ABSTRACT: The clinical efficacy of functional electrical stimulation (FES) is limited by the rapid onset of fatigue. Functional electrical stimulation applications typically stimulate skeletal muscles with constant-frequency trains (CFTs). Our laboratory has identified trains that we call doublet-frequency trains (DFTs) and that produce greater forces than CFTs, but more fatigue during repetitive activation than comparable CFTs. The purpose of this study was to see whether a series of CFTs followed by DFTs would reach a targeted isometric peak force more times than either train type alone during repetitive isometric activation of the paralyzed quadriceps muscles of subjects with spinal cord injuries (SCI). The combination of CFTs followed by DFTs reached the targeted isometric force 14% more often than the CFTs alone and 18% more often than the DFTs alone. These findings confirm that switching train types may be a useful strategy to offset the rapid fatigue of the functionally important quadriceps muscle that persons with SCI experience when using FES.

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SWITCHING STIMULATION PATTERNS IMPROVES PERFORMANCE OF PARALYZED HUMAN QUADRICEPS MUSCLE

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Functional electrical stimulation (FES) produces muscle contractions that may result in functional movements in individuals with spinal or supraspinal lesions.[24] The use of electrical stimulation to produce force from a muscle results in more rapid fatigue, that is, loss in the force-generating ability of the muscle due to prior activation, than comparable voluntary contractions.[23] In addition, after spinal cord injury (SCI), paralyzed muscles often become more easily fatigued.[10,11,18] Consequently, rapid fatigue has been one of the factors limiting the clinical effectiveness of FES.[19,21,22,32]

Clinical applications of FES have traditionally used constant-frequency trains (CFTs) to activate muscles.[21,24,25] Constant-frequency trains consist of brief pulses of stimuli separated by regular interpulse intervals (IPI). However, variable-frequency trains (VFTs) that take advantage of the catchlike property of skeletal muscle[8] can augment forces compared to CFTs in nonfatigued mammalian single motor units,[2,9,38] including human thenar motor units[34] and whole muscle.[5,7,33] Variable-frequency trains typically begin with two (a doublet) or three (a triplet) pulses separated by brief IPIs (e.g., 5–10 ms) followed by regularly spaced pulses with longer IPIs. The catchlike property is the force enhancement observed when the initial brief IPI is added to the beginning of a subtetanic train of pulses.[8] In the nonparalyzed muscles of able-bodied subjects, some researchers have found that VFTs do not augment force in a nonfatigued condition,[4,5] but all studies that compared the forces produced by CFTs and VFTs in a fatigued condition have found that VFTs augment the force response of the muscle.[1,2,5,6,22,28] Although VFTs may augment force production compared to CFTs, Binder-Macleod and colleagues[6,7] found that repetitively activating the nonparalyzed

Abbreviations: CFT, constant-frequency train; DFT, doublet-frequency train; FES, functional electrical stimulation; IPI, interpulse interval; MTF, maximum twitch force; SCI, spinal cord injury; VFT, variable-frequency train

Key words: doublet-frequency trains; functional electrical stimulation; paralyzed quadriceps muscle; spinal cord injury

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human quadriceps muscle exclusively with VFTs led to a greater attenuation of its force-generating ability than repetitive activation with comparable CFTs.

A mathematical model that accurately predicts the force generated by brief stimulation trains, such as those used in FES, developed in our laboratory,[3,14] shows that a doublet-frequency train (DFT) should produce greater forces than either VFTs or CFTs. The DFT is a train consisting entirely of doublets (5 ms IPI) separated by longer interdoublet intervals, rather than single pulses. In able-bodied subjects, DFTs augment force production in nonfatigued, and, to a greater extent, fatigued human quadriceps muscle than comparable CFTs and VFTs.[3,7,31] Interestingly, during voluntary contractions, action potentials with short IPIs, such as those that occur with DFTs, were more often observed when muscles were fatigued.[20] However, similar to repetitive activation with VFTs, repetitive activation with DFTs produces a greater attenuation of the force-generating ability of the muscle than repetitive activation with comparable CFTs or VFTs.[7,31]

Such findings led us to explore a strategy of switching train types rather than using any single train type to activate a muscle repetitively.[31] We predicted that by initially using CFTs to meet the targeted force, we would avoid the greater fatigue associated with repetitive DFTs. Furthermore, knowing that DFTs produce more force in fatigued muscle than CFTs, we suspected that by using DFTs after the CFTs were incapable of meeting the targeted force, additional successful contractions would be produced. We demonstrated in able-bodied subjects that the combination of six-pulse 30-Hz CFTs followed by six-pulse 30-Hz DFTs reached or exceeded the target force more times than either of the train types alone.[31]

The purpose of the present study was to compare the number of contractions that reached or exceeded a targeted isometric peak force when using CFTs followed by DFTs to the number of contractions produced when only CFTs or DFTs were used in subjects with SCI. It was unclear what effect the physiological changes that occur in the paralyzed quadriceps muscles of persons with SCI would have on the force responses to different patterns of stimulation. Following SCI, paralyzed quadriceps muscles become weak, less resistant to fatigue, and contract and relax faster than nonparalyzed muscles.[18] We chose to study the quadriceps muscle because of its role in functionally important FES tasks such as ambulation and sit-to-stand. We hypothesized, based on our prior results from able-bodied subjects, that the combination of trains would produce more successful contractions than the DFTs alone, and that the DFTs alone would produce more successful contractions than the CFTs alone.

MATERIALS AND METHODS

Subjects. Data were collected on 9 subjects (3 women). Inclusion criteria for the study were a current ASIA classification of A or B (motor complete) as determined by a medical resident or physical therapist, at least 1 year post-SCI or when neurologically stable, no lower motor neuron involvement of the quadriceps muscle (determined by an ability of the muscle to produce a strong contraction in response to brief pulses of surface electrical stimulation), no history of orthopedic knee injuries or spontaneous lower-extremity fractures, and a passive knee joint flexion of 100° in sitting. Additionally, the hip joints of each subject were assessed for risk of dislocation. Subjects were not included if they had a history of heart disease, peripheral vascular disease, current neoplasms, or any neurological disorder (other than SCI) affecting the lower extremities. No evaluation of spasticity was performed. Subjects were recruited from Shriners Hospital for Children in Philadelphia, and were thus limited to children and young adults (< 25 years old). The subjects ranged in age from 9 to 24 years old (16.7 ± 1.6; mean ± SE). Seven subjects had thoracic and two subjects had cervical level injuries. The time from injury ranged from 10 to 99 months (38.2 ± 10.9). Four subjects reported using electrical stimulation to regularly activate their paralyzed muscles. The contractile characteristics of adolescents and young adults with SCI are similar to those of adults with SCI (unpublished observations). Participation was voluntary and subjects were free to withdraw from the study at any time. Prior to the experiments, subjects and their legal representatives (if subjects were minors) reviewed and signed an informed consent form that had been approved by the institutional review boards of the University of Delaware and Temple University, which serves as the oversight committee for Shriners Hospital for Children in Philadelphia. In addition, minors signed an assent form that was approved by both oversight committees.

Experimental Design. Subjects were tested during two sessions separated by at least 24 h. The order in which each subject received the two fatiguing protocols was randomized. SCI subjects' quadriceps muscles were tested using a computer-controlled dynamometer (KinCom II 500-H; Chattecx Corp., Chattanooga, TN). Electrical stimulation was delivered by a Grass S88 stimulator with a SIU8T stimulus isolation unit (Grass Instrument Company, Quincy, MA). All testing was isometric with the subjects' knees flexed to 90° and hip flexion of approximately 75°. Two 7.5 cm × 12.5 cm self-adhesive electrodes (Versa-stim; Conmed Corp., Utica, NY) were used for electrical stimulation of the muscle. For subjects with small legs, 5 cm × 9 cm electrodes were used to activate the muscle. One electrode was placed over the rectus femoris muscle belly and the other over the belly of the vastus medialis. Each session began with testing for proper electrode placement using a 1-s 20-Hz train. A smooth rate of rise and a plateau in force at an intensity sufficient to evoke a subject's maximum twitch force (during the second session) or a force that we estimated to be near their maximum twitch force (during the first session) indicated that a consistent population of motor units was being recruited throughout the stimulation train. Otherwise, the electrode placement was shifted until a smooth rate of rise and plateau in force were achieved.

Muscle Testing. Following testing for electrode placement, maximum twitch force (MTF) testing was performed by recording the force response of the paralyzed muscle to a series of single pulses (600-μs pulse width) with the stimulator intensity incrementally increased to its maximum of 150 V. Pulses were delivered at a rate of one every 10 s, and were stopped when the peak force did not increase in response to three successive pulses. The data were then analyzed and the highest peak force in response to the pulses was taken as the subject's MTF. The MTF recorded during the first session was used as the MTF for both testing sessions.

Next the stimulation intensity for the remainder of the testing session was set by adjusting the stimulator voltage until a six-pulse 30-Hz CFT produced a peak force equal to the subject's MTF. The twitch-to-tetanus ratio of the paralyzed human quadriceps is approximately 0.25[18]; therefore, we believe the subjects were producing approximately 25% of the force-generating ability of the paralyzed muscles when stimulated with the six-pulse 30-Hz CFT. The intensity was kept constant for the remainder of the session in an attempt to recruit a consistent population of motor units. The paralyzed muscles were not potentiated prior to testing because pilot work demonstrated that it was difficult to potentiate the muscle without simultaneously producing fatigue.

The target force used in the experiments was 75% of each subject's MTF. Following a 5-min rest, a

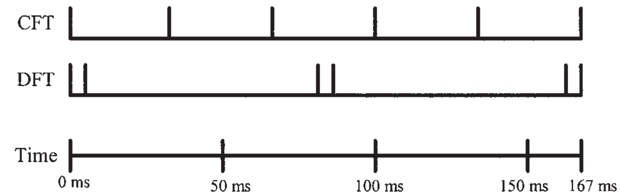

FIGURE 1. Schematic representation of the constant-frequency train (CFT) and doublet-frequency train (DFT) used to repetitively activate the quadriceps muscles in this study. The vertical lines within the CFT and DFT represent the individual pulses of stimulation. Each train had a mean frequency of 30 Hz.

fatiguing protocol was initiated. One protocol consisted of 150, six-pulse, 30-Hz DFTs delivered once every 667 ms (167 ms train, 500 ms off time, 25% duty cycle). The other fatiguing protocol began with six-pulse, 167-ms, 30-Hz CFTs (i.e., the same train used to set the intensity) that were delivered once every 667 ms. However, once the peak force generated by two successive CFTs dropped below the target force, custom-written software (Labview 5.0; National Instruments, Austin, TX) switched the stimulation train type to the six-pulse 30-Hz DFT. The software ensured the time between trains (500 ms) remained the same during the switch and that subsequent DFTs were delivered at the same rate as the CFTs (i.e., once every 667 ms). The CFTs-to-DFTs combination fatiguing protocol was terminated when two successive peak forces produced by the DFTs failed to reach the target force. The six-pulse CFTs and DFTs had the same train duration (167 ms) and consequently the same mean frequency of 30 Hz (Fig. 1). The frequency is similar to that commonly used to activate the quadriceps femoris during FES-assisted ambulation.[21,24]

The initial forces produced by the protocol that used the six-pulse 30-Hz CFTs began at each subject's MTF because the six-pulse 30-Hz CFT train was used to set the intensity. Although the DFT fatiguing protocol used the same intensity as the CFT protocol, it did not necessarily start at the same force level. The same target force (75% of MTF) was used to evaluate the number of successful contractions produced in response to the different fatiguing protocols.

Data Analysis. The entire force record for each fatiguing protocol was digitized on-line at a frequency of 200 Hz and stored for subsequent analysis. Data were analyzed using custom-written software (Labview 5.0). The primary dependent variable analyzed in this study was the number of contractions that reached the target force in response to the CFTs alone, the DFTs alone, and the CFTs-to-DFTs combination. From the session that used CFTs followed by a switch to DFTs, the number of successful contractions for the CFTs alone were calculated, as well as the number of successful contractions for the CFTs-to-DFTs combination. For the latter calculation, the last two CFTs that failed to reach the target force immediately prior to the switch were not included in the combination total. From the fatiguing protocol that only used DFTs, the number of contractions before two successive trains failed to reach the target force was calculated. Data were analyzed using a one-way, within-subjects ANOVA. One-tailed paired *t*-tests were used for post-hoc testing because we hypothesized that the number of successful contractions produced by the combination would be greater than the DFTs alone which, in turn, would produce more successful contractions than the CFTs alone.

Paired *t*-tests were also used to compare the peak forces produced by the initial DFT versus the initial CFT from the two fatiguing protocols. In addition, we calculated two measures to compare the fatigue produced in response to repetitive activation with CFTs and DFTs. The decline in peak force (in newtons) per contraction for each subject to the CFTs alone and the DFTs alone was calculated. We calculated this value by subtracting the target peak force from the initial peak force and dividing the total by the number of successful contractions. Also, for each subject we compared the peak force produced by the first DFT that occurred following the switch during the combination fatiguing protocol to the DFT peak force that occurred following the same number of DFT-evoked contractions during the DFTs-alone fatiguing protocol. This comparison was always possible because the 150 trains of the DFT-alone fatiguing protocol were always greater than the number of CFTs delivered in the CFT-to-DFT fatiguing protocol. Paired *t*-tests were used to compare the decline in peak force and the DFT peak forces following activation by the same number of CFTs versus DFTs. Results are reported as mean ± standard error of the mean unless otherwise indicated. Statistical significance was accepted at $P \leq 0.05$.

RESULTS

Complete data sets were collected on 8 of the 9 subjects. However, the data from 2 subjects were not included in the analyses because fluctuations in their force responses to one of the fatiguing protocols resulted in unreliable data and were assumed to indicate that populations of motor units were being recruited or derecruited during the repetitive stimulation. We have observed similar fluctuations in able-bodied subjects. Unfortunately, limited access to the patients prevented retesting. Another subject was excluded from most analyses because the software malfunctioned and there was no switch from the CFTs to DFTs during the CFTs-to-DFTs combination. Consequently, 6 subjects were included in the statistical analyses unless otherwise noted.

A typical subject's peak force responses to the two fatiguing protocols are shown in Figure 2A. As for the group, the combination of CFT and DFT trains produced the greatest number of successful contractions for this individual. Both for this subject and for the group, the DFTs alone did not outperform the CFTs alone. Also, similar to the group, this subject produced slightly greater peak forces in response to the initial DFT than in response to the initial CFT (Fig. 2B), and the response to the first DFT following the CFTs during the combination protocol was greater than the response to the comparable DFT in the DFTs-alone protocol. Figure 2C shows the force augmentation of the first DFT in comparison to the last CFT at the switch during the CFTs-to-DFTs combination protocol for this subject.

For the group, there was a main effect for fatiguing protocol on the number of successful contractions produced ($F = 6.27$, $P < 0.05$). Post-hoc testing revealed the combination produced more successful contractions than the DFTs alone and the CFTs alone ($P < 0.05$ for both; Fig. 3). There was no difference in the number of successful contractions produced by the DFTs or CFTs alone. The DFTs following the CFTs produced additional successful contractions for 5 of the 6 subjects (Table 1). They averaged approximately 8 additional successful contractions for the group. The combination produced on average approximately 10 more successful contractions for the group than the DFTs alone and the most successful contractions for all 6 subjects.

The peak force responses to the first train of each of the two fatiguing protocols were different (Fig. 4A). The subject who had the software malfunction during his testing was included in this analysis because the malfunction did not affect the forces produced in response to the initial stimulation trains of the two fatiguing protocols. The DFTs produced 6% greater peak forces than the CFTs ($P < 0.05$). The decline in peak force per contraction in response to the DFTs alone (0.52 ± 0.11 N) was greater than the decline in peak force per contraction in response to the CFTs alone (0.44 ± 0.11 N; $P < 0.05$; Fig. 4B). The subject for whom the software malfunctioned was included in the decline in peak force per con-

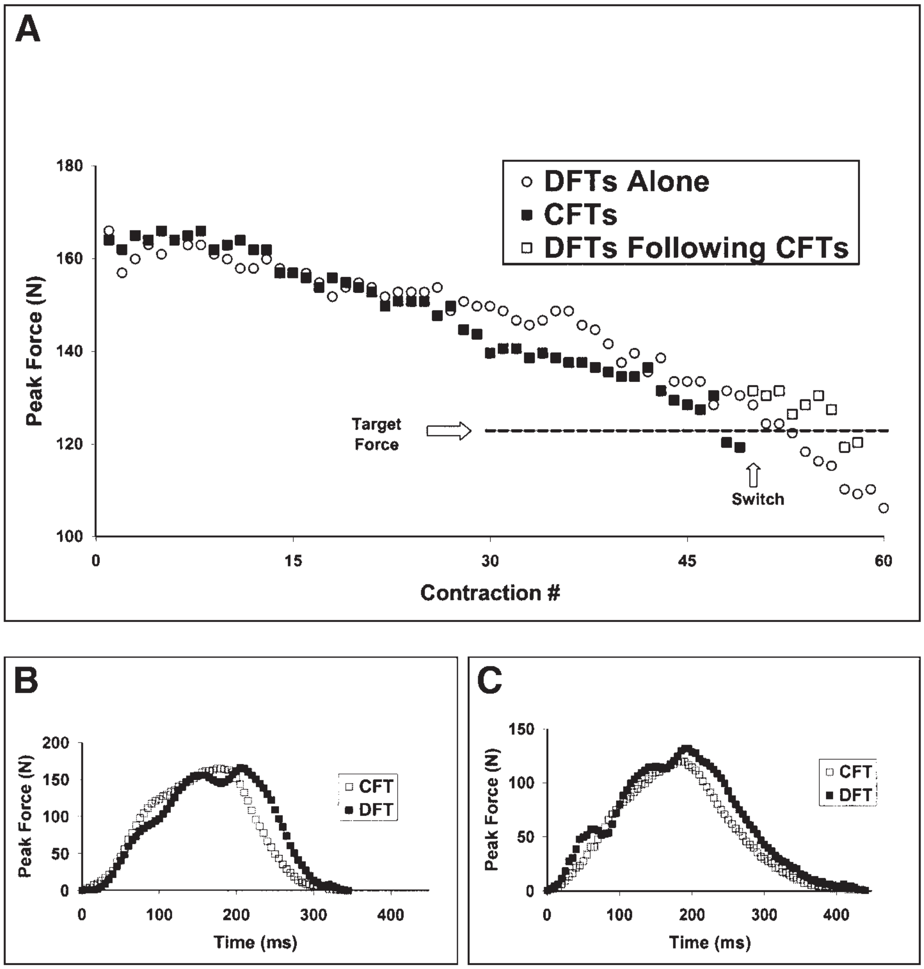

FIGURE 2. (A) Typical subject's peak force responses to each stimulation train from the DFTs-alone and the CFTs-to-DFTs fatiguing protocols. The horizontal line represents the target force that was used to determine successful contractions, and consequently, determine the switching point in the CFTs-to-DFTs fatiguing protocol after the muscle failed to produce the target peak force in response to two successive contractions. The vertical arrow below the 50th contraction shows the point at which the stimulation pattern was switched from CFTs to DFTs during the CFTs-to-DFTs combination. **(B)** Force responses to the initial CFT and DFT of the two fatiguing protocols from the same subject. **(C)** Force responses to the last CFT prior to the switch, and the first DFT after the switch during the CFTs-to-DFTs combination from the same subject showing the augmentation in force provided by the DFT.

traction analysis as well. In addition, the initial DFT following the CFTs during the CFTs-to-DFTs combination protocol produced 14% greater peak forces than the comparable DFT in the DFTs-alone fatiguing protocol ($P < 0.05$; Fig. 4C).

DISCUSSION

This study demonstrated that a combination of electrical stimulation train types increased muscle performance during repetitive isometric contractions of the paralyzed quadriceps of SCI subjects. A combination of CFTs followed by DFTs reached a targeted isometric peak force more times than either the CFTs alone for 5 of the 6 subjects or the DFTs alone for all of the subjects. Consistent with data from two previous studies with able-bodied subjects from our laboratory, the 30-Hz DFT initially produced higher peak forces than the 30-Hz CFT.[7,31] The greater peak forces produced by the first DFT following the CFTs compared with the comparable DFT in the DFTs-alone fatiguing protocol, and the greater decline in peak force per contraction with repetitive activation with DFTs than CFTs indicates that repetitive activation with DFTs was more fatiguing than repetitive activation with CFTs, as with able-bodied subjects.[7,31]

In able-bodied subjects the greater fatigue generated by repetitive activation with the DFTs than CFTs was more than off-set by the force augmentation of the DFTs, resulting in the DFTs alone pro-

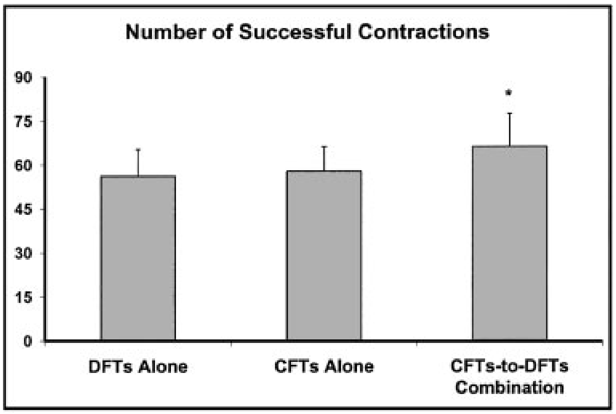

FIGURE 3. The number of successful contractions produced in response to the three stimulation strategies. * indicates the CFTs-to-DFTs combination significantly different from the DFTs-alone and the CFTs-alone strategy ($P < 0.05$ for both).

ducing more successful contractions than the CFTs alone.[31] This was not the case with the SCI subjects. In the able-bodied subjects the switch to DFTs following repetitive activation with CFTs resulted in additional successful contractions for all 15 subjects tested, but only 5 of the 6 SCI subjects.[31] However, the group means for the number of additional successful contractions produced by the able-bodied subjects and SCI subjects were similar (~ 8 for both groups).[31] Additionally, the ranges of the successful additional contractions produced by the DFTs that followed the CFTs were similar, 2 to 25 and 2 to 24 for the able-bodied subjects and SCI subjects, respectively.[31]

Although no research has been conducted to investigate the underlying mechanisms for the force augmentation associated with DFTs, a number of studies have explored VFTs. Presumably VFTs and DFTs augment force production by the same mechanism because both contain doublets. Variable-frequency trains augment force production by increasing the Ca^{2+} release from the sarcoplasmic reticulum as a result of the initial high-frequency burst.[1,15,28] Russ and Binder-Macleod[29] showed that VFT force augmentation was directly correlated to

Table 1. Number of successful contractions produced in response to the three stimulation strategies and the number of additional successful contractions produced by the DFTs during the CFTs-to-DFTs combination.

Subject	DFTs alone	CFTs alone	Additional DFTs	Combination total
1	84	82	24	106
2	52	47	7	54
3	17	27	0	27
4	61	67	2	69
5	53	51	5	56
6	70	74	12	86
Mean ± SD	56.2 ± 22.6	58.0 ± 20.2	8.3 ± 8.7	66.3* ± 27.5

**indicates the combination produced significantly more successful contractions than the DFTs alone or the CFTs alone (P < 0.05 for both).*

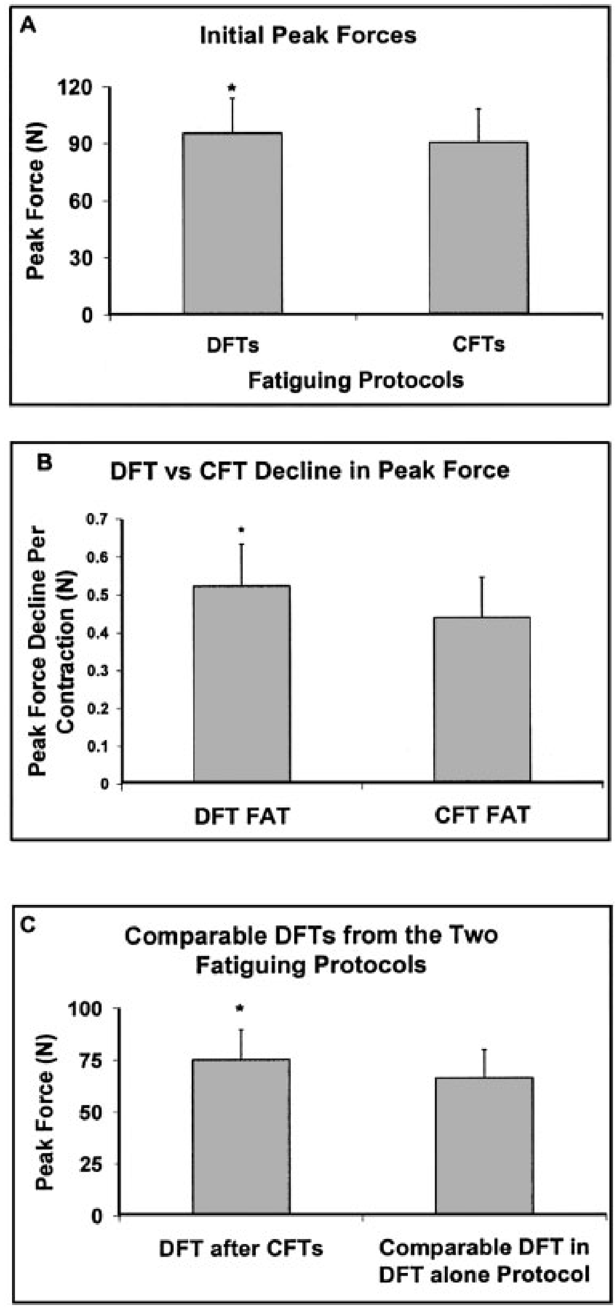

FIGURE 4. The DFT and CFT peak forces ($n = 7$) in response to the initial trains of the two fatiguing protocols **(A)**, the DFT and CFT decline in peak force ($n = 7$) per contraction during the two fatiguing protocols **(B)**, and the DFT peak forces ($n = 6$) following repetitive activation of the muscles by the same number of CFTs and DFTs **(C)**. * indicates significant difference ($P < 0.05$).

the amount of low-frequency fatigue, which is thought to be caused by an impairment of Ca^{2+} release during excitation–contraction coupling.[12,13,35] This finding also supports the hypothesis that enhanced Ca^{2+} release is the source of the force augmentation from stimulation trains containing doublets.

However, elevated intracellular Ca^{2+} concentrations are associated with fatigue.[37] Consequently, the increased Ca^{2+} release in response to doublets may have contributed to the attenuation of the force-generating ability associated with repetitive activation exclusively with the DFTs. Another possibility is that the higher forces that the DFTs produced in the DFTs-alone fatiguing protocol resulted in an increased metabolic demand on the muscle. The metabolic cost of contractions has been shown to increase as the forces generated increase.[26,30] The build-up of inorganic phosphate (P_i) by ATP hydrolysis and the phosphocreatine energy system has been strongly implicated in fatigue, as have other metabolic factors such as glycogen, ATP, lactate, Mg^{2+}, and radical oxygen species.[17,27,36] Many of these metabolic factors are also thought to result in reduced Ca^{2+} release during fatigue.[16,36] Consequently, during the DFTs-alone fatiguing protocol, there would be a loss of force-generating ability as less Ca^{2+} was released from the sarcoplasmic reticulum due to metabolic build-up or depletion of substrate. In the SCI subjects the decreased fatigue resistance of the paralyzed muscle most likely resulted in more rapid fatigue in response to the higher forces produced by the DFTs than occurred in the able-bodied subjects and therefore, no improvement in performance with repetitive activation with DFTs compared with CFTs, as we observed with able-bodied subjects.[31]

This work presents the novel strategy of combining different patterns of stimulation trains to improve performance in persons with SCI. This work, however, was carried out under static conditions rather than during dynamic movements such as those that would occur during most FES applications. Future work should explore the use of combining different train patterns of stimulation during actual FES applications. Additionally, optimal patterns of stimulation and electrode placement need to be determined for subjects to maximize performance and prevent fluctuations in force, such as those that eliminated two subjects from this study. Furthermore, combining different train patterns during repetitive activation represents a single strategy to increase performance of the activated motor units. For maximum paralyzed muscle performance, strategies that affect the force production from the activated motor units, such as varying train duration or stimulation pulse pattern or frequency, may need to be combined with strategies for increasing the number of motor units activated, such as varying the pulse duration or stimulation intensity.

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