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Enhancing Muscle Force and Femur Compressive Loads via Feedback-Controlled Stimulation of Paralyzed Quadriceps in Humans

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Abstract

Objective—To compare paralyzed quadriceps force properties and femur compressive loads in an upright functional task during conventional constant-frequency stimulation and force feedback-modulated stimulation.

Design—Crossover trial.

Setting—Research laboratory.

Participants—Twelve men and one woman with motor complete SCI.

Intervention—Subjects performed 2 bouts of 60 isometric quadriceps contractions while supported in a standing frame. On separate days subjects received constant-frequency stimulation at 20 Hz (CONST) or frequency-modulated stimulation (FDBCK). During FDBCK, a computer algorithm responded to each 10% reduction in force with a 20% increase in stimulation frequency.

Main Outcome Measure—A biomechanical model was used to derive compressive loads upon the femur, with a target starting dose of load equal to 1.5 times body weight.

Results—Peak quadriceps force and fatigue index were higher for FDBCK than CONST ($p < 0.05$). Within-train force decline was greater during FDBCK bouts but mean force remained above CONST values ($p < 0.05$). As fatigue developed during repetitive stimulation, FDBCK was superior to CONST for maintenance of femur compressive loads ($p < 0.05$).

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Conclusions—Feedback-modulated stimulation in electrically-activated stance is a viable method to maximize the physiologic performance of paralyzed quadriceps muscle. Compared to CONST, FDBCK yielded compressive loads that were closer to a targeted dose of stress with known osteogenic potential. Optimization of muscle force with FDBCK may be a useful tactic for future training-based anti-osteoporosis protocols.

Keywords

spinal cord injuries; fatigue; electrical stimulation; osteoporosis

The disruption of normal mechanical, neural, and hormonal factors after spinal cord injury (SCI) triggers rapid loss of bone mineral density (BMD) in paralyzed extremities. Post-SCI trabecular BMD may be 50% to 70% lower than non-SCI BMD^{1–3}, placing individuals with SCI at an elevated risk for fracture⁴. The hazard for mortality is estimated to be 78% higher for people with SCI who sustain a lower extremity fracture than their peers without fractures⁵. Rehabilitation interventions to prevent post-SCI osteoporosis are therefore in great demand.

BMD loss in paralyzed extremities can be partially prevented^{2, 6–8} or partially reversed⁹ by the reintroduction of mechanical loads via electrically-evoked muscular contraction. Electrical stimulation protocols must be thoughtfully and carefully administered, however, to ensure that mechanical loads do not exceed the breaking strength of osteoporotic post-SCI bones. Because bone is an anisotropic material, shear forces (askew to the long axis of the bone) carry a greater risk for fracture than compressive forces, which bone is ideally suited to withstand. Shear forces during common therapeutic activities (seated knee extension) may be sufficient to cause distal femur fractures^{10–11}. In contrast, shear forces are minimized during electrically-activated isometric quadriceps contractions in supported stance¹². Estimated compressive forces at the start of standing bouts can exceed 150% of body weight (150 %BW); a dose of loading that has previously yielded preservation of BMD in subjects with SCI^{2, 6–8}. Subjects who performed three years of unilateral daily soleus contractions at this magnitude of load demonstrated ~31% higher distal tibia BMD in trained limbs than in contra-lateral, untrained limbs². Because the distal femur is one of the most common sites for post-SCI fractures^{13–17}, our goal is to deliver a comparable dose of load (starting ~150% BW) to the femur via electrically-activated standing. We chose the standing position because it relieves deleterious seated pressures for individuals with poor skin sensation, because individuals with SCI enjoy standing and report subjective health benefits (bowel/bladder, spasticity, etc)^{18–19}, and because our biomechanical model supported that shear forces through the distal femur are low¹².

Previous work supports that the magnitude of compressive load may be a critical determinant of the effectiveness of post-SCI loading interventions for bone^{6, 20}. Muscle fatigue during repetitive electrical stimulation limits the muscle forces, and thus the peak compressive loads, experienced by the skeletal system during a training bout. Modulation of the stimulus frequency, intensity, or pulse width can mitigate force decline in electrically activated paralyzed muscle^{21–24,40}. To deliver the target load to bone, muscle recruitment (and therefore stimulus intensity) must be high throughout a loading bout^{2, 6–8}, minimizing the utility of intensity modulation in this context. As an alternate approach, we previously tested a feedback-controlled stimulus frequency modulation system to minimize soleus muscle fatigue during repetitive stimulation²¹. When presented in a competitive fashion, upward modulation of stimulus frequency was superior to downward modulation or to paired-pulse interposition for maintaining muscle force. However, because the soleus has a unique slow-oxidative profile, it is unclear whether upward modulation of stimulus frequency would be similarly effective in other muscle groups. Because our goal is to

understand the therapeutic training dose for the quadriceps muscle and distal femur, we wished to determine whether upward modulation of stimulus frequency would mitigate quadriceps fatigue during electrically-activated standing. The purpose of this study is to compare quadriceps force properties during conventional constant-frequency stimulation (20 Hz) versus force feedback-modulated stimulation in a novel electrically-activated isometric standing protocol. If feedback-controlled stimulation enhances muscle force and skeletal loading, it may be an important intervention to deliver efficient therapeutic stress to muscle and bone in individuals with paralysis.

Methods

Subjects

Twelve men and one woman with motor-complete SCI (ASIA A and B)²⁵ participated in the study (Table 1). All subjects signed an Informed Consent document approved by our institution's Humans Subjects Office. Inclusion criteria were SCI above T12, BMD over 60 mg/cm³, experience with activating with electrical stimulation, and intact peripheral innervation as demonstrated by evoked muscle contractions. Exclusion criteria were pressure ulcers, peripheral/systemic infection, a history of bone pathology (i.e. bone metabolic disease, cancer, etc.), thyroid disorder, or lower extremity fractures at the time of SCI. Subjects were not excluded if they sustained lower extremity fractures in adolescence and thereafter returned to routine sporting activities (subject 5, Table 1).

Active-Resisted Standing

All subjects had experience with standing and stimulation as a prerequisite for admission into this study. The standing system consisted of a modified standing frame with a padded plate positioned against the anterior surface of the subject's knee (Figure 1). Velcro straps secured the knee against the plate. A force transducer (1500ASK-200, Interface, Scottsdale AZ) mounted in series with the plate measured the isometric knee extension resultant force during quadriceps activation. Signals from the force transducer were amplified 500 times (Therapeutics Unlimited, Iowa City, IA) and sampled at 2000 Hz (Datapac 2K2, RUN Technologies, Mission Viejo, CA). A monitor positioned in front of the standing frame allowed the subject and the investigator to observe quadriceps forces in real-time. The knee was positioned in 20 degrees of flexion during standing. Anthropometric data and measured quadriceps force were input into a biomechanical model that we previously developed¹², which derived distal femur compressive and shear forces. Compression and shear were expressed as a percent of each subject's body weight. Compressive loads from contracting muscle are a chief source of loads for the healthy skeletal system and may therefore provide an anabolic stimulus for post-SCI bone. While in the healthy skeleton shear loads may be another trigger for bone anabolism, osteoporotic bones may lack sufficient strength to resist shear forces. Based on our previous findings regarding the long-term skeletal adaptations to SCI^{2, 6-8, 26-27} we designed this biomechanical intervention to emphasize compressive loads and minimize shear forces at the distal femur during quadriceps activation¹².

The experiment was controlled by custom-designed software, which directed digital pulses from a data-acquisition board (Metabyte DAS 16F, Keithley Instruments Inc., Cleveland, OH) housed in a microcomputer. The microcomputer output was conveyed via shielded cabling to a muscle stimulator unit (Digitimer model DS7A, Digitimer Ltd., Welwyn Garden City, Hertfordshire, England). We delivered sixty 100-pulse trains (200 microseconds, 200 milliamps) to the quadriceps via reusable carbon adhesive electrodes. Each train was followed by 5 seconds of rest, yielding a 1:1 work/rest ratio. A longer rest phase would have considerably lengthened the 25-minute experiment (two ten-minute bouts and a 5 minute

rest interval). A longer experiment would have been problematic for SCI subjects with varying levels of standing tolerance.

Force-Feedback Testing

On two separate days, subjects performed electrically-activated standing using 20 Hz constant-frequency stimulation (CONST) or a force feedback-controlled stimulation protocol (FDBCK). The order of sessions was randomly determined and sessions were separated by at least 7 days. Both sessions began with 10 warm-up 20 Hz contractions (100 pulses) to potentiate the quadriceps force. Subjects then immediately performed one bout of sixty contractions, rested for 5 minutes, and performed a second bout of sixty contractions.

In CONST sessions, 20 Hz stimulation was the only frequency used. In FDBCK sessions, a real time software controller monitored force and modulated the stimulation frequency. FDBCK stimulation began at 20 Hz and a 10% drop in peak force triggered a 20% increase in stimulation frequency for the subsequent train. If force increased by less than 5% as a result of the modulation, the stimulation frequency reverted to the previous frequency. If force increased by 5% or more, the higher stimulus frequency was viewed as successful and was adopted for subsequent contractions. The force benchmark was re-established at each new accepted value. Stimulation trains continued until the software detected the next 10% drop in force, at which time another high-frequency strategy was automatically given and evaluated. Up to 8 increments of stimulus frequency were possible (24, 28, 32, 36, 40, 44, and 48 Hz), depending upon the degree of fatigue demonstrated by the quadriceps during repetitive stimulation (Figure 2).

We chose to begin stimulation at 20 Hz in order to generate a baseline quadriceps force that was associated with femur compressive loads of ~150% BW at the outset of stimulation¹². Pilot work supported that 20% frequency increments: a) yielded 5% improvements in force approximately 50% of the time, and; b) did not drive the stimulation frequency to the highest levels until at least two-thirds of the bout had elapsed. Our previous work supports that the linear portion of the force frequency curve for paralyzed muscle is between 10 and 40 Hz²⁸. Stimulation frequencies greater than 50 Hz are beyond the linear portion of the force frequency curve^{24, 29}. Thus stimulation frequencies higher than 48 Hz were not used in the FDBCK because of the likelihood of eliciting neuromuscular transmission failure (particularly given the duration of contractions; 5 seconds).

Dependent Variables

The resultant peak force, mean force, fatigue index, potentiation index, within train force decline, and femur compressive load were calculated for FDBCK and CONST for each subject. To compensate for between-subject differences in force output, force values were normalized to the force of the 1st contraction in Bout 1 for each subject. Fatigue index for the quadriceps was computed as the quotient of the minimum and the maximum quadriceps force for each session, expressed as a percent.

A high fatigue index represents a low level of fatigue. Repetitive stimulation of paralyzed muscle yields low-frequency fatigue (LFF)³⁰, indicative of excitation-contraction coupling compromise³¹. Upon resumption of stimulation after a period of inactivity (5 minutes of rest), force potentiation occurred over the first 5–10 contractions (post-fatigue potentiation³⁰). We quantified potentiation by dividing the maximum force in Bout 2 by the initial force in Bout 2, yielding a potentiation index. If FDBCK stimulation in Bout 1 led to lower Bout 2 potentiation than CONST, the usefulness of FDBCK for repetitive stimulation may be limited.

Frequency modulation in FDBCK sessions yielded stimulus trains of progressively declining duration, which would tend to decrease the force-time integral independently of any possible fatigue processes within the muscle. To allow for more appropriate comparisons of the integral between FDBCK and CONST bouts, we divided the force-time integral for each contraction by the contraction duration, yielding “mean force”. We then normalized mean force to the 1st contraction of Bout 1 for each subject.

We previously observed that repetitive stimulation induced high frequency fatigue (HFF) in paralyzed muscle, confirmed by reduction of M-wave size during 20 Hz stimulation trains³². In pilot work we observed that within-train force decline occurred during the FDBCK protocol (Figure 2), prompting us to question whether HFF occurred in this protocol. We examined the decline of quadriceps force within the 100-pulse train as surrogate of HFF. Because no subject experienced stimulation above 36 Hz in Bout 1, we examined Bout 2 data. For each subject we selected the first contraction at each frequency increment (20, 24, 28, 32 Hz and so on). For each of these selected contractions, we captured the force associated with each of the 100 within-train stimulus pulses, then omitted the first 30 values (the force rise and plateau zone, when HFF would be least prevalent) (Figure 3). All force values for pulses 31–100 were normalized to the subject’s maximum force for bout 2. We then obtained the slope of the normalized instantaneous force values as a function of pulse number, yielding an estimate of the within-train force decline. Based on the representative data displayed in Figure 2, it appeared that little within-train force decline occurred during CONST bouts. To verify this, we selected the CONST contractions that were numerically identical to the previously-selected FDBCK contractions at each frequency and calculated within-train force decline values in the manner described above.

For each subject, quadriceps force values were input to a biomechanical model¹², along with the subject’s height, weight, and joint angles during standing. We previously validated this model as means to calculate distal femur compression and shear forces, expressed as a percent of the subject’s body weight. Thus, muscle forces and the subsequent femur compressive loads could be contrasted between CONST and FDBCK strategies.

Statistical Analysis

For peak force, mean force, and compressive load, we compared FDBCK vs. CONST at several points during the stimulation bouts (contractions 1, 20, 40 and 60). Each dependent variable was analyzed with a two way repeated measures analysis of variance (ANOVA) (contraction number $\times$ stimulus strategy) for Bout 1 and for Bout 2. In the event of a significant interaction, follow-up tests (Tukey) were conducted. Fatigue index was compared between CONST and FDBCK via one-way repeated measures ANOVAs for Bout 1 and for Bout 2. Potentiation index from Bout 2 data was compared between CONST and FDBCK via one-way repeated measures ANOVA. Alpha was set at 0.05 for all tests and Bonferroni adjustments were made to account for multiple comparisons.

To determine whether within-train force decline differed according to frequency in bout 2 FDBCK bouts, we performed a repeated measures one-way ANOVA. During bout 2 FDBCK bouts, not all subjects experienced the highest-frequency stimulus trains. We therefore pooled all within-train force decline values at frequencies at and above 40 Hz into a single treatment level for the ANOVA. Finally, we used a one-way ANOVA to determine whether within-train slope decline differed between FDBCK and CONST conditions.

Results

Frequency Progression in FDBCK

In bout 1, FDBCK triggered an average of 5.15 increments in frequency. Of these, an average of 2.46 (43.70%) were accepted (because they yielded a 5% increase in force). Stimulus frequency reached the maximal allowed value (48 Hz) for only one subject in bout 1. In bout 2, the software algorithm triggered an average of 6.31 frequency increments; an average of 4.46 (71.21%) were accepted. Stimulus frequency reached the maximal allowed value (48 Hz) for three subjects in bout 2.

FDBCK vs. CONST

Figure 4A depicts normalized force values for the FDBCK and the CONST protocols. Mean (SD) bout 1 peak quadriceps force was 26.27 kg (8.86) for FDBCK and 25.85 kg (9.17) for CONST sessions ($p > 0.05$). This corresponds to a mean horizontal resultant value of 33%BW for the cohort (Table 1). Bout 1 peak force was 18.00% (s.d. 77.74) and 26.92% (s.d. 20.78) higher for FDBCK than for CONST at contractions 40 and 60, respectively (Figure 4A). Bout 1 mean force, on the other hand, did not differ between FDBCK and CONST at contractions 20, 40, or 60 ($p > 0.05$, Figure 4B). Bout 1 fatigue index was 28.09% (s.d. 20.15) higher for FDBCK than CONST ($p < 0.05$) (Figure 4C).

At the resumption of stimulation in bout 2, normalized quadriceps force did not differ between strategies ($p > 0.05$), nor did it differ after potentiation of force (by contraction 10; $p > 0.05$). The contraction number at which potentiation was complete did not differ between strategies (mean: contraction 4.54 and 4.31 for FDBCK and CONST respectively, $p > 0.05$). Mean (SE) potentiation index was 1.21 (0.21) for FDBCK and 1.37 (0.51) for CONST ($p > 0.05$). As in Bout 1, Bout 2 force was significantly higher for FDBCK than CONST at contractions 40 and 60 (26.95% (s.d. 27.92) and 27.97% (s.d. 30.01), respectively ($p < 0.05$))(Figure 4A). Unlike in Bout 1, in Bout 2 mean force was significantly higher for FDBCK than CONST at contractions 20, 40, and 60 (mean (SD) differences of 31.37% (41.23), 48.45% (58.69), and 50.51% (53.82) respectively ($p < 0.05$)) (Figure 4B). Bout 2 fatigue index was 39.85% (s.d. 27.09) higher for the FDBCK strategy than for CONST ($p < 0.05$) (Figure 4C).

Within-Train Force Decline

For the FDBCK protocol, the within-train force slopes differed systematically across frequencies ($p < 0.05$), with steeper negative slopes at the progressively higher frequencies. Follow-up testing revealed a significant pairwise difference in within-train slope for the lowest (20 Hz) and highest (pooled > 40 Hz) frequency conditions. As might be expected, no systematic differences in within-train force slopes appeared across the 60 contractions in the CONST sessions ($p > 0.05$).

Modeled Compressive Load

In Bout 1, modeled distal femur compressive load was significantly higher for FDBCK than for CONST at contractions 40, 50, and 60 ($p < 0.05$)(Figure 5), but the overall percent difference between strategies was small (6.07% at contraction 60, SE 4.50). For Bout 2, FDBCK was significantly higher than CONST from contraction 20 onward ($p < 0.05$) (Figure 5) and the percent difference between strategies was small (4.37% (SE 5.28)). The maximum compressive load developed by any subject was 212.97% body weight (%BW) (subject 11, Table 1), corresponding to a shear force of 22%BW.

Discussion

The purpose of this study is to compare paralyzed quadriceps force properties and femur compressive loads in an upright functional task during conventional constant-frequency stimulation and force feedback-modulated stimulation. In FDBCK and CONST bouts with uniform starting force (bout 1) or a uniform degree of post-fatigue potentiation (bout 2), feedback-controlled stimulation was superior for mitigation of fatigue during repetitive stimulation. By inserting quadriceps peak force values into a previously published biomechanical model, we illustrate how feedback-controlled stimulation enhances skeletal loading. This study confirms, in a model that is conceptually novel and functionally relevant, that closed-loop feedback control of stimulation can optimize loading conditions in stance during electrical stimulation of paralyzed limbs.

Feedback-control of stimulation mitigated quadriceps fatigue during repetitive contractions against isometric resistance. To ensure an equal advantage to the FDBCK and CONST protocols, we randomized the presentation of the protocols (Table 1) and for each subject, elicited uniform starting force for both protocols. Early in the stimulus bout, no force difference emerged between protocols because few FDBCK strategies had been offered and accepted (Figure 4). Strategies offered early in the bout generally failed to elicit the requisite 5% increase in force, causing the frequency to revert to 20 Hz. Upward modulation of stimulus frequency was thus ineffective for offsetting fatigue early in the bout. Successful strategies typically began to appear by contraction 16 for bout 1 and by contraction 13 for bout 2. These incremental frequency increases helped to preserve peak FDBCK force, such that differences between FDBCK and CONST appeared by mid-bout (contraction 40). The greater effectiveness of FDBCK in the latter two-thirds of the bout suggests that the fatigue mechanisms late in the bout may differ at least partly from the fatigue mechanisms in operation early in the bout. The final normalized peak force value at the end of bout 1 was 26.92% higher for the FDBCK protocol than for CONST. Fatigue index was likewise higher for FDBCK at the end of bout 1 (28.09% higher than CONST). The FDBCK strategy outperformed CONST by an even greater margin at the end of bout 2 (contraction 60; peak force 27.97% higher, FI 39.85% higher). Thus during bout 2, when muscle fatigue was most prevalent (Figure 4), FDBCK was at its most advantageous.

Based on our previous work with short 20 Hz stimulus trains³², we expected that the FDBCK protocol would elicit within-train force decline as the frequency was modulated upward (Figure 3). We observed progressively steeper negative within-train force slopes as a function of frequency, culminating in a significant difference between 20 Hz and the highest frequencies (40 Hz and higher). In contrast we observed no changes in within-train force decline in CONST bouts despite the development of fatigue (reduced peak force). The intensification of within-train force decline *only* in bouts that used upward modulation of frequency suggests a role for neuromuscular transmission compromise and HFF in FDBCK bouts. Conclusive identification of HFF would require analysis of quadriceps m-waves, which was not technically feasible in this experimental design but is an item for further study.

Despite inducing within-train force decline, mean force was higher for the FDBCK strategy than CONST at contractions 20 through 60 in bout 2. This indicates that the decline in quadriceps force-time integral over the course of the progressively-shorter FDBCK contractions was largely offset by the increase in quadriceps peak force achieved by FDBCK at the beginning of each contraction. Upward modulation of stimulus frequency may thus be a useful strategy for tasks that require prolonged quadriceps work. Other studies have explored the combination of frequency and stimulus intensity modulation for prolonging quadriceps work^{22, 33}. These studies suggest that when the goal is to maximize the number

of successful submaximal contractions, such as in gait-related tasks, upward modulation of stimulus *intensity* can be advantageous. However, to achieve our target starting level of distal femur compressive loads (~150% BW), a high stimulus intensity (200 mA) was required at the beginning of the bouts in this study, limiting the possibility of further upward modulation of intensity.

Another method commonly used to offset quadriceps fatigue is to capitalize on the catch-like property of paralyzed skeletal muscle by starting the stimulus train with a doublet with a short interpulse interval (a variable frequency train, or VFT)^{34–36}. Stimulation protocols that incorporate VFTs have been shown to be effective at offsetting fatigue in some³⁶ but not all instances^{34–35}. Our previous work with the paralyzed soleus indicated that when doublets, high-frequency, and low-frequency modulation were offered in a competitive manner during a repetitive stimulation protocol, high-frequency modulation resulted in the best force outcome 90% of the time²¹. The dominance of the FDBCK strategy prompted us to investigate its usefulness for the quadriceps in the present study.

The issue of prolonging contractile work is worth considering when investigating feedback controlled-stimulation of paralyzed muscle. In the present study, we strove to maximize peak muscular forces in an effort to optimize peak compressive loads experienced by the skeletal system. Bone is less responsive to static loads than to dynamic loads^{37–38}, thus the prolongation of muscular loads is less critical for our purposes than the peak muscular load transmitted to bone. Our previous work demonstrated that very short muscular contractions (10 pulses covering just 667 ms) were effective for mitigating BMD decline in paralyzed limbs^{2, 6–8}. Short contractions were possible in our previous work because we applied stimulation to a single limb segment (tibia) in a non-weight bearing, mechanically constrained fashion. In a standing model with multiple constrained limb segments, longer contractions are needed for subject comfort and to overcome the unavoidable mechanical compliance of a multi-segmental model. We do not believe that the duration of the contractions applied in the present report (five seconds) is a key feature for the theoretical osteogenic potential of these muscular loads. Rather, given what is known about the response of bone to load strain rate³⁹, the rapid development of peak force (Figure 2) is probably the more noteworthy feature, from the perspective of bone adaptation.

Estimated distal femur compressive loads, expressed as a percent of each subject's body weight, were ~150% BW at the beginning of bout 1. As quadriceps fatigue developed, the FDBCK strategy maintained peak compressive loads at significantly higher levels than CONST for contractions 40 through 60 (Figure 5). FDBCK was similarly effective for optimizing compressive loads in bout 2. However, the relative difference in compressive load between the two strategies was between 4 and 6 percent. The possible significance of this level of difference, particularly when considered in the context of a long-term training protocol, is a matter of speculation. The number of large loads bone must experience per day to preserve BMD is currently unknown. In animal models of disuse (wing or limb unloading), very few load cycles per day are necessary to completely mitigate BMD decline^{40–41}. The selection of 2 bouts of 60 contractions for the current protocol was based on our past experience with training paralyzed muscle for high-load musculoskeletal training protocols^{2, 8, 30}. In the paralyzed human musculoskeletal system, it may be the case that a sufficient osteogenic stimulus is supplied by the first few contractions in a loading bout. However, in order for paralyzed muscle to remain an effective generator of large loads, it must undergo repetitive stimulation in order to provide an "overload stimulus"⁴² to the contractile apparatus and associated metabolic systems. Adaptations in muscle force and fatigue resistance arise only as the muscle is challenged via repetitive stimulation, even if skeletal mechano-transducing mechanisms saturate early during the activity. On the other hand, even 2 bouts of 60 contractions may be an insufficient mechanical stimulus to

preserve distal femur bone mineral density. Longitudinal experiments are underway in our laboratory to determine the dose-response nature of muscular loads for BMD preservation.

Study Limitations

It is important to consider that while large compressive loads (~150% BW) have been shown to attenuate BMD decline after SCI^{2, 6–8}, smaller loads may also possess osteogenic potential. Though we designated 60 contractions for this protocol to provide an overload stimulus for the muscular system, the lower loads (~120% BW) at the end of the standing bouts could also provide an anabolic stimulus to bone. Further work is necessary to determine the minimal effective dose of muscular load in the paralyzed human model. Importantly, at the opposite end of the loading continuum, small magnitude oscillatory loads make up the majority of the loads experienced by bone⁴³. Several recent animal experiments support that vibratory loads, even in the absence of weight bearing^{44–45}, can trigger bone anabolism⁴⁶.

A second consideration is that all subjects in this study had previously developed standing and stimulation tolerance. Therefore the magnitude of fatigue may be slightly underestimated in this study. Because of severe hypotension from disruption of the autonomic nervous system after SCI, it takes several weeks to months for individuals to become accustomed to the upright position. Accordingly, the findings from this study apply to individuals who have already achieved a level of upright conditioning with stimulation.

Finally, though our previous work supports that bone loads approximating 150% BW possess anabolic potential for bone, it is important to note that the subjects in those studies began electrical stimulation training shortly after SCI. If the load per unit area of bone is a critical factor for bone adaptation, then bones with established osteoporosis may experience an osteogenic stimulus with much lower levels of compressive loading. Future studies must determine the dose-response relationship of loading in bones with varying initial BMD status.

Conclusions

Force feedback-controlled electrical stimulation was superior to constant-frequency stimulation for maintaining paralyzed quadriceps peak force and the associated modeled femur compressive loads. Despite inducing within-train force decline, mean force (an indicator of prolonged contractile work) was superior with feedback-controlled stimulation. The novel aspects of this study were 1) the use of a clinically-pertinent standing task, and; 2) the estimation of compressive loads to the distal femur. Force-feedback stimulation offered a means to optimize skeletal loading conditions according to a predetermined target dose. Optimization of loading may be a key feature of future anti-osteoporosis interventions.

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List of Abbreviations

SCI	spinal cord injury
BMD	bone mineral density
CONST	constant-frequency stimulation

FDBCK	force feedback-controlled stimulation protocol
LFF	low-frequency fatigue
HFF	high frequency fatigue
ANOVA	analysis of variance
VFT	variable frequency train

References

1. Eser P, Frotzler A, Zehnder Y, Wick L, Knecht H, Denoth J, et al. Relationship between the duration of paralysis and bone structure: a pQCT study of spinal cord injured individuals. *Bone* 2004;34:869–80. [PubMed: 15121019]
2. Shields RK, Dudley-Javoroski S. Musculoskeletal plasticity after acute spinal cord injury: Effects of long-term neuromuscular electrical stimulation training. *J Neurophysiol* 2006;95:2380–90. [PubMed: 16407424]
3. Shields RK, Dudley-Javoroski S. Musculoskeletal adaptation in chronic spinal cord injury: effects of long-term soleus electrical stimulation training. *Journal of Neurorehabilitation and Neural Repair* 2006;21(2):169–79.
4. Vestergaard P, Krogh K, Rejnmark L, Mosekilde L. Fracture rates and risk factors for fractures in patients with spinal cord injury. *Spinal Cord* 1998;36(11):790–6. [PubMed: 9848488]
5. Krause JS, Carter RE, Pickelsimer EE, Wilson D. A prospective study of health and risk of mortality after spinal cord injury. *Arch Phys Med Rehabil* 2008;89(8):1482–91. [PubMed: 18674984]
6. Dudley-Javoroski S, Shields RK. Dose estimation and surveillance of mechanical loading interventions for bone loss after spinal cord injury. *Phys Ther* 2008;88:387–96. [PubMed: 18202080]
7. Dudley-Javoroski S, Shields RK. Asymmetric bone adaptations to soleus mechanical loading after spinal cord injury. *J Musculoskelet Neuronal Interact* 2008;8(3):227–38. [PubMed: 18799855]
8. Shields RK, Dudley-Javoroski S, Frey Law L. Electrically-induced muscle contractions influence bone density decline after spinal cord injury. *Spine* 2006;31(5):548–53. [PubMed: 16508550]
9. Frotzler A, Coupaud S, Perret C, Kakebeeke TH, Hunt KJ, Donaldson Nde N, et al. High-volume FES-cycling partially reverses bone loss in people with chronic spinal cord injury. *Bone* 2008;43(1):169–76. [PubMed: 18440891]
10. Hartkopp A, Murphy RJ, Mohr T, Kjaer M, Biering-Sorensen F. Bone fracture during electrical stimulation of the quadriceps in a spinal cord injured subject. *Arch Phys Med Rehabil* 1998;79(9):1133–6. [PubMed: 9749697]
11. Franco JC, Perell KL, Gregor RJ, Scremin AM. Knee kinetics during functional electrical stimulation induced cycling in subjects with spinal cord injury: a preliminary study. *J Rehabil Res Dev* 1999;36(3):207–16. [PubMed: 10659804]
12. Frey Law L, Shields RK. Femoral loads during passive, active, and active-resistive stance after spinal cord injury: a mathematical model. *Clinical Biomechanics* 2004;19:313–21. [PubMed: 15003348]
13. Biering-Sorensen F, Bohr HH, Schaadt OP. Longitudinal study of bone mineral content in the lumbar spine, the forearm and the lower extremities after spinal cord injury. *Eur J Clin Invest* 1990;20(3):330–5. [PubMed: 2114994]
14. Garland DE, Stewart CA, Adkins RH, Hu SS, Rosen C, Liotta FJ, et al. Osteoporosis after spinal cord injury. *J Orthop Res* 1992;10(3):371–8. [PubMed: 1569500]
15. Uebelhart D, Demiaux-Domenech B, Roth M, Chantraine A. Bone metabolism in spinal cord injured individuals and in others who have prolonged immobilisation. A review. *Paraplegia* 1995;33(11):669–73. [PubMed: 8584303]
16. Eser P, Frotzler A, Zehnder Y, Denoth J. Fracture threshold in the femur and tibia of people with spinal cord injury as determined by peripheral quantitative computed tomography. *Arch Phys Med Rehabil* 2005;86(3):498–504. [PubMed: 15759235]

17. Comarr AE, Hutchinson RH, Bors E. Extremity fractures of patients with spinal cord injuries. *Am J Surg* 1962;103:732–9. [PubMed: 13880733]
18. Eng JJ, Levins SM, Townson AF, Mah-Jones D, Bremner J, Huston G. Use of prolonged standing for individuals with spinal cord injuries. *Phys Ther* 2001;81(8):1392–9. [PubMed: 11509069]
19. Shields RK, Dudley-Javoroski S. Monitoring standing wheelchair use after spinal cord injury: a case report. *Disabil Rehabil* 2005;27(3):142–6. [PubMed: 15823996]
20. Crameri RM, Cooper P, Sinclair PJ, Bryant G, Weston A. Effect of load during electrical stimulation training in spinal cord injury. *Muscle Nerve* 2004;29(1):104–11. [PubMed: 14694505]
21. Shields RK, Dudley-Javoroski S, Cole K. Feedback-controlled stimulation enhances human paralyzed muscle performance. *J Appl Physiol* 2006;101:1312–19. [PubMed: 16809630]
22. Chou LW, Lee SC, Johnston TE, Binder-Macleod SA. The effectiveness of progressively increasing stimulation frequency and intensity to maintain paralyzed muscle force during repetitive activation in persons with spinal cord injury. *Arch Phys Med Rehabil* 2008;89(5):856–64. [PubMed: 18452732]
23. Kebaetse MB, Lee SC, Johnston TE, Binder-Macleod SA. Strategies that improve paralyzed human quadriceps femoris muscle performance during repetitive, nonisometric contractions. *Arch Phys Med Rehabil* 2005;86(11):2157–64. [PubMed: 16271564]
24. Kesar T, Chou LW, Binder-Macleod SA. Effects of stimulation frequency versus pulse duration modulation on muscle fatigue. *J Electromyogr Kinesiol* 2008;18(4):662–71. [PubMed: 17317219]
25. Association ASI. International Standards for Neurological Classification of SCI. Atlanta, Georgia: American Spinal Injury Association; 2002. Revised 2002
26. Shields RK, Dudley-Javoroski S, Boaldin KM, Corey TA, Fog DB, Ruen JM. Peripheral quantitative computed tomography: measurement sensitivity in persons with and without spinal cord injury. *Arch Phys Med Rehabil* 2006;87(10):1376–81. [PubMed: 17023249]
27. Shields RK, Schlechte J, Dudley-Javoroski S, Zwart BD, Clark SD, Grant SA, et al. Bone mineral density after spinal cord injury: a reliable method for knee measurement. *Arch Phys Med Rehabil* 2005;86(10):1969–73. [PubMed: 16213240]
28. Shields RK, Chang Y-J. The effects of fatigue on the torque-frequency curve of the human paralysed soleus muscle. *J Electromyogr Kinesiol* 1997;7(1):3–13. [PubMed: 20719687]
29. Scott WB, Lee SC, Johnston TE, Binkley J, Binder-Macleod SA. Contractile properties and the force-frequency relationship of the paralyzed human quadriceps femoris muscle. *Phys Ther* 2006;86(6):788–99. [PubMed: 16737404]
30. Shields RK, Dudley-Javoroski S, Littmann AE. Post-fatigue potentiation of paralyzed soleus muscle: Evidence for adaptation with long-term electrical stimulation training. *J Appl Physiol* 2006;101:556–65. [PubMed: 16575026]
31. Westerblad H, Duty S, Allen DG. Intracellular calcium concentration during low-frequency fatigue in isolated single fibers of mouse skeletal muscle. *J Appl Physiol* 1993;75(1):382–8. [PubMed: 8397180]
32. Chang YJ, Shields RK. Within-train neuromuscular propagation varies with torque in paralyzed human muscle. *Muscle Nerve* 2002;26(5):673–80. [PubMed: 12402290]
33. Chou LW, Kesar TM, Binder-Macleod SA. Using customized rate-coding and recruitment strategies to maintain forces during repetitive activation of human muscles. *Phys Ther* 2008;88(3):363–75. [PubMed: 18174446]
34. Thomas CK, Griffin L, Godfrey S, Ribot-Ciscar E, Butler JE. Fatigue of paralyzed and control thenar muscles induced by variable or constant frequency stimulation. *J Neurophysiol* 2003;89(4):2055–64. [PubMed: 12611940]
35. Bickel CS, Slade JM, VanHiel LR, Gordon WL, Dudley GA. Variable-frequency-train stimulation of skeletal muscle after spinal cord injury. *J Rehabil Res Dev* 2004;41(1):33–40. [PubMed: 15273895]
36. Scott WB, Binder-Macleod SA. Changing stimulation patterns improves performance during electrically elicited contractions. *Muscle Nerve* 2003;28(2):174–80. [PubMed: 12872321]
37. Turner CH. Three rules for bone adaptation to mechanical stimuli. *Bone* 1998;23(5):399–407. [PubMed: 9823445]

38. Lanyon LE, Rubin CT. Static vs dynamic loads as an influence on bone remodelling. *J Biomech* 1984;17(12):897–905. [PubMed: 6520138]
39. Turner CH, Owan I, Takano Y. Mechanotransduction in bone: role of strain rate. *Am J Physiol* 1995;269(3 Pt 1):E438–42. [PubMed: 7573420]
40. Rubin CT, Lanyon LE. Regulation of bone formation by applied dynamic loads. *J Bone Joint Surg Am* 1984;66(3):397–402. [PubMed: 6699056]
41. Fluckey JD, Dupont-Versteegden EE, Montague DC, Knox M, Tesch P, Peterson CA, et al. A rat resistance exercise regimen attenuates losses of musculoskeletal mass during hindlimb suspension. *Acta Physiol Scand* 2002;176(4):293–300. [PubMed: 12444935]
42. Mueller MJ, Maluf KS. Tissue adaptation to physical stress: a proposed “Physical Stress Theory” to guide physical therapist practice, education, and research. *Phys Ther* 2002;82(4):383–403. [PubMed: 11922854]
43. Fritton SP, McLeod KJ, Rubin CT. Quantifying the strain history of bone: spatial uniformity and self-similarity of low-magnitude strains. *J Biomech* 2000;33(3):317–25. [PubMed: 10673115]
44. Garman R, Gaudette G, Donahue LR, Rubin C, Judex S. Low-level accelerations applied in the absence of weight bearing can enhance trabecular bone formation. *J Orthop Res* 2007;25(6):732–40. [PubMed: 17318899]
45. Garman R, Rubin C, Judex S. Small oscillatory accelerations, independent of matrix deformations, increase osteoblast activity and enhance bone morphology. *PLoS ONE* 2007;2(7):e653. [PubMed: 17653280]
46. Rubin C, Turner AS, Mallinckrodt C, Jerome C, McLeod K, Bain S. Mechanical strain, induced noninvasively in the high-frequency domain, is anabolic to cancellous bone, but not cortical bone. *Bone* 2002;30(3):445–52. [PubMed: 11882457]

Figure 1.

Schematic representation of the active-resisted stance experimental paradigm. The force transducer measures the posterior force during the isometric activation of the quadriceps. The biomechanical calculation of compressive (F_c), shear (F_s) and quadriceps force (F_q) is detailed by Frey Law and Shields¹². The model uses the subject's height, weight, and hip/knee position to resolve the compression and shear forces at the distal femur, expressed as a percent of the subject's body weight.

Figure 2. Representative example of CONST (left) and FDBCK (right) bouts. Representatives of all frequencies are plotted (20, 24, 28, 32, 36, 40, 44, and 48 Hz) in the FDBCK bout. The corresponding contractions for the CONST bout are also depicted.

Figure 3.

Representative example of a 48 Hz FDBCK contraction, showing the instantaneous force values associated with each of the 100 stimulus pulses. The dotted line illustrates the within-train force decline slope for pulses 30–100.

Figure 4. Mean (SE) normalized quadriceps force (A), normalized mean force (B), and fatigue index (C) during repetitive stimulation. Percentages to the right of the plots in (A) and (B) correspond to the value of contraction 60. * = greater than corresponding CONST bout ($p < 0.05$).

Figure 5. Modeled femur compressive load, expressed as a percent of body weight (%BW). * = significant difference between FDBCK and CONST for bout 1 ($p < 0.05$). ** = significant difference between FDBCK and CONST for bout 2 ($p < 0.05$).

Table 1

Subject demographics

Subject	Gender	Age	Years Post-SCI	ASIA Score	SCI Level	Height (cm)	Weight (kg)	Limb Tested	Test Order
1	M	42	3.4	A	T8	188	77	R	F/C
2	M	30	2.7	A	T7	193	71	L	F/C
3	M	35	1.4	A	T11	168	68	L	F/C
4	M	62	13.5	B	T11	168	73	L	C/F
5	M	27	1.3	A	T10	175	100	L	F/C
6	M	29	2.6	A	T6	185	77	R	F/C
7	M	45	1.0	A	T4	175	85	L	C/F
8	M	38	0.6	A	T10	183	95	L	C/F
9	M	35	2.1	A	T6	188	95	R	C/F
10	F	27	1.6	A	C5-6	167	50	R	C/F
11	M	21	0.3	A	T7	183	82	R	C/F
12	M	29	6.89	A	T4	185	80	R	F/C
13	M	27	5.75	A	T4	188	85	R	C/F

F/C: FDBCK followed by CONST. C/F: CONST followed by FDBCK.