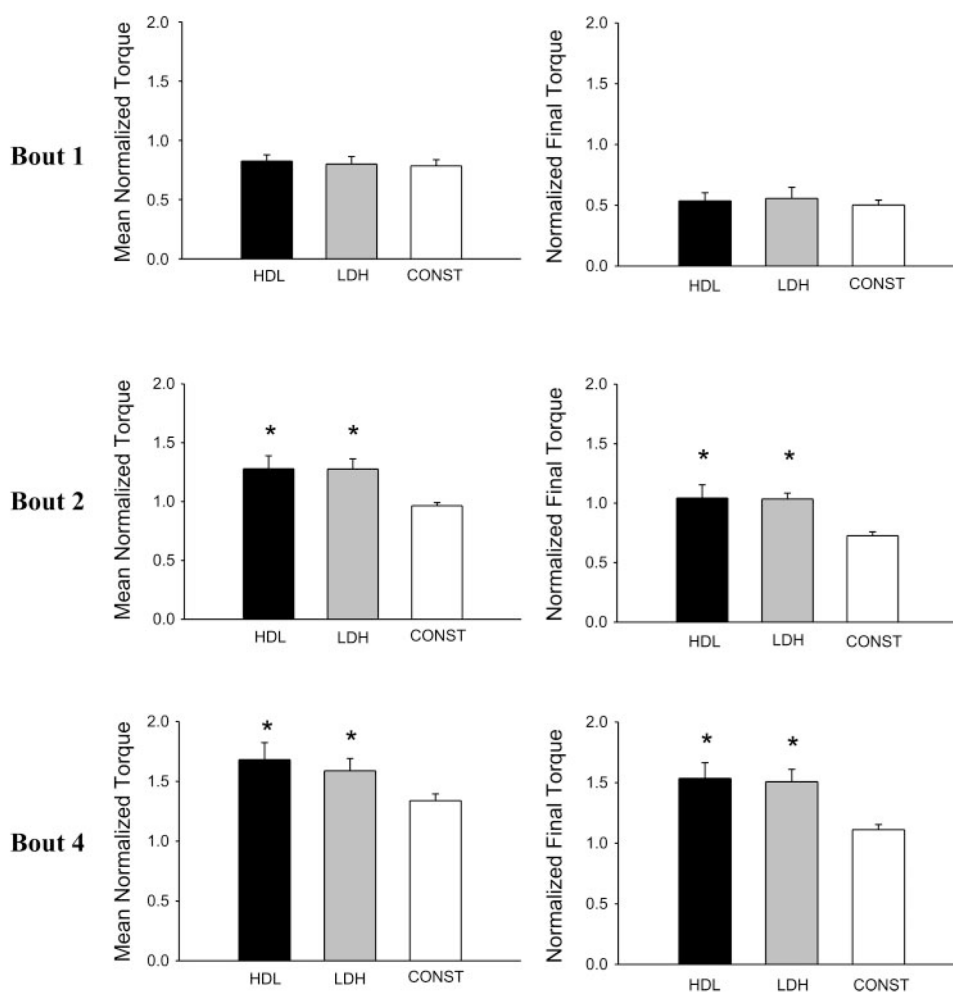
Fig. 4.
Mean torque over 125 trains (*left*) and final torque (*right*), normalized to *train 1* torque. The CONST bouts accompanying the HDL and LDH protocols are combined into a single vertical bar (open) for each plot. *Significantly greater than CONST ($P < 0.05$). For *bouts 2* and *4*, note that normalized torque values exceed 1.0 because postfatigue potentiation occurred during the first several contractions after resumption of stimulation (as depicted in Figs. 2 and 3).
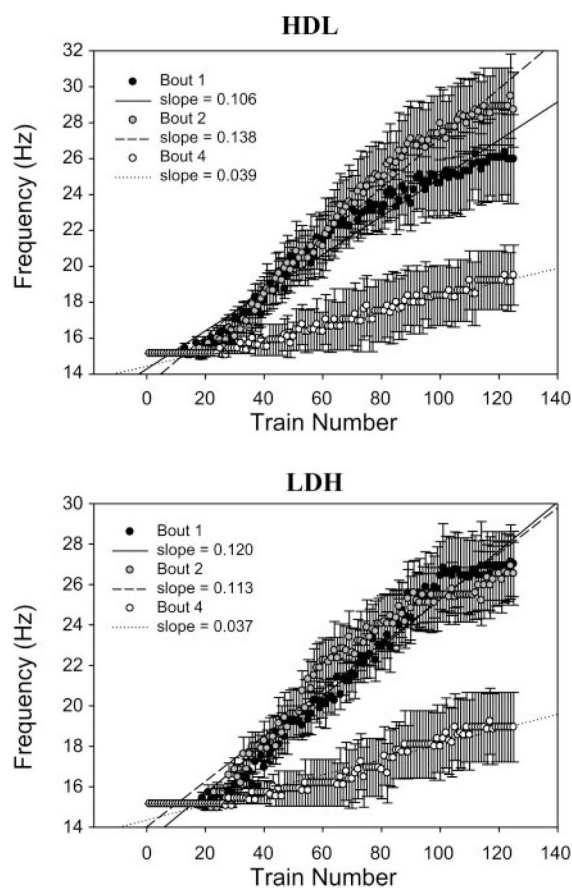
Fig. 5.
Mean frequency of stimulation used to elicit each train during the feedback control protocols (HDL, LDH).

Table 1

Subject characteristics

Subject No.	Age, yr	SCI Level	Years Post-SCI	Fatigue Index
1	68	T_5	12.04	56.80
2	23	T_4	2.43	37.36
3	33	T_4	13.94	57.65
4	26	T_4	3.92	48.05
5	49	T_7	2.08	27.28
6	55	T_6	9.94	48.78
7	31	C_6	1.27	27.47
8	37	T_1	11.92	30.38

Fatigue index was calculated as 100·final torque/peak torque during constant-frequency stimulation. SCI, spinal cord injury.

Table 2

Group mean (SE) torque values: average over 125 trains and final torque (train 125)

	Bout 1	Bout 2	Bout 4
Mean torque			
HDL			
FDBCK	27.65 (0.36)	21.94 (0.20)	13.15 (0.12)
CONST	26.78 (0.35)	20.69 (0.23)	12.36 (0.16)
LDH			
FDBCK	26.94 (0.29)	22.10 (0.17)	14.39 (0.14)
CONST	26.04 (0.31)	19.89 (0.18)	12.65 (0.18)
Final torque			
HDL			
FDBCK	17.60 (2.20)	17.69 (1.68)	12.15 (1.27)
CONST	17.39 (2.25)	15.65 (1.50)	10.27 (1.51)
LDH			
FDBCK	17.78 (1.92)	18.15 (1.49)	13.69 (1.53)
CONST	16.25 (1.64)	14.91 (1.25)	10.74 (1.82)

All torque values are in N · m. H, high-frequency strategy; L, low-frequency strategy; D, doublet strategy; FDBCK, feedback-controlled session; CONST, constant-frequency session.