

# New Look at Force-Frequency Relationship of Human Skeletal Muscle: Effects of Fatigue

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**Binder-Macleod, Stuart A., Samuel C. K. Lee, April D. Fritz, and Lorin J. Kucharski.** New look at force-frequency relationship of human skeletal muscle: effects of fatigue. *J. Neurophysiol.* 79: 1858–1868, 1998. A muscle does not have a unique force-frequency relationship; rather, it is dynamic and depends on the activation history of muscle. The purpose of this study was to investigate the force-frequency relationship of nonfatigued and fatigued skeletal muscle with the use of both catchlike-inducing trains (CITs) that exploited the catchlike property of skeletal muscle and constant-frequency trains (CFTs). Quadriceps femoris muscles were studied during isometric contractions in twelve healthy subjects (5 females, 7 males). Both the peak force and force-time integrals produced in response to each stimulation train were analyzed. Compared with nonfatigued muscles, higher frequencies of activation were needed to produce comparable normalized peak forces when the muscles were fatigued (i.e., a “rightward” shift in the force-frequency relationship) for both the CFTs and the CITs. When using the normalized force-time integral to measure muscle performance, the CFTs required slightly higher frequencies to produce comparable normalized forces from fatigued muscles, but the CITs did not. Furthermore, when the muscles were fatigued, the CITs produced greater peak forces and force-time integrals than all comparable CFTs with frequencies  $\leq 20$  pps. In general, the lower the frequency the greater the augmentation produced by the CITs. In addition, the CIT that elicited the greatest force-time integral produced a 25% greater force-time integral than the best CFT. Because the CITs augmented forces across a wide range of physiological relevant activation rates, these results may have important clinical implications when using electrical stimulation to aid patients with paralysis. The results of this study contribute to our understanding of the relationship between the activation pattern of a muscle and the force output produced.

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## INTRODUCTION

The activation frequency of skeletal muscle affects the generation, maintenance, and decline (fatigue) of force. Traditionally, the responses of nonfatigued muscles to a series of trains of electrical pulses have been used to explore the relationship between the activation frequency of a muscle and the force output produced. The pulses within each stimulation train can be separated by regular intervals so that each train contains a single activation frequency. By using these constant-frequency trains (CFTs) of pulses, an approximately sigmoid relationship was obtained between the activation frequency of a muscle and the peak force generated (Cooper and Eccles 1930; Kernell 1995). A muscle does not have a unique force-frequency relationship; rather, the force-frequency relationship is dynamic and depends on the activation history of the muscle (Binder-Macleod and Clamann 1989). Furthermore, during volitional activation of

muscle, motor units often fire with varying discharge patterns that include brief, high-frequency bursts of activity (humans: Marsden et al. 1983; Maton and Gamet 1989; cats: Severin et al. 1967; rats: Hennig and Lømo 1985). These variations in the activation rate may allow the central nervous system (CNS) to take advantage of the catchlike property of skeletal muscle (Burke et al. 1976) and make it difficult to predict the force output of a motor unit from the observed stimulation pattern.

The catchlike property of skeletal muscle is the tension enhancement produced when an initial brief high-frequency burst of pulses (2–4 pulses) is used at the onset of a subsequent subtetanic CFT to activate the muscle (Binder-Macleod and Barrish 1992; Binder-Macleod and Clamann 1989; Burke et al. 1970, 1976). This phenomenon is distinct from the true catch property of molluscan muscle, which does not require continued stimulation of the muscle to maintain force (Burke et al. 1976). The catchlike property has been shown to increase the force-time integrals produced by muscles over CFT stimulation and is a fundamental property of muscle cells that is not due to properties of the motor axon or neuromuscular junction (Bevan et al. 1992; Burke et al. 1970; Wilson and Larimer 1968; Zajac and Young 1980). The observation that the amplitude of the compound muscle action potential in response to the second pulse of a high-frequency two-pulse train (doublet) is the same or smaller than the first response supports this argument (Bevan et al. 1992; Burke et al. 1970; Karu et al. 1995). Thus the tension enhancement produced by the catchlike property is not due to additional muscle fiber recruitment.

Muscle wisdom is a description for the process by which the activation rates of motor units are modulated by the CNS to optimize force during sustained contractions (Marsden et al. 1976, 1983; for review see Binder-Macleod 1995; Stuart and Callister 1993). Specifically, Marsden and colleagues (1983) argued that during a prolonged contraction the contractile rate of the muscle slows, allowing lower activation rates to produce the maximum force from the muscle during fatigue. Most studies of human muscle, however, have observed shifts in the force-frequency relationship to higher stimulus rates (Binder-Macleod and McDermond 1992; Cooper et al. 1988; Edwards et al. 1977; Jones 1981; Stokes et al. 1989). Interestingly, no previous studies have looked at changes during fatigue in the force-frequency relationship of trains that take advantage of the catchlike property of skeletal muscle. All previous studies have only used CFTs to describe the changes in the force-frequency relationship with fatigue. In addition, as noted above, the peak force produced by each train has been used as the measurement

plotted for the force-frequency relationship. In contrast, studies that have investigated the effects of the catchlike property have used the force-time integral as the measurement of force production. It is presently unclear which force parameter(s) the CNS attempts to optimize during volitional contractions. Hence, conclusions regarding the optimal strategy for activation of a muscle may depend on the force parameters under consideration.

The purpose of this study was to investigate the force-frequency relationship of nonfatigued and fatigued skeletal muscle in response to CFTs and trains that exploited the catchlike property of skeletal muscle. Both the peak force and the force-time integral produced in response to each stimulation train were analyzed. Preliminary results have been previously reported (Binder-Macleod 1995).

## METHODS

**SUBJECTS.** Twelve healthy subjects (5 females, 7 males) ranging in age from 19 to 28 yr ( $23.4 \pm 3.8$ , mean  $\pm$  SD) voluntarily participated in this study, which was approved by the University of Delaware Human Subjects Review Board. All subjects signed informed consent forms.

**EXPERIMENTAL SETUP.** Subjects were seated on a computer-controlled dynamometer (KIN-COM II; Chattecx, Chattanooga, TN) with their hips flexed to  $\sim 75$  degrees. The pelvis, leg, and thigh were stabilized with Velcro straps (see Fig. 1A). The right leg of each subject was tested unless the subject had a prior orthopedic injury, in which case the left lower extremity was used (3 subjects). The knee joint was positioned at  $90^\circ$  of flexion and its axis of rotation was aligned with the dynamometer axis. The quadriceps femoris muscle was stimulated with the use of a stimulator equipped with a stimulus isolation unit. All stimulus pulses were  $600 \mu\text{s}$  in duration. Two 7.5-cm-diam round carbon-rubber electrodes were secured to the extremity with elastic straps. Sponges saturated with tap water served as the conducting medium. The cathode was placed distally over the vastus medialis and the anode was placed proximally over the rectus femoris portions of the quadriceps muscle. The position of the electrodes were adjusted to find the location that produced maximum force from the muscle for a given stimulator intensity. A personal computer, equipped with an A/D board, digitized the force data on-line at 200 samples  $\text{s}^{-1}$ . Custom software was used to calculate the dependent variables of interest (see DATA MANAGEMENT) for each force response.

**TRAINING SESSION.** All subjects participated in one training session to familiarize them with the experimental protocol and train them to refrain from voluntarily contracting the thigh muscles during electrical stimulation of their quadriceps femoris muscle. The maximum voluntary isometric contraction (with the knee maintained in  $90^\circ$  of flexion) was determined for each subject by using a burst superimposition technique similar to that previously described (Snyder-Mackler et al. 1993). Briefly, this technique used a 100-pps, 10-pulse tetanic stimulus train delivered to the muscle at supramaximal intensities while the subject attempted to produce a maximum voluntary contraction. If the amplitude of the superimposed tetanic contraction was  $>5\%$  of the volitional contraction, testing was repeated after a 5-min rest. All subjects were trained to meet our criteria within three attempts.

**EXPERIMENTAL SESSION.** After completion of the training session, subjects rested a minimum of 5 min before beginning the experimental session. The experimental session consisted of a control (nonfatiguing) and fatigue-producing protocol. All stimulation trains contained 6 pulses (5-interpulse intervals). The CFTs had equal interpulse intervals from 10 ms and increased by 10-ms

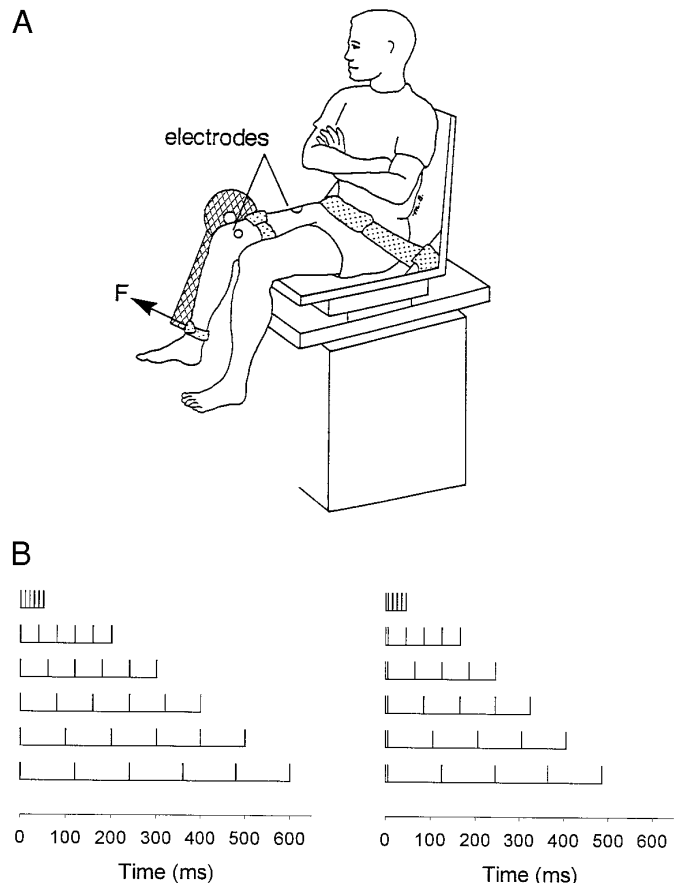
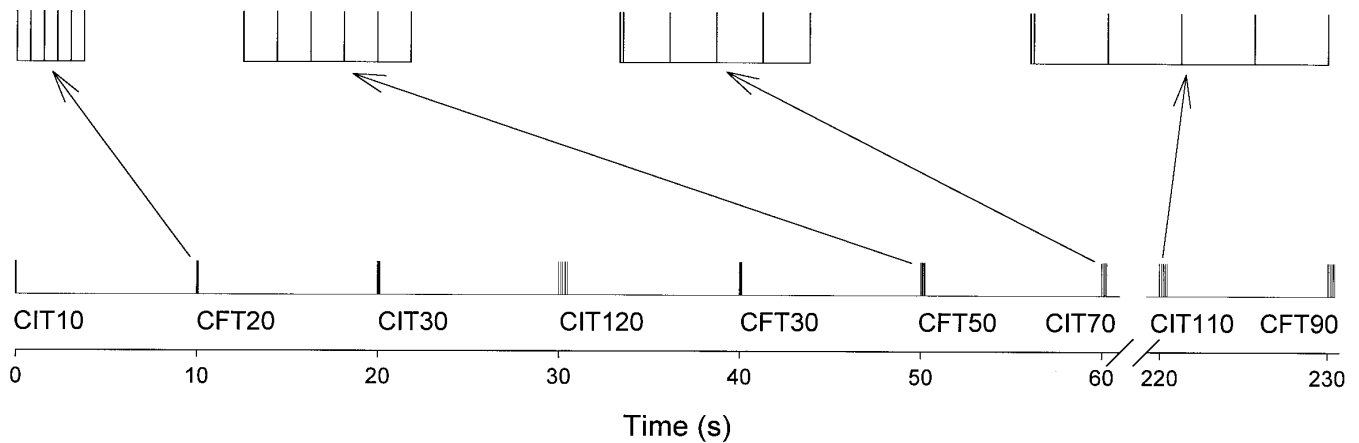


FIG. 1. Schematic representation of the experimental set up and stimulation trains used during the study. *A*: drawing of experimental setup used to test right quadriceps femoris muscle. *B*: schematic representation of 6 of the 12 constant-frequency trains (CFTs; *left panel*) and 6 comparable catchlike-inducing trains (CITs; *right panel*) used during the study. |, each pulse within a train. Traces shown are examples of 6-pulse CFTs (*left*) with interpulse intervals equal to 10-, 40-, 60-, 80-, 100-, and 120-ms, respectively, and comparable CITs. All CITs have an initial interpulse interval of 5 ms.

intervals up to 120 ms (12 CFTs total; see Fig. 1B, *left panel*). Because of the reciprocal relationship between interpulse interval and frequency, these trains had frequencies ranging from 100 to 8.3 pps. The trains used to elicit a catchlike response [henceforth called catchlike-inducing trains (CITs)] (see Binder-Macleod and Lee 1996) had one initial brief interpulse interval equal to 5 ms followed by constant-frequency portions containing interpulse intervals comparable with the twelve CFTs (i.e., 4 equal interpulse intervals ranging from 10 to 120 ms; total of 12 CITs; see Fig. 1B, *right panel*). For CITs, one initial interpulse interval of 5–10 ms was found to produce the greatest force-time integral for a variety of muscles including the human quadriceps femoris muscle (Binder-Macleod et al. 1997).

To set the “stimulus intensity,” the output of the stimulator was adjusted to elicit a force equal to  $\sim 20\%$  of the subject’s maximum voluntary isometric contraction of the quadriceps muscle when stimulated with a 6-pulse, 100-pps train. Trains were then delivered once every 5 s until the muscle was potentiated (i.e., forces did not increase with 3 successive trains). Such potentiation occurred within 5–10 trains. Stimulation was continued to allow the stimulation intensity to be readjusted to elicit 20% of the maximum voluntary isometric contraction from the potentiated muscle. Stimulation was then stopped, and the intensity was not changed for the remainder of the session to attempt

## Control Protocol



## Fatiguing Protocol

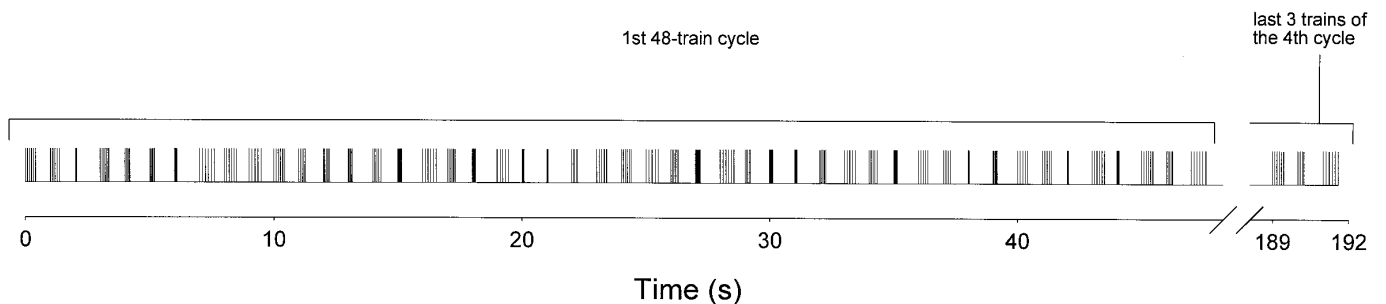


FIG. 2. Schematic representation of stimulation protocols used during experimental sessions. Control protocol (*top*) consisted of a random sequence of the 12 CFTs and 12 CITs. One train was delivered every 10 s. Labels along time axis indicate the type of train (CFT or CIT) and the interpulse interval duration (in ms) of the constant-frequency portion of the train. Arrows point to schematic enlargements of the 20- and 50-ms interpulse interval CFTs and the CITs with 70- and 110-ms interpulse interval constant-frequency portions. The fatigue-producing protocol (*bottom*) commenced 10 s after the completion of the control protocol. A total of 192 trains were used, with 1 train delivered each second. The 192-train protocol consisted of 4 cycles of 48 trains. See text for additional details.

to recruit a consistent population of motor units during the entire experimental session.

**CONTROL PROTOCOL.** Within 5 s of adjustment of the stimulation intensity, the control protocol began. It consisted of a random sequence containing the 12 CFTs and 12 CITs (24 trains total). One train was delivered every 10 s (Fig. 2, *top*). For each subject, one control protocol was randomly selected from among five different random nonfatiguing sequences of stimulation trains. Different random sequences of stimulation trains were used to control for the influence of previous activation history on force responses.

**FATIGUE-PRODUCING PROTOCOL.** Ten seconds after the completion of the control protocol, the fatigue-producing protocol commenced. The fatigue-producing protocol consisted of a pseudorandom sequence of 192 trains with 1 train delivered each second (Fig. 2, *bottom*). Two different random sequences of the 24 stimulation trains were selected to construct this protocol. This cycle of 48 trains was then repeated four times to complete the 192-train fatigue-producing protocol. The same 192-train sequence was used for each subject to allow train by train comparisons across subjects.

**DATA MANAGEMENT.** The dependent variables investigated were the force-time integral and peak force in response to each train of

pulses. The nonfatigued data used for all analyses consisted of the 12 CFTs and the 12 catch-inducing trains collected during the control protocol. Fatigue data used for all analyses were calculated from the last 48 contractions of the 192-contraction fatigue test. The last 48 trains consisted of two occurrences of each CFT and each CIT. The responses of the two like trains were averaged and then analyzed. The last 48 contractions were used because, as can be seen in Fig. 4, after the ~100th contraction, a stable level of fatigue was observed. Two responses to each train were averaged to minimize the effect of the differences in the previous activation history of the muscle on the response to each of the test trains.

In addition, the time to reach 80% of the peak force ( $T_{80}$ ), was calculated from the nonfatigued and fatigued responses during stimulation with the 80-ms interpulse interval CFT and the comparable CIT (i.e., the CIT whose constant-frequency portion consisted of 80-ms interpulse intervals).  $T_{80}$  is the time from the onset of force to when the force first equals 80% of the peak force and measures the time required to develop tension during the initial portion of the response when force is rapidly developed (Binder-Macleod and Barrish 1992). The responses to the 80-ms trains were used because they best characterized the changes in the rate of rise of muscle force seen in response to CFT and

CIT activation. Linear interpolation between data points was used to estimate  $T_{80}$ .

The twitch contraction and one-half relaxation times were calculated from nonfatigued and fatigued force responses to examine the changes in the twitch properties of the muscle. The twitch contraction time was defined as the time from the onset of force production to the peak force in response to the first stimulus pulse in a train. One-half relaxation time was defined as the time from the peak force response of the last stimulus pulse in a train to the first occurrence of a value equal to one-half of its peak force. The 120-ms interpulse interval CFT was used for these analyses because each subject's force response displayed a clear peak, followed by nearly complete relaxation, in response to each pulse within the train. The responses to the first and last pulses of the train were used to calculate the twitch-contraction time and one-half relaxation time, respectively.

### Data analysis

**CHANGES IN FORCE-FREQUENCY RELATIONSHIP WITH FATIGUE.** The peak force responses to constant-frequency stimulation for each subject during the control protocol were normalized to the maximum response to constant-frequency stimulation occurring during that protocol to investigate changes in the force-frequency relationship with fatigue. Similarly, for the fatigue-producing protocol, peak force responses to constant-frequency stimulation were normalized to the maximum response occurring during fatigue before averaging the two like responses for each subject. Responses to CITs were normalized to the maximum CIT responses in the same manner. Normalized force data were averaged across all subjects and plotted as a function of frequency, rather than interpulse interval (reciprocal of frequency), to allow comparison to existing literature. Separate two-way repeated measures of analysis of variance (ANOVAs) were performed for normalized CFT and CIT data to test the effects of fatigue state (nonfatigued vs. fatigued) and stimulation frequency. Bonferroni-corrected, posthoc, two-tailed, paired *t*-tests were performed to compare the normalized nonfatigued and fatigued force responses at each frequency tested only if significant main effects were observed. The same approach was used on the force-time integral data to investigate changes in the force-time integral produced at each frequency tested with fatigue.

**COMPARISONS OF CFT AND CIT STIMULATION.** Nonnormalized, nonfatigued and fatigued peak force and force-time integral data were averaged across all subjects and plotted as a function of interpulse interval. Data were plotted as a function of interpulse interval (vs. frequency) to allow comparison to existing literature on the catchlike property of skeletal muscle (Binder-Macleod and Lee 1996; Binder-Macleod et al. 1992, 1997; Hennig and Lomo 1987; Karu et al. 1995; Parmiggiani and Stein 1981; Stevens 1996; Zajac and Young 1980). Two-way repeated measures of ANOVAs were performed on the effects of train-type (CFT vs. CIT) and interpulse interval on the nonnormalized force data. Separate ANOVAs were used to compare the CFTs with the CITs in the nonfatigued and fatigued muscles. Furthermore, within each fatigue state, peak force and force-time integral data were analyzed separately. If significant effects were observed, Bonferroni-corrected, posthoc, two-tailed, paired *t*-tests were used to compare the responses of the CFTs with the responses to CITs at each interpulse interval (e.g., the 40-ms interpulse interval CFT vs. the 40-ms interpulse interval CIT). Finally, for both the nonfatigued and fatigued data, two-tailed paired *t*-tests were performed to compare the "best" CFT with the best CIT for each of the two force measures (peak force and force-time integral) to determine which stimulus pattern produced the best overall performance.

**CHANGES IN CONTRACTILE PROPERTIES OF MUSCLE.** For  $T_{80}$  data, a two-way ANOVA was performed on the effects of fatigue

state and train type. If significant effects were observed, two-tailed *t*-tests were performed. Two-tailed paired *t*-tests were performed on the twitch contraction and one-half relaxation time data to determine if the twitch properties of the muscle differed in the nonfatigued and fatigued states.

For all group data, means  $\pm$  SE are plotted within the figures. An observation was significant if  $P \leq 0.05$  for all statistical analyses.

## RESULTS

Complete data sets were collected for all twelve subjects. Figure 3 shows the nonfatigued and fatigued force responses to stimulation with the 40- and 80-ms interpulse interval CFTs and CITs of a representative subject. Responses to the 40- and 80-ms trains are featured because these interpulse intervals produced maximum or near maximum force-time integrals for the CFTs and the CITs, respectively, when the muscles were fatigued. The CITs produced greater rates of rise of force in both the nonfatigued and fatigued conditions, with the differences increasing in the fatigued muscle. No difference was noted between the peak forces produced in response to the CFT and the CIT for the nonfatigued muscle when the 40-ms interpulse interval duration was used. For the 80-ms interpulse interval duration, greater peak forces were produced by the CIT than the CFT. In contrast, the 40- and 80-ms CITs produced marked augmentation of peak forces versus the CFTs when the muscle was fatigued. For this subject and the group, the 40- and 80-ms CITs produced force-time integrals that were less than those produced by the comparable CFTs when the muscle was not fatigued. The CITs produced greater force-time integrals versus the CFTs, however, when the muscle was fatigued. It should be noted that because all trains contained six pulses, the CIT response always ended sooner than the response of the comparable CFT. Thus for a CIT to show a greater force-time integral, any increase in force produced at the onset of stimulation must be greater than the area "lost" at the end of the train.

Plots of the peak forces and force-time integrals in response to each train of the fatigue-producing protocol show that the muscle was fully potentiated at the onset of the test (i.e., no increase in force was observed; see Fig. 4). Both force measurements declined approximately linearly for the first  $\sim 75$  contractions and there was little change in the responses after  $\sim 100$  contractions. The fatigue test responses of the 40- and 80-ms interpulse interval trains show that CITs produced approximately the same peak forces as CFTs at the beginning of the test and greater peak forces than CFTs as the muscle fatigued. In contrast, both CFTs produced greater force-time integrals than CITs at the beginning of the test, but not when the muscle was fatigued.

### Changes in force-frequency relationship with fatigue

**NORMALIZED PEAK FORCES.** Analysis of the group data shows that the nonfatigued normalized peak forces are generally greater than the fatigued normalized peak forces for all frequencies  $\leq 33$  pps for CFTs (Fig. 5A) and for all frequencies  $\leq 25$  pps for CITs (Fig. 5B). For the nonfatigued muscles, frequencies of 25 and 20 pps were needed to produce the maximum peak forces when using the CFTs and CITs, respectively. In contrast, when fatigued, frequencies of 100

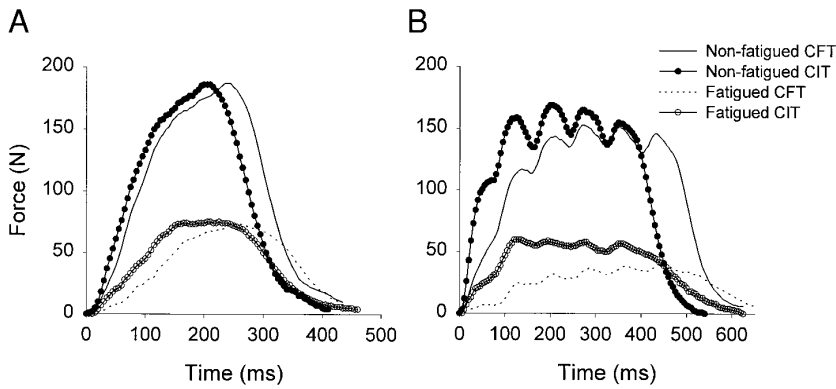


FIG. 3. Force responses from a representative subject. *A*: representative responses to trains with 40-ms interpulse intervals. *B*: representative responses to trains with 80-ms interpulse intervals.

and 50 pps were needed. Thus higher frequencies of activation are needed to produce comparable submaximal forces when fatigued (“rightward” shift in the force-frequency relationship). For example, when not fatigued, a stimulation frequency of 16.67 pps (60-ms interpulse interval) generated ~90% of normalized peak force. In contrast, when fatigued, a 50-pps (20-ms interpulse interval) stimulation frequency was required to produce approximately the same normalized peak force. A similar shift in frequencies was observed for fatigued normalized peak forces in response to CITs.

**NORMALIZED FORCE-TIME INTEGRALS.** The maximum force-time integrals produced by CFTs for nonfatigued and fatigued muscles occurred with activation frequencies of ~11 and ~25 pps, respectively. For frequencies from 9 to 12.5 pps, CFT activation of nonfatigued muscles produced greater normalized force-time integrals versus the fatigued muscle (Fig. 5C). For frequencies from 20 to 100 pps, however, fatigued normalized force-time integrals were greater than nonfatigued responses.

With CIT stimulation the frequency for optimal normalized force-time integral did not change with fatigue. The greatest

normalized force-time integral produced by both the nonfatigued and fatigued muscle in response to CIT stimulation was produced at ~11 pps (see Fig. 5D). The CITs produced greater normalized force-time integrals from fatigued muscle than nonfatigued muscle for frequencies  $\geq 20$  pps.

#### Comparison of CFT and CIT stimulation

**PEAK FORCES.** The CITs produced greater peak forces than comparable CFTs from nonfatigued muscle for all interpulse intervals  $\geq 100$  ms and from fatigued muscle for all interpulse intervals  $\geq 50$  ms (Fig. 6). In general, the augmentation in peak force produced by the CITs increased as the interpulse interval increased. Within each train type, the greatest peak forces were produced by CFTs with interpulse intervals ranging from 20 to 40 ms and by CITs with interpulse intervals ranging from 20 to 50 ms for nonfatigued muscle. When the muscles were fatigued, the 10-ms CFT and the 20-ms CIT produced the greatest peak forces. There was no significant difference in the peak forces produced between the best CFT and the best CIT in either the nonfatigued or fatigued conditions.

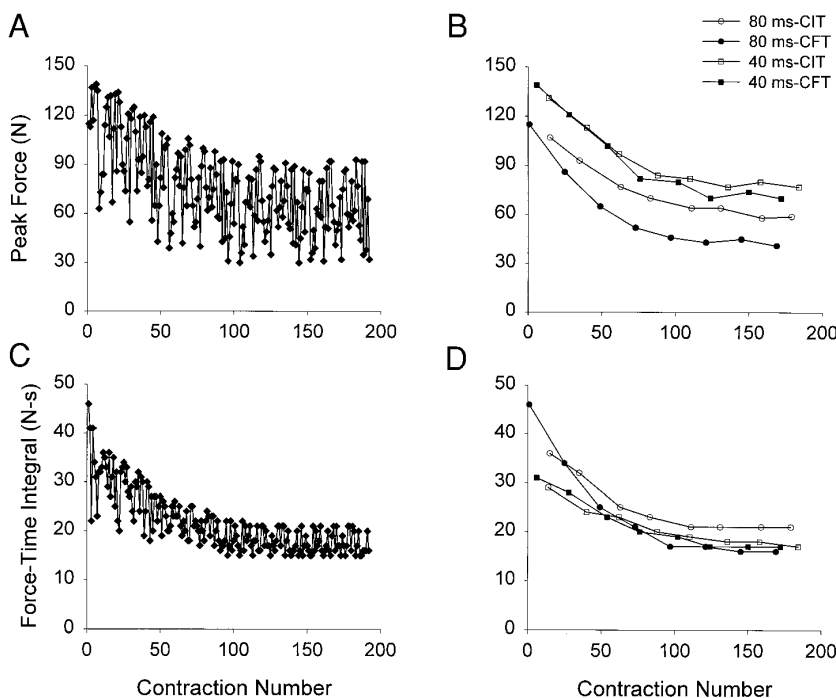


FIG. 4. Averaged group force responses ( $n = 12$ ) during the fatigue-producing protocol. *A*: peak force, *C*: force-time integral responses to each of the 192 stimulation trains; *B*: peak force, *D*: force-time integral responses only to stimulation trains with 40-ms interpulse intervals ( $\square$ ,  $\blacksquare$ ) and 80-ms interpulse intervals ( $\circ$ ,  $\bullet$ ) plotted for clarity.  $\blacksquare$  and  $\bullet$ , CFTs;  $\square$  and  $\circ$ , CITs.

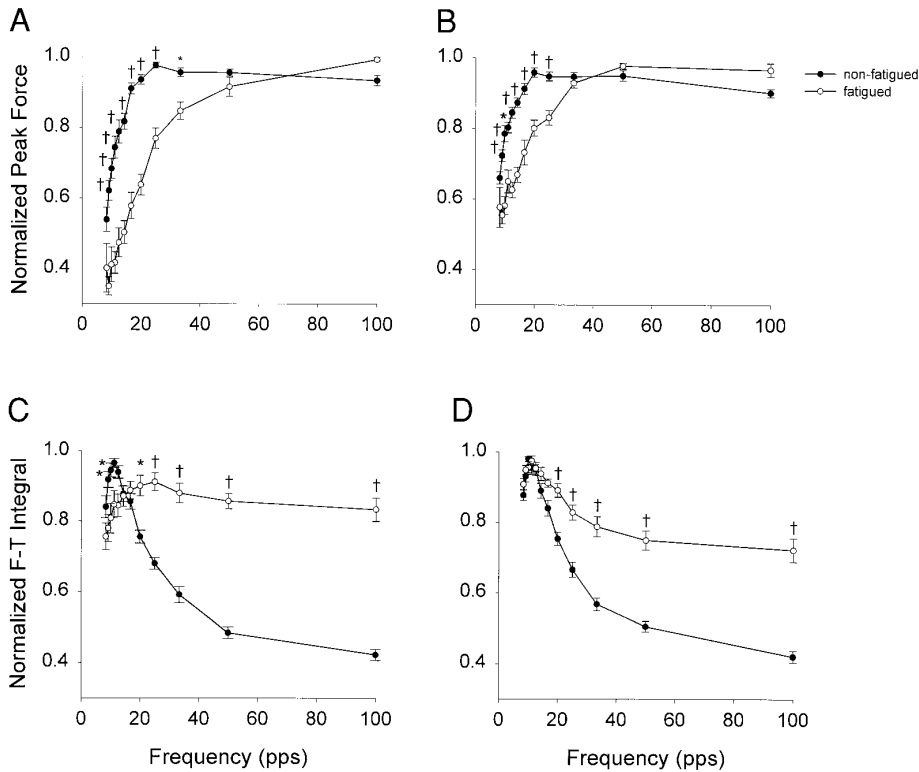


FIG. 5. Normalized group ( $n = 12$ ) force-frequency relationships in response to CFT and CIT stimulation. Normalized peak force plotted as function of frequency for nonfatigued ( $\bullet$ ) and fatigued muscles ( $\circ$ ) in response to CFT stimulation (A) and in response to CIT stimulation (B). Normalized force-time integrals plotted as a function of frequency for nonfatigued and fatigued muscles in response to CFT stimulation (C), and in response to CIT stimulation (D). For each subject, CFT and CIT force data are normalized to their respective maximums occurring during the control and fatigue tests and are then averaged across subjects. Bonferroni-corrected, 2-tailed, paired  $t$ -tests were used to compare nonfatigued and fatigued force responses at each frequency tested. \*  $P \leq 0.05$ ; †  $P \leq 0.01$ ; see text and APPENDIX for additional details.

**FORCE-TIME INTEGRAL.** For nonfatigued muscle, CITs generally produced a slight decrease in the force-time integral than comparable CFTs (Fig. 6). In contrast, for fatigued muscle, CITs produced greater force-time integrals than CFTs for all interpulse intervals  $\geq 50$  ms. In general, the augmentation in the force-time integrals produced by the CITs increased as the interpulse interval increased. CITs

with interpulse intervals of 100 and 90 ms (10 and 11.1 pps, respectively) produced maximal force-time integrals in both the nonfatigued and fatigued states, respectively. A 90-ms interpulse interval was needed to produce the maximal force-time integrals from nonfatigued muscles in response to CFT stimulation. For the fatigued condition, the 40-ms interpulse interval CFT was the CFT that produced the greatest force-

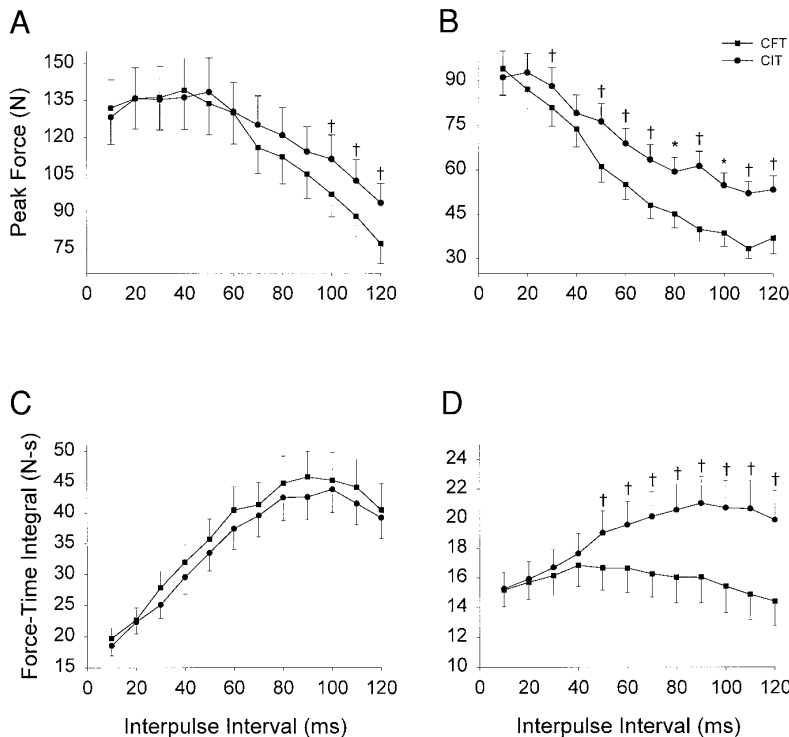


FIG. 6. Averaged group ( $n = 12$ ) nonfatigued and fatigued peak forces and force-time integrals in response to CFT and CIT stimulation. Nonfatigued (A) and fatigued (B) peak forces plotted as a function of interpulse interval; nonfatigued (C) and fatigued (D) force-time integral plotted as a function of interpulse interval. Comparison of the best CFT with the best CIT within each condition demonstrated that only for the fatigued force-time integral data were significant differences observed, with the best 90-ms interpulse interval CIT producing 25% greater force-time integrals than the 40-ms interpulse interval CFT ( $P < 0.05$ ). Bonferroni-corrected, 2-tailed, paired  $t$ -tests were used to compare force responses to CFTs and CITs at each interpulse interval. \*  $P \leq 0.05$ ; †  $P \leq 0.01$ ; see text and APPENDIX for additional details.

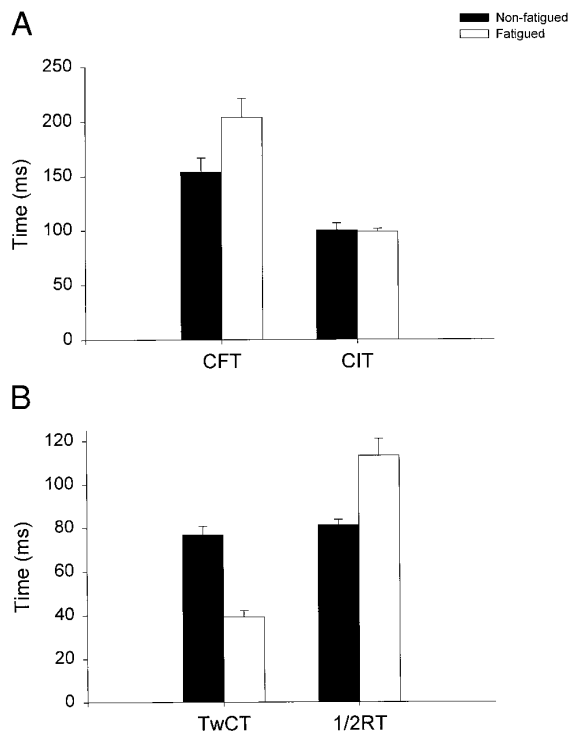


FIG. 7. Averaged group ( $n = 12$ ) nonfatigued and fatigued time to reach 80% of peak force ( $T_{80}$ ) and twitch characteristics. *A*: CFT and CIT  $T_{80}$  data. CITs needed significantly shorter  $T_{80}$ 's than CFTs for nonfatigued ( $P < 0.001$ ) and fatigued ( $P < 0.001$ ) muscles. CFTs required longer  $T_{80}$ 's as the muscle fatigued ( $P \leq 0.05$ ), whereas the CIT  $T_{80}$ 's remained unchanged. *B*: twitch contraction time (TwCT) and 1/2 relaxation time (1/2RT) data. TwCT for fatigued muscle was significantly shorter than when the muscle was not fatigued ( $P \leq 0.001$ ). In contrast, with fatigue RT significantly increased ( $P \leq 0.001$ ).

time integral. In the nonfatigued condition, there was no significant difference between the force-time integrals produced by the best CFT (90 ms) and the best CIT (100 ms). When the muscles were fatigued, the best CIT (90 ms) produced significantly greater ( $\sim 25\%$ ) force-time integrals than the best CFT (40 ms).

$T_{80}$ . In both the nonfatigued and fatigued states, CITs had significantly shorter  $T_{80}$ 's than CFTs (Fig. 7A).  $T_{80}$ 's produced by CITs were  $\sim 54$  and  $\sim 105$  ms shorter than nonfatigued and fatigued CFTs, respectively. Interestingly, for CFTs,  $T_{80}$ 's slowed by  $\sim 50$  ms as the muscle fatigued, whereas, the  $T_{80}$  for CITs did not change as the muscle fatigued. The slowing in the rate of rise of force for CFTs and the preservation of the rate of rise of force for CITs are evident in the group force responses illustrated in Fig. 8.

**TWITCH PROPERTIES.** The twitch properties of the quadriceps femoris muscle changed significantly from the nonfatigued to fatigued state (Fig. 7B). A decrease in twitch contraction time ( $\sim 78$  vs.  $\sim 40$  ms) and an increase in one-half relaxation time ( $\sim 81$  vs.  $\sim 113$  ms) of the muscle was observed when comparing nonfatigued with fatigued responses.

## DISCUSSION

This study investigated the changes in the forces-frequency relationship produced by skeletal muscle fatigue,

noting responses to both constant-frequency stimulus trains and trains that took advantage of the catchlike property of skeletal muscle. Both peak force and force-time integral responses were studied.

### Implications for muscle wisdom

In 1983 Marsden and colleagues outlined the description termed "muscle wisdom," arguing that the force development during a sustained contraction depends on a "compromise between the activation of tension generation and a concomitant aggravation of activation failure." This conclusion was based on the findings that the activation rate of motor units during prolonged, maximal, voluntary contractions declined over time from an initial rate of  $\sim 60$  to 20 pps after 30 s of a sustained contraction (Marsden et al. 1971) and that the electrical activation of muscle using supramaximal tetanic stimulation cannot overcome the force loss seen during a sustained maximal contraction performed by adequately motivated and trained subjects (Bigland-Ritchie et al. 1979). The results of the supramaximal tetanic stimulation showed that decreased CNS drive was not the cause of fatigue but, rather, that the CNS can activate skeletal muscle maximally during fatiguing contractions (Marsden et al. 1976; Merton 1954). Also, in support of the muscle wisdom description that a reduction in activation frequency would serve to reduce the fatigue produced by a muscle, several investigators have shown that a reduction in the activation rate of a muscle from  $\sim 60$  to 20 pps during either sustained (Jones et al. 1979; Marsden et al. 1976, 1983) or intermittent electrical stimulation (Binder-Macleod and Guerin 1990) of human muscles can result in less fatigue than if the initial high frequency of activation is maintained.

Bigland-Ritchie and colleagues (1983a) demonstrated that motor unit discharge rates during maximal volitional contractions typically commence at  $\sim 27$  pps and decline nearly 50% during the first minute of a sustained fatiguing contraction. They suggested that the apparent paradox of motor units being maximally activated throughout a sustained voluntary contraction despite a reduction in the motoneuron discharge rate can be explained by the observed parallel slowing of muscle contractile speed (relaxation rate) with fatigue, which should theoretically shift the steep part of the force-frequency curve to the left (see Fig. 6 in Bigland-Ritchie et al. 1983a). The shift in the force frequency relationship would explain how lower excitation rates could produce maximal tetanic force, whereas the decline in discharge rate would produce more effective rate coding by the CNS during fatigue by allowing the range of motoneuron firing rates to fall within the steep part of the curve.

Interestingly, Fuglevand (1996; personal communication) showed that when stimulation frequency progressively decreased over a range similar to that seen during a sustained maximum voluntary contraction (i.e., from 30 to 15 pps), force loss was greater than when stimulus frequency was maintained at 30 pps. In addition, consistent with the present results, previous studies of human muscle have failed to support Bigland-Ritchie and colleagues' (1983a,b) suggestion that the steep portion of the force-frequency relationship should shift toward lower frequencies (Binder-Macleod and McDermond 1992; Cooper et al. 1988; Edwards et al.

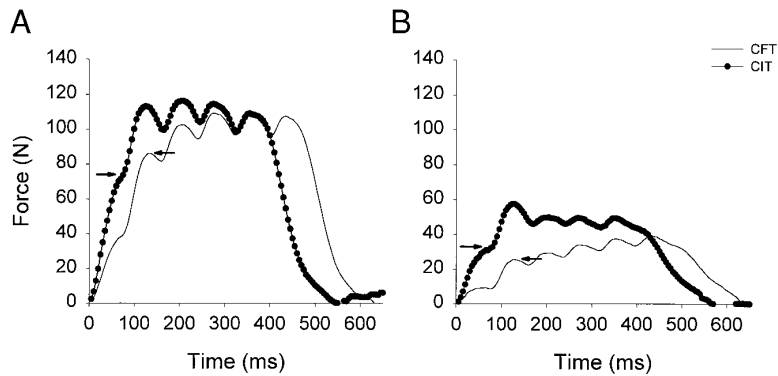


FIG. 8. Averaged group force responses ( $n = 12$ ) to the 80-ms CFT and 80-ms CIT. *A*: nonfatigued force responses. *B*: fatigued force responses. Note slowing of CFT force response with muscle fatigue.  $\rightarrow$ , responses to 1st 2 pulses of the CIT (i.e., the initial doublet);  $\leftarrow$ , responses to 1st 2 pulses of the CFT. Initial doublet produced greater forces than 1st 2 pulses of the CFT only when muscles were fatigued.

1977; Jones 1981; Stokes et al. 1989). In fact, consistent with the present peak force results, the relationship has been shown to shift toward higher frequencies, with frequencies of 50–100 pps needed to produce maximum peak forces. Thus the present peak force data and the recent findings of Fuglevand (1996) fail to show how the reduction in activation rates seen during voluntary contractions can maintain the maximum force output from skeletal muscle.

In contrast, the force-time integrals produced in response to the CITs suggest a mechanism by which optimal force can be maintained during a volitional contraction while using low mean activation rates. When the force-time integral data were used to measure muscle performance in response to CITs, the frequencies required to produce optimal performance were  $\sim 9$ –12.5 pps for both nonfatigued and fatigued muscles. These frequencies are within the range of activation rates seen during volitional contractions of fatigued muscles (Bigland-Ritchie et al. 1983a). If the force-time integral produced by each active motor unit during a prolonged voluntary contraction is important in determining the mean force produced by the muscle, then varying the activation rate of each motor unit to take advantage of the catchlike property could explain how low mean activation rates may produce optimal forces from a muscle. Patterns of activation that take advantage of the catchlike property have been reported to occur during voluntary contractions (Bawa and Calancie 1983; Griffin et al. 1996). Although care must be drawn in extrapolating the present results seen in response to intermittent electrical stimulation to the force responses produced during sustained volitional contractions, the present results raise questions that require additional study.

#### *Reasons for observed shifts in force-frequency relationships*

The present study was not designed to elucidate mechanisms behind the observed changes in the normalized peak forces or force-time integrals. Several interesting observations can be made, however. First, the presently used fatigue-producing protocol, consisting of brief stimulation trains containing a large range of frequencies, produced considerable “low-frequency fatigue.” Such fatigue is defined as a preferential depression of the twitch and lower frequency responses (Edwards et al. 1977) and is thought to be primarily the result of an impairment of excitation-contraction coupling (Chin and Allen 1996; Jones 1981). The present results show marked attenuation of the twitch forces relative

to the tetanic forces produced by the muscles (see Fig. 5). This is consistent with low-frequency fatigue and it should shift the normalized peak forces toward higher frequencies (i.e., a shift to the right) (Kernell 1995). Second, the observed decrease in the twitch contraction time should shift the normalized peak forces by requiring higher frequencies to produce comparable force summations within each stimulation train (Kernell 1995; Ranatunga 1982). Decreases in the twitch contraction time with fatigue have been previously reported for human quadriceps femoris (Binder-Macleod and McDermond 1992) and adductor pollicis (Bigland-Ritchie et al. 1983b) muscles. However, other human studies have shown no changes with fatigue (Bigland-Ritchie et al. 1992; Fitch and McComas 1985) whereas animal studies have shown increases in the twitch contraction times (Thompson et al. 1992) with fatigue. The discrepancies between the results of these studies may depend on the motor unit composition of the muscles being studied (Dubose et al. 1987; Powers and Binder 1991), the temperature changes within the muscle (Ranatunga 1982), or how much impairment in excitation-contraction coupling was produced by the fatigue-producing protocol (Thomas et al. 1991). Finally, an increase in the one-half relaxation time was observed, which should shift the force-frequency relationship toward lower frequencies. Slowing in the one-half relaxation time is a commonly reported change with muscle fatigue (Bigland-Ritchie et al. 1983b; Fitts 1994; Thompson et al. 1992) and served as the basis for the theoretical shift in the steep part of the force-frequency curve toward lower frequencies suggested by Bigland-Ritchie and colleagues (1983b). Thus the present results show that for the fatigued human quadriceps muscle, the changes in contractile properties that produced greater force-decreasing effects at lower frequencies of activation (i.e., low-frequency fatigue and decrease in twitch-contraction time) had a greater effect on the peak forces produced at each frequency than the observed increase in the one-half relaxation time.

The most interesting findings from the normalized force-time integral data are that relatively low frequencies could produce the maximum response in either the nonfatigued or fatigued states and that the normalized force-time integral increased with fatigue for all frequencies  $\geq 20$  pps. Although few previous studies have investigated the force-time integrals produced by a muscle as a function of stimulation frequency, the present data are consistent with the report by Burke and colleagues (1976), which showed that a muscle produces the greatest force-time integral by using trains with

interpulse intervals to approximately equal one to two times the twitch contraction time of the muscle (see Fig. 2 in Burke et al. 1976). The present mean twitch contraction time for the nonfatigued muscles was  $\sim 78$  ms and the interpulse interval of the trains that produced the greatest force-time integrals were  $\sim 80$ – $100$  ms; i.e., 1.03–1.28 times the twitch contraction time. When the muscle fatigued, the mean twitch contraction time decreased to  $\sim 40$  ms and the CFT with the 40-ms interpulse interval produced the greatest force-time integrals from the muscle. Thus whereas the force-time integrals produced by the muscle became less sensitive to changes in the activation frequency when the muscle was fatigued, a comparable decline in the optimal interpulse interval accompanied the decrease in the twitch contraction time of the muscle.

#### *CITs enhance force production during muscle fatigue*

A major finding of this study was that CITs produced greater force outputs from the fatigued muscle than all CFTs. Although previous studies have shown that trains that take advantage of the catchlike property of skeletal muscle can produce greater forces from fatigued muscle than subtetanic CFTs (Bevan et al. 1992; Binder-Macleod and Lee 1996; Binder-Macleod et al. 1991), no previous studies have compared the force response of CITs with a CFT that produced the optimal forces from a muscle. The best CIT produced  $\sim 25\%$  greater force-time integral than the best CFT when the muscle was fatigued.

#### *Potential mechanisms for catchlike property of skeletal muscle*

Parmiggiani and Stein (1981) proposed that one mechanism for the catchlike property of skeletal muscle is enhancement of muscle stiffness. They likened the series elastic component to an elastic band held at slack length in which the first pulse delivered to the muscle must take up the slack in the series elastic component before force is produced; subsequent pulses in the stimulus train contribute primarily to increasing force. The initial doublet, by rapidly increasing force and stiffness, allows all subsequent pulses to produce greater forces. Curtin and Edman (1994) noted a decrease in the stiffness of frog muscle fibers with fatigue and attributed the decrease in stiffness to fewer attached crossbridges. Thus if stiffness were decreased with fatigue, then improving muscle stiffness may be more efficacious in augmenting force in the fatigued state. In fact, Fig. 8 shows that for the nonfatigued muscle, the force produced by the doublet is slightly less than the force produced by the first two pulses of the CFT. However, when the muscle is fatigued the doublet produces greater force than the first two pulses of the CFT. This difference may be due to increased muscle stiffness and increased calcium release during the doublet stimulation.

Another mechanism for the tension enhancing property of CIT stimulation could be excitation-contraction coupling mechanisms related to intracellular  $\text{Ca}^{2+}$  movements. Duchateau and Hainaut (1986) showed that in nonfatigued single barnacle muscle fibers the tension enhancements with doublets were due both to augmented muscle stiffness and to changes in the ionized calcium concentration in the cell

cytosol. The changes in  $\text{Ca}^{2+}$  concentration reflected augmented  $\text{Ca}^{2+}$  release by the second pulse. Recently, Westerbblad and Allen (1993) showed that the rate of decline in the free myoplasmic  $\text{Ca}^{2+}$  concentration was reduced with fatigue. Thus it is possible that the greater than linear summation of the force produced by the doublet during fatigue may be caused by greater summation of  $\text{Ca}^{2+}$  produced by the closely spaced pulses than with the first two pulses of the CFT.

The ability of the CIT to augment force-time integrals appears related to their ability to maintain the rate of rise of muscle force in the presence of fatigue. The  $T_{80}$ 's increased for CFTs with fatigue but showed no change for the CITs. In contrast, the CITs produced greater peak forces from both the nonfatigued and fatigued muscles. However, the greater peak forces were not sufficient to compensate for the shorter train duration of the CITs versus the CFTs when the muscle was not fatigued. Thus the CITs produced slightly lower force-time integrals than the CFTs when the muscles were not fatigued. In contrast, with fatigue the time required to generate force of the CFTs increased and the CITs produced greater force-time integrals from the muscle.

#### *Use of short-duration stimulation trains*

This study contrasts with previous investigations of the force-frequency relationship because the present trains were much shorter. Short-stimulation trains were used because short bursts of activity typify the activation patterns needed to produce most functional movements. As shown by Hennig and Lømo (1987), motor unit discharge patterns in awake and freely behaving animals typically involved  $\leq 6$  action potentials. In addition, because functional human movements typically require brief periods of activation of each muscle (e.g., walking, eating), we anticipate that electric stimulators designed to perform functional electrical stimulation will require brief trains of activation to mimic natural movements. In addition, in cardiomyoplasty, a procedure in which a skeletal muscle is wrapped around the heart and stimulated to assist systole, all present stimulators use 6-pulse trains (Chachques et al. 1988).

#### *Clinical implications*

The present results may have important clinical implications when using electrical stimulation to aid patients with lower extremity paralysis to stand or walk (Bajd et al. 1982; Kralj et al. 1988; Marsolais and Kobetic 1988). Current clinical protocols use  $\sim 30$ – $60$  pps CFTs to activate the muscles. A major limitation of this application, however, is the rapid muscle fatigue experienced during stimulation (Kralj et al. 1988; Marsolais and Edwards 1988). Using stimulation trains with lower frequencies could reduce the rate of fatigue (Binder-Macleod et al. 1995). However, lower-frequency trains produce lower rates of rise in force and lower peak forces than higher-frequency trains. The present study suggests that greater forces and more rapid rates of rise of force in fatigued muscle can be obtained with the use of CITs containing a low-frequency component than with any CFT. Future studies are needed to determine if these CITs will serve to minimize fatigue versus higher frequency CFTs.

The present study also helps to identify the boundary conditions for the appearance of force augmentation by using stimulation trains that take advantage of the catchlike property of skeletal muscle. Franken and colleagues (1994) showed that no augmentation occurred with CITs when the interpulse interval of the constant-frequency portion of the train was 22 ms for activation of either the nonfatigued or fatigued quadriceps femoris muscles of patients with spinal cord injuries. Our results are consistent with these findings; when the muscle was fatigued the CITs did not produce greater force-time integrals than the CFTs until the interpulse intervals were  $\geq 30$  ms. One limitation of the present study is that we studied only isometric contractions near the optimal length of the muscle. Although recent studies have shown that CIT activation can enhance force production from human and cat muscles during isovelocity contractions (Binder-Macleod and Lee 1996; Sandercock

and Heckman 1997), additional studies are needed using movements similar to those performed during actual clinical applications.

These results may shed some light on the controversy regarding the functional significance of the decrease in activation rates with fatigue observed during voluntary contractions. The present analyses show that activation rates within the range of discharge frequencies seen for motor units during fatiguing contractions can produce near maximal force-time integrals from the muscle when using brief trains of stimulation pulses. The present results also show that trains that take advantage of the catchlike property of skeletal muscle can maximize the force output from the fatigued human quadriceps femoris muscle and that this force optimization may have clinical implications during the use of electrical stimulation for the activation of skeletal muscle.

#### APPENDIX 1. ANOVA summary tables

Force Parameter	Test	Train Type	Fatigue State	Frequency	Interaction
<i>A. Normalized data</i>					
Peak	2-way ANOVA	CFT	$F = 108.10, P < 0.001$	$F = 81.391, P < 0.001$	$F = 20.169, P < 0.001$
Peak	2-way ANOVA	CIT	$F = 39.998, P < 0.001$	$F = 20.492, P < 0.001$	$F = 49.433, P < 0.001$
Force-time integral	2-way ANOVA	CFT	$F = 12.254, P < 0.01$	$F = 20.492, P < 0.01$	$F = 49.433, P < 0.01$
Force-time integral	2-way ANOVA	CIT	$F = 76.880, P < 0.001$	$F = 105.28, P < 0.001$	$F = 27.261, P < 0.001$
Force Parameter	Test	Fatigue State	IPI	Train Type	Interaction
<i>B. Non-normalized data</i>					
Peak	2-way ANOVA	Non-fatigued	$F = 44.943, P < 0.01$	$F = 14.780, P < 0.01$	$F = 10.836, P < 0.01$
Peak	2-way ANOVA	Fatigued	$F = 53.028, P < 0.001$	$F = 53.326, P < 0.001$	$F = 13.126, P < 0.001$
Force-time integral	2-way ANOVA	Non-fatigued	$F = 65.937, P < 0.01$	$F = 9.012, P < 0.01$	NS
Force-time integral	2-way ANOVA	Fatigued	$F = 5.013, P < 0.001$	$F = 253.08, P < 0.001$	$F = 28.688, P < 0.001$
Test	Fatigue State	Train Type	Interaction		
<i>C. T80 data</i>					
2-way ANOVA	$F = 5.705, P < 0.05$	$F = 64.454, P < 0.05$	$F = 9.268, P < 0.05$		

ANOVA, analysis of variance; CFT, constant-frequency train; CIT, catchlike-inducing trains; IPI, interpulse interval; NS, not significant.

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