

ABSTRACT: Variable-frequency stimulation trains (VFTs) that take advantage of the catchlike property of skeletal muscle have been shown to augment the force production of fatigued muscles compared with constant-frequency trains (CFTs). The present study is the first to report the force augmentation produced by VFTs after fatiguing the muscle with VFTs versus fatiguing the muscle with CFTs. Data were obtained from the human quadriceps femoris muscles of 12 healthy subjects. Each subject participated in three experimental sessions. Each session fatigued the muscle with one of three protocols: CFTs with 70-ms interpulse intervals (CFT70); CFTs with 55.5-ms interpulse intervals (CFT55.5); or VFTs. Following each fatiguing protocol the muscles were tested with all three stimulation patterns (i.e., CFT55.5, CFT70, and VFT). At the end of the fatiguing protocol the VFT produced force-time integrals and peak forces ~18% and 32% greater than the CFT70, respectively. The testing trains showed that the VFT produced ~25–35% greater force-time integrals than either CFT and ~35–47% greater peak forces than the CFT70. For each testing train, ~10–15% greater force-time integrals were seen when the muscles were fatigued with the CFTs than when fatigued with the VFTs. These results support suggestions that VFTs may be useful during clinical applications of electrical stimulation.

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EFFECTS OF ACTIVATION PATTERN ON HUMAN SKELETAL MUSCLE FATIGUE

STUART A. BINDER-MACLEOD, PhD, PT, SAMUEL C.K. LEE, MPT,
DAVID W. RUSS, MPT, and LORIN J. KUCHARSKI, BS

Department of Physical Therapy, University of Delaware, 315 McKinly Laboratory,
Newark, Delaware, USA

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The catchlike property of skeletal muscle is the tension enhancement seen when a brief, high-frequency burst is added to the beginning of a sub-tanic train of pulses.^{10,13,36} The catchlike property is an inherent property of muscle cells, and not a function of the motor neuron, the neuromuscular junction, or increased motor unit recruitment.^{3,13,37} The force augmentation produced by exploitation of the catchlike property is not constant; rather, it depends upon the activation history¹⁴ and fatigue state of the muscle.^{3,4,6} Interestingly, the activation pattern shown to maximize the force augmentation is similar for both fast- and slow-twitch muscles, and for single motor units and whole muscle.^{6,10,37} This pattern is a variable frequency train (VFT) that begins with one

or two, brief (5–10-ms) interpulse intervals (i.e., a doublet or a triplet), followed by a constant-frequency burst of pulses with an interpulse interval slightly greater than or equal to the twitch contraction time of the muscle.^{4,6,14,31,37} Furthermore, studies have shown that doublets and triplets occur during volitional contractions in both humans^{2,17,21} and animals,^{22,32} in some muscles and under some conditions, but not all.³⁷

The force augmentation produced by VFT stimulation may have important implications for functional electrical stimulation (FES).^{5,9,10,34} FES is the use of electrical stimulation to activate skeletal muscle to perform functional movements.²⁷ Examples of FES include: stimulation of the dorsiflexors to treat footdrop^{11,27}; stimulation of lower extremity muscles to help individuals with paraplegia stand or walk^{25,30}; and stimulation of transplanted skeletal muscle to assist cardiac function.²⁸ Although these applications show promise, the clinical application of FES is often limited by the rapid rate of muscle fatigue that accompanies its use.^{23,30} Because

Abbreviations: ANOVA, analysis of variance; CFT, constant-frequency stimulation train; E-C, excitation-contraction coupling; FES, functional electrical stimulation; MVIC, maximum voluntary isometric contraction; VFT, variable-frequency stimulation train

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Correspondence to: Dr. Stuart A. Binder-Macleod

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VFT stimulation of fatigued muscles produces greater forces than constant-frequency train stimulation, it has been suggested that the use of VFTs may decrease the fatigue produced by FES, which traditionally employs CFT stimulation.^{9,20,34}

The hypothesis that VFT stimulation produces less fatigue than CFT stimulation, however, has not yet been tested. All studies showing that VFTs augment the force production of fatigued muscles as compared with CFTs have used pseudorandom sequences of VFTs and CFTs to induce fatigue.^{3,9,10,20} Thus, they did not compare the fatigue-producing properties of VFT versus CFT stimulation. The purpose of this study is to compare the forces produced by repetitive VFT activation of the human quadriceps femoris muscle of healthy subjects to the forces produced by activation with CFTs. Preliminary results have been reported in abstract form.^{7,8}

METHODS

Data were obtained from 12 healthy subjects (6 males) ranging in age from 20 to 37 years (mean 24.25, SD 4.59 yr), with no history of lower extremity orthopedic problems. All subjects signed informed consent forms. This study was approved by the University of Delaware Human Subjects Review Board.

Subjects were seated on a computer-controlled dynamometer (KinCom III 500-11, Chattecx Corp., Chattanooga, TN) with their right knees flexed to 90°. The pelvis, right leg, and right thigh were stabilized with Velcro straps. The dynamometer axis was aligned with the knee joint axis and the force transducer pad was positioned against the anterior surface of the leg, ~3 cm proximal to the lateral malleolus. The right quadriceps femoris muscle was stimulated using a Grass S8800 stimulator with a SIUST stimulus isolation unit. All pulses were 600 μ s in duration. Two 4" \times 5" self-adhesive electrodes were used to electrically stimulate the muscle. The anode was placed proximally, over the motor point of the rectus femoris, and the cathode was placed distally, over the motor point of the vastus medialis portions of the quadriceps muscle. The stimulator was driven by a personal computer that controlled all the timing parameters of each stimulation protocol. All force data were digitized on-line at a sampling frequency of 200 samples per second and stored for subsequent analyses.

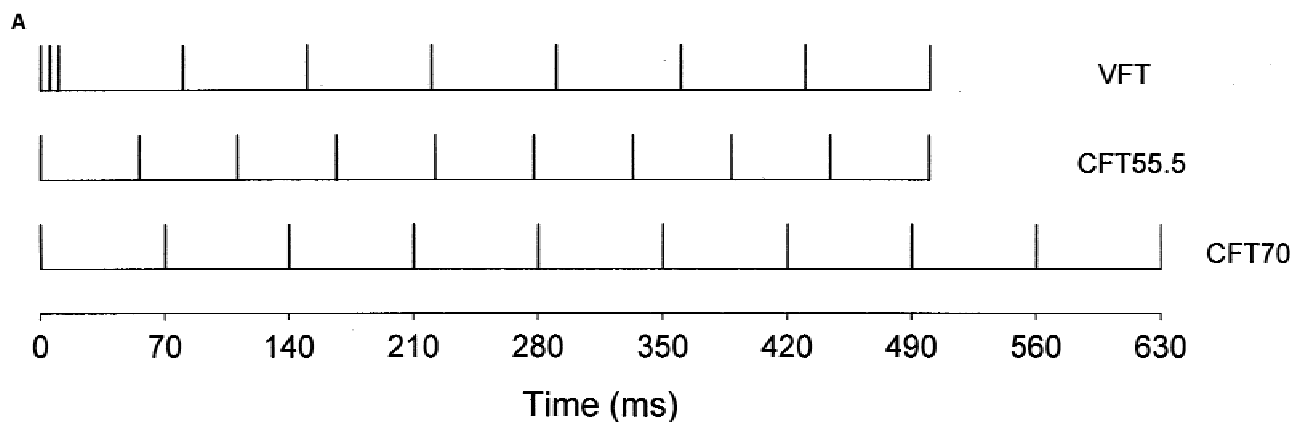
Prior to the commencement of the experimental sessions, subjects were trained to relax and refrain from volitional contractions during stimulation of their quadriceps femoris muscle. All subjects performed a maximum voluntary isometric contraction

(MVIC). The MVIC was determined using a burst superimposition technique, in which a 100-Hz, ten-pulse CFT at supramaximal stimulation intensity was delivered to the quadriceps muscle during an attempted maximal volitional contraction.³³

Each subject participated in three *experimental sessions*. Sessions were separated by at least 48 h. Subjects were asked to refrain from strenuous exercise at least 24 h prior to each session. Before the administration of each experimental protocol, MVIC testing was conducted. If the subject was unable to perform an MVIC that was $\geq 95\%$ of the previously determined MVIC, the session was postponed and conducted on another day. During each session, subjects were fatigued with one of three different stimulation protocols. All three stimulation protocols consisted of 191 ten-pulse trains (nine interpulse intervals); trains were repeated once every second. Each stimulation protocol consisted of two portions: the *fatiguing portion*, consisting of the first 179 trains, and the *testing portion*, consisting of the last 12 trains (see Fig. 1). The fatiguing portion of one protocol consisted of CFTs with all nine interpulse intervals separated by 70 ms (CFT70). The fatiguing portion of the second protocol used CFTs with all interpulse intervals equal to 55.5 ms (CFT55.5). The third protocol had a fatiguing portion consisting of VFTs with two, initial 5-ms interpulse intervals followed by a constant-frequency portion containing seven 70-ms interpulse intervals. Thus, the VFT duration (500 ms) approximately equaled that of the CFT55.5 (499.5 ms). The testing portion of each protocol contained all three stimulation trains (i.e., CFT55.5, CFT70, and VFT) (see Fig. 1 for details).

During each experimental session, to set the stimulation intensity, 55.5-ms CFTs were delivered to the muscle once every 5 s. The stimulator was first adjusted to elicit ~20% of each subject's MVIC. The stimulation intensity was then held constant until the muscle was potentiated (i.e., force did not increase over three successive trains). This typically required activation of the muscle with five to ten stimulation trains. Following potentiation, the stimulation intensity was readjusted to produce 20% of the subject's MVIC. Stimulation intensity was then kept constant throughout the session. Before commencing each stimulation protocol, the muscle was reopotiated with the CFT55.5. After potentiation occurred, the protocol was started within 5 s.

Data Management. Two force measurements, the force-time integral and peak force, were calculated in response to each train of both the fatiguing and testing portions of the stimulation protocol (see Fig.



B

Fatiguing Portion	Testing Portion											
	CFT70	VFT	CFT70	CFT70	CFT55.5	CFT70	CFT70	CFT70	CFT55.5	CFT70	CFT70	VFT
CFT 70	CFT70	VFT	CFT70	CFT70	CFT55.5	CFT70	CFT70	CFT70	CFT55.5	CFT70	CFT70	VFT
CFT 55.5	CFT55.5	VFT	CFT55.5	CFT55.5	CFT70	CFT55.5	CFT55.5	CFT55.5	CFT70	CFT55.5	CFT55.5	VFT
VFT	VFT	CFT70	VFT	VFT	CFT55.5	VFT	VFT	VFT	CFT55.5	VFT	VFT	CFT70
Train # 1-179	180	181	182	183	184	185	186	187	188	189	190	191

FIGURE 1. (A) Schematic representation of stimulus trains used to test each subject. Each vertical line represents a 600- μ s stimulation pulse. The 70-ms constant-frequency train (CFT) had constant interpulse intervals = 70 ms (CFT70) (bottom). The 55.5-ms CFT had constant interpulse intervals = 55.5 ms (CFT55.5) (middle). The variable-frequency train (VFT) had the first two interpulse intervals = 5 ms and the remaining interpulse intervals = 70 (top). **(B)** Table outlining the three stimulation protocols used to fatigue and test each subject. Stimulation trains were delivered at 1/s to the muscle. The first column indicates the stimulus train used to fatigue the muscle. The testing portion consisted of testing trains (shaded) and intervening trains (nonshaded). Intervening trains were used to maintain muscles in a consistent level of fatigue.

2). The force–time integral is a measure of the total force output of the muscle in response to stimulation, and has commonly been used to quantify the force augmentation produced by the catchlike property.^{31,37} Peak force is the greatest amount of force produced in response to the stimulation train. Additionally, a measure of the rate of rise of force, the time to reach 80% of the peak force (T80), was calculated during the testing portion of the protocol.^{5,9} All variables were computed using custom software (LabView 4.0).

The responses to the first stimulation train of the fatiguing portion of each protocol were used to determine the nonfatigued force–time integrals and peak forces produced by the muscles. The fatigued force–time integral and peak force values were determined by averaging the responses to the last five trains of the fatiguing portion of each protocol. The responses to the two occurrences of each testing

train were averaged to determine the peak force, force–time integral, and T80 values for the testing portion of the protocol.

Data Analysis. One-way repeated-measure analyses of variance (ANOVAs) were used to compare the forces produced in response to the fatiguing portion of the three stimulation patterns. Separate ANOVAs were performed for the force–time integral and peak force data. Furthermore, for each force measurement, separate ANOVAs were performed to analyze the nonfatigued and fatigued force responses. Two-way repeated-measure ANOVAs were performed using the testing train data to test for main effects of the three fatiguing protocols and three testing train stimulation patterns. Paired *t*-tests, with a Bonferroni correction for multiple comparisons, were used for post hoc testing. Statistical significance was established at $P \leq 0.05$.

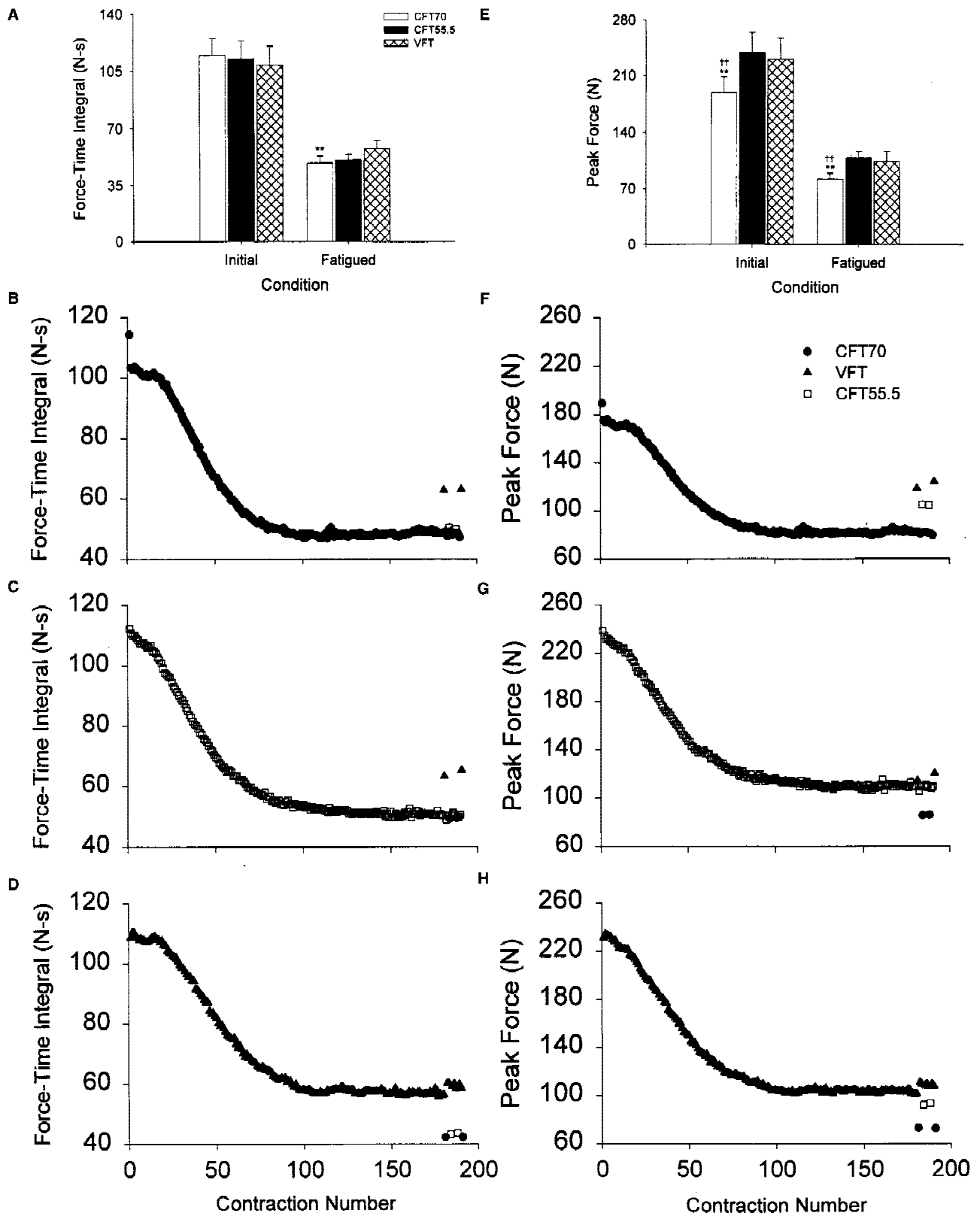


FIGURE 2. Plots of the force–time integrals (B–D) and peak forces (F–G) in response to each fatiguing and testing train of each fatiguing protocol ($n = 12$). Average (\pm SE) initial and fatigued force–time integral (A) and peak force (E) responses to the fatiguing portion of each protocol. Asterisks (*) show significant t -tests between each CFT versus VFT. Daggers (†) show significant t -tests between CFT70 versus CFT55.5. * $P \leq 0.05$; ** $P \leq 0.01$; † $P \leq 0.05$; †† $P \leq 0.01$.

RESULTS

Complete data sets were collected for all 12 subjects. The response to the fatiguing trains showed a steady decline in both force measurements until contraction ~60, and by contraction ~100 a stable level of fatigue was established (see Fig. 2).

Fatiguing Portion of the Protocol. *Force-Time Integral.* No significant differences were observed in the initial force-time integral values among the three protocols (Fig. 2). A significant difference, however, was noted among the force-time integrals produced at the end of the fatiguing protocols ($F = 5.004$, $P < 0.05$). The VFT produced force-time integrals ~18% greater than the CFT70. No significant differences were seen between the force-time integrals produced by the CFT55.5 and the VFT or the CFT70. A trend, however, was noted for the VFT to produce greater (~14%) force-time integrals than the CFT55.5 ($P = 0.09$).

Peak Force. A significant difference was present among the peak forces in the nonfatigued state ($F = 26.730$, $P < 0.01$) (Fig. 2). No significant difference was seen between the nonfatigued peak forces produced by the CFT55.5 and the VFT. The VFT and CFT55.5, however, produced significantly greater initial peak forces than the CFT70 (26.1% and 22.1%, respectively). When the muscles were fatigued, the same relationships were observed ($F = 8.226$, $P \leq 0.01$), with the VFT and CFT55.5 producing 32% and 27% greater peak forces than the CFT70, respectively.

Testing Portion. Force responses from a typical subject to the testing trains are presented in Figure 3. As was characteristic for the group responses (see subsequent text), this subject showed the greatest force-time integrals, the greatest peak forces, and the most rapid rates of rise of force in response to the VFTs. Fatiguing the muscle with the VFTs, however, produced greater attenuation of each testing train than fatiguing the muscle with either CFT.

Force-Time Integral. Both the fatiguing protocol ($F = 3.56$, $P < 0.05$) and the stimulation pattern ($F = 116.688$, $P < 0.001$) significantly affected the force-time integrals produced during the testing portion of the protocol (Fig. 4). No interaction was observed between these two main effects. Comparison of the three fatigue protocols used to fatigue the muscle showed that, for each of the testing trains, ~10–15% greater force-time integrals were seen when the muscles were fatigued with either CFT than when fatigued with the VFTs. Post hoc statistical testing compared the responses to the CFT70 testing trains

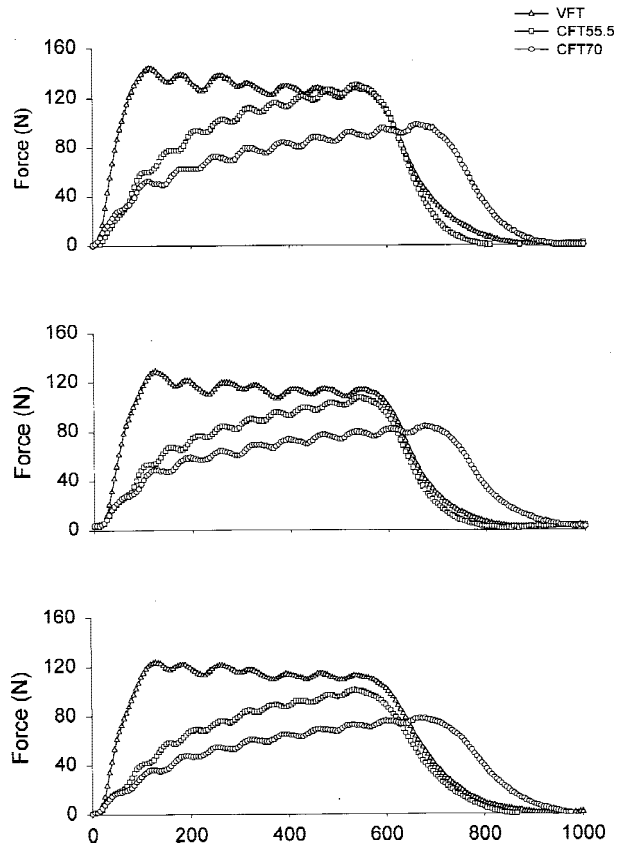


FIGURE 3. Force responses of a typical subject to constant-frequency and variable-frequency testing trains after the muscle had been fatigued with either the CFT70 (top), CFT55.5 (middle), or VFT (bottom). Within each fatiguing protocol, the VFT testing trains produced greater forces than CFT70 (same number of pulses) and CFT55.5 testing trains (same number of pulses and same duration). Note the rapid rate of rise of force produced by the VFT.

after the muscles were fatigued with the CFT70 versus the VFT, the CFT55.5 testing trains after the muscles were fatigued with the CFT55.5 versus the VFT, and the VFT testing trains after the muscles were fatigued with the VFT versus each of the CFTs. The responses to the CFT70 testing trains were significantly smaller after fatiguing stimulation with the VFT than the CFT70 ($P = 0.011$). The responses to the CFT55.5 testing trains showed a trend toward greater attenuation of the force-time integral after fatiguing stimulation with the VFT than the CFT55.5 ($P = 0.069$). The responses to the VFT were significantly smaller after fatiguing stimulation with the VFT versus the CFT70 ($P = 0.044$), but only showed a trend toward greater attenuation after fatiguing stimulation with the CFT55.5 ($P = 0.130$).

Comparison of the force-time integrals produced in response to the three stimulation patterns used during the testing trains showed that the VFTs

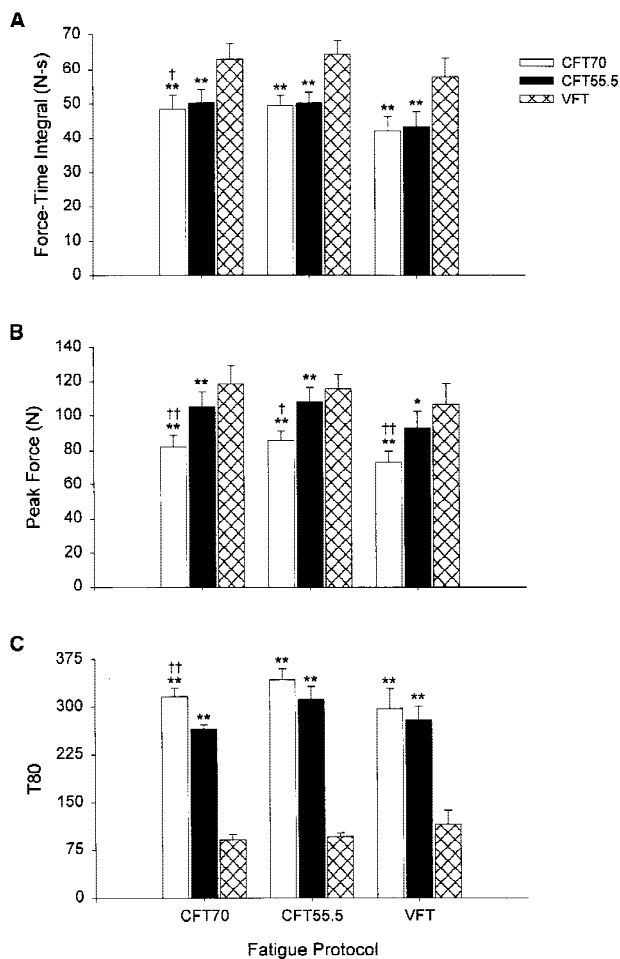


FIGURE 4. (A) Force-time integral, (B) peak force, and (C) T80 responses (\pm SE) to testing trains following CFT70, CFT55.5, and VFT fatiguing protocols ($n = 12$). Asterisks (*) show significant *t*-tests between each CFT versus VFT within each fatigue protocol. Daggers (†) show significant *t*-tests between CFT70 versus CFT55.5. * $P \leq 0.05$; ** $P \leq 0.01$; † $P \leq 0.05$; †† $P \leq 0.01$.

always produced greater force-time integrals than either CFT testing train (see Fig. 4). When the CFT70, the CFT55.5, and the VFT were used to fatigue the muscle, the VFT test trains produced ~25%, 28%, and 35% greater force-time integrals, respectively, than either CFT train.

Peak Force. Only the stimulation pattern ($F = 42.925$, $P < 0.001$) significantly affected the peak forces produced during the testing portion of the protocol (Fig. 4). The VFT produced ~7%, 13%, and 15% greater peak forces than the CFT55.5 when the muscle was fatigued with the CFT55.5, CFT70, and VFT, respectively. Similarly, the VFT produced ~35%, 45%, and 47% greater peak forces than the CFT70 when the muscle was fatigued with the CFT55.5, CFT70, and VFT, respectively.

Time to 80% Peak Force (T80). Only the stimula-

tion pattern ($F = 115.765$, $P < 0.001$) significantly affected the rate of rise of force in response to the testing trains. The VFT testing trains produced significantly faster T80s than the CFT70 and CFT55.5 testing trains, whether the muscle was fatigued with the VFT or either CFT. The VFTs required ~160–245 fewer milliseconds to reach T80 than the CFTs (see Fig. 4).

DISCUSSION

Previous studies comparing the effects of VFTs on fatigued muscle to those of CFTs have used various combinations of VFTs and CFTs to produce fatigue. Thus, this is the first study to investigate the effects of repetitive activation of muscle with VFTs versus CFTs. At the end of the fatiguing portion of the three protocols, the VFTs produce greater forces than the CFTs, consistent with previous studies investigating the catchlike property of skeletal muscle.^{3,6,10} In the present study, however, analysis of the responses during the fatiguing portion of the protocol reveals that VFT stimulation produces only ~18% greater force-time integrals and ~20% greater peak forces versus the CFT70 and only a trend toward augmentation of the force-time integral versus the CFT55.5 (~14%) (see Fig. 4). This augmentation is less than the 25–35% increases in force-time integral and 35–45% increases in peak force previously reported by our laboratory.^{4,10} The results of the testing portions of each protocol show, however, that the VFT testing trains produce force-time integrals 25–37% greater than either CFT and peak forces that are 34–46% and 6–15% greater than those produced in response to the CFT70 and CFT55.5, respectively (see Fig. 4). These findings are consistent with the results of our earlier studies.^{4,10} Thus, the 10–15% greater attenuation of the force-time integral produced when the muscle was fatigued with the VFT versus CFTs appears to reduce the VFT augmentation during the fatiguing portion of the protocol.

The current data show, therefore, that although repetitive activation of a muscle with VFTs produce greater forces than activation with either CFT, VFTs appear to cause greater attenuation of the force-generating ability of muscle than the CFTs. The mechanism for the differences in the amount of fatigue produced is unclear. Marsden and colleagues have theorized that the rate of fatigue during electrical muscle stimulation is due to the number of pulses delivered to the muscle.²⁹ The results of subsequent studies have challenged this hypothesis by showing that the stimulation train frequency may affect the rate of fatigue, independent of the number of pulses.^{3,5,10,19} The present data further support

the contention that the number of pulses alone cannot account for the rate of fatigue because all three protocols used stimulation trains containing the same number of pulses. Furthermore, the VFT and CFT55.5 have the same train duration and the same mean frequency, and the constant-frequency portion of the VFT has the same frequency as the CFT70. This suggests that the pattern of stimulation must also be considered a factor in fatigue production during repetitive, intermittent stimulation. Stevens has theorized that there may be some hidden penalty to exclusive use of VFTs, based on the observation that doublets and triplets are not ubiquitous in volitional contractions.³⁴ The increased fatigue caused by the VFTs in the present study may be the hidden penalty that Stevens suggested.

One possible cause for the greater fatigue seen with VFT stimulation may relate to a proposed mechanism behind VFT force augmentation. It has been suggested that increased Ca^{2+} release from the sarcoplasmic reticulum is the cause of the force augmentation seen with VFT stimulation of fatigued muscles.¹⁸ A recent study by Chin and Allen¹⁶ has shown, however, that elevated resting Ca^{2+} levels, combined with increased tetanic Ca^{2+} levels, results in an impairment of sarcoplasmic Ca^{2+} release and concurrent loss of force-generating ability. Thus, high Ca^{2+} levels resulting from the initial doublet of the VFT may add to the impairment of excitation-contraction (E-C) coupling, and contribute to the increased fatigue seen in this study.

Impairment of E-C coupling is believed to be the cause of low-frequency fatigue.^{16,26,35} Low-frequency fatigue is characterized by: a proportionately greater loss of force at low-frequency stimulation (e.g., 20 Hz) than at high-frequency stimulation (e.g., 50 Hz); a slow rate of recovery of force-generating ability; and persistence of this low force without marked electrical or metabolic disturbances.²⁴ Studies have found that low-frequency fatigue results from intermittent isometric contractions in both isolated muscle fibers^{16,26} and whole muscle.¹ If VFT stimulation impairs E-C coupling because of the high calcium concentrations it produces, this could explain the greater fatigue seen with VFT stimulation. One method of examining this possibility would be to compare the force responses to high- and low-frequency testing trains after fatiguing VFT stimulation with the force responses following comparable constant-frequency stimulation. It may also be useful to make these comparisons during recovery, when low-frequency fatigue becomes more apparent.

The ability of the catchlike property to augment force during fatigue has important implications for

FES in the restoration of functional movements. FES-assisted ambulation requires repetitive stimulation of muscles and is limited by high energy costs³⁰ and rapid muscle fatigue.^{12,25,30} The present results support earlier work,³⁻⁵ which showed that VFTs produce greater forces in fatigued muscles than the traditionally used CFTs. Given that fatigue will occur with repetitive activation, this means that VFTs may produce sufficient force to produce functional movement in the fatigued state without requiring large increases in stimulation intensity.

Furthermore, Marsolais and Kobetic found that increasing walking speed while using FES, lowered the rate of energy consumption.³⁰ They attributed this conservation of energy to the fact that stance time decreases as walking speed increases. This results in fewer stimulation trains being required to stabilize the limb during the stance phase. Greater walking speeds, however, allow less time for generation of the forces required during the gait cycle.¹⁵ A rapid rate of rise of force, therefore, is essential to achieve faster rates of ambulation. The present results show that VFTs produce faster rates of rise of force compared with either CFT tested, as indicated by the smaller T80 values (Fig. 4). By producing greater forces and a more rapid rate of force generation, VFT stimulation has the potential to improve the use of FES.

CONCLUSION

These results support earlier studies that showed VFTs increased the force-time integral, peak force, and rate of rise of force produced by fatigued muscles versus comparable CFTs and that suggested VFTs may be useful during clinical applications of electrical stimulation. However, the exclusive use of VFTs resulted in less force augmentation than previously reported. This loss of augmentation appears to be due to greater attenuation of the force-generating ability of muscle after repetitive activation with VFTs versus comparable CFTs. Also, it appears that factors influencing fatigue are more complex than the number of pulses delivered to the muscle, and that subtle variations in stimulation patterns can significantly affect the amount of muscle fatigue induced by repetitive stimulation.

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