ABSTRACT: Muscles paralyzed by injury or disease fatigue excessively when stimulated. This study examined whether the first few paralyzed thenar motor units recruited by electrical stimulation of the median nerve were more fatigue resistant than the total thenar motor unit population. The paralyzed thenar muscles of four subjects with chronic cervical spinal cord injury were fatigued by a 2-min intermittent 40-Hz protocol on 2 days. One experiment involved submaximal stimulation, the other supramaximal stimulation. These stimuli resulted in activation of part and all of the thenar muscles, respectively. Relative force loss, force–time integral decline, and slowing of half-relaxation time were always significantly less when only part rather than all of the muscles was fatigued. The part of the paralyzed muscles that was activated was also relatively fatigue resistant compared with control single thenar motor units. Thus, a reversal of recruitment order from fatigable to fatigue-resistant units cannot explain the extreme fatigability of paralyzed muscles. Use of submaximal stimulation during functional electrical stimulation may therefore help to reduce muscle fatigue because it recruits the more fatigue-resistant units.


DIFFERENTIAL FATIGUE OF PARALYZED THENAR MUSCLES BY STIMULI OF DIFFERENT INTENSITIES

SHARLENE GODDREY, BA,¹ JANE E. BUTLER, PhD,¹ LISA GRIFFIN, PhD,¹ and CHRISTINE K. THOMAS, PhD¹,²

¹ The Miami Project to Cure Paralysis, Department of Neurological Surgery, University of Miami School of Medicine, P.O. Box 016960 (R-48), Miami, Florida 33136, USA
² Department of Physiology and Biophysics, University of Miami School of Medicine, Miami, Florida, USA

Accepted 26 March 2002

Electrical stimulation can be used to restore some function to muscles that have been paralyzed by disorders such as spinal cord injury, stroke, or multiple sclerosis. However, when stimulated, chronically paralyzed muscles fatigue much more than nonparalyzed or healthy muscles.¹²,¹⁸,²⁶,²⁹ This fatigue may limit the effectiveness of electrically evoked contractions. One reason suggested to explain the excessive fatigability of paralyzed muscles is a reversed order of motor unit recruitment. Electrical stimulation is proposed to evoke contraction of strong, fatigable motor units with fast conduction velocities, followed by the activation of weaker, fatigue-resistant units with slower conduction velocities. This is the converse of the order in which motor units are activated during voluntary contractions.⁵,¹⁴,²²

Although electrical stimulation of axons in animals recruits fast-conducting fibers before slow-conducting fibers,²,¹⁰ this has not always been the case in human studies. Some studies have shown that the first few units stimulated electrically are recruited in the same order as in a voluntary contraction.¹¹,¹⁷ Others have found a fast-to-slow contracting unit recruitment order,³³ or no particular order for unit recruitment.⁷,²¹ In a study of the entire population of units in paralyzed or partially paralyzed human thenar muscles, motor units with weak forces were generally recruited by electrical stimulation of the median nerve before motor units with strong forces.³² These results strongly suggest that the recruitment order of motor units is not necessarily reversed by electrical stimulation of peripheral nerve. This discrepancy in recruitment order of units in animal and human experiments may relate to the different methods of stimulation. Generally, human axons are recruited by transcutaneous stimulation either over the motor point or a peripheral nerve, whereas in animal experiments the axons are stimulated directly.

If the first-recruited units in paralyzed muscles are the weaker units, they may also be the more
fatigue-resistant units. In the current study, our aim was to compare the fatigability of paralyzed thenar muscles when the median nerve was stimulated supramaximally or submaximally. These stimuli evoked contraction of all of the thenar muscles or only a portion of these muscles, respectively. We hypothesized that submaximal electrical stimulation of the median nerve would recruit only a few of the more fatigue-resistant motor units in paralyzed thenar muscles. If so, the extreme fatigability of these paralyzed muscles cannot be entirely attributed to a reversal of motor unit recruitment order by electrical stimulation.

METHODS

Subjects. Eight individuals (6 men and 2 women, 29–44 years) with completely paralyzed (no voluntary control) thenar muscles in one or both hands due to chronic (4–16 years) cervical spinal cord injury were selected for study. If the thenar muscles of both hands were paralyzed, the hand that the subject judged to have the poorer sensation was studied. These subjects were injured in accidents involving diving (2), sport (2), a gunshot (2), a fall (1), or a motor vehicle (1). Current injury level (2 at C-4, 3 at C-5, and 3 at C-6) was defined according to American Spinal Injury Association criteria. All experimental procedures were approved by the local ethics committee and were in accordance with the Declaration of Helsinki. Informed written consent was obtained from each subject before participation in the study.

Experimental Setup. Each subject remained in a wheelchair with the test forearm and hand resting on a tray. The forearm was stabilized in a vacuum cast. The hand was embedded in clay (Thera-Putty, North Coast Medical, Inc., San Jose, CA). A metal plate was strapped across the fingers to immobilize them. The thumb was extended and positioned against a force transducer that registered the isometric abduction and flexion forces at right angles to each other.

Three electrodes made of 3-cm-long strands of braided, silver-coated copper wire were used to record electromyographic activity (EMG) from the distal and proximal surfaces of the thenar muscles (abductor pollicis brevis, flexor pollicis brevis, and opponens pollicis). One electrode was placed along the base of the thumb (proximal). Another electrode was positioned over the metacarpophalangeal joint (distal). Both of these electrodes were referred to a third electrode, placed between them across the eminence of the thenar muscles (common). A ground electrode was placed across the wrist crease.

The median nerve was stimulated just proximal to the wrist using a bipolar electrode with the cathode distal (Teca 6030-1, Oxford Instruments, Hawthorne, NY). Stimuli (50-µs duration) were delivered from a constant-current stimulator (DS7H, Digitimer Ltd., Hertfordshire, UK) that was controlled by a computer using Fystat software (Dataid, Umeå, Sweden). Each electromyogram (EMG) was monitored continuously on an oscilloscope (Tektronix, Inc., Wilsonville, OR) to ensure that the same units were being activated throughout each experiment.

Protocol. Two experiments were performed on each subject at least 2 days apart to ensure that the thenar muscles had recovered from the previous stimulation. In one experiment the median nerve was stimulated supramaximally. This activated all of the thenar muscle fibers and was termed the “whole-muscle” experiment. In the other experiment, the median nerve was stimulated submaximally, activating only a portion of the muscles. This was termed the “part-muscle” experiment.

During the whole- and part-muscle experiments the protocol was almost identical. First, the optimal position for stimulating the median nerve was determined by delivering low-intensity pulses every 2 s just proximal to the wrist and searching for the site at which the largest EMG response was evoked from the thenar muscles. The stimulating electrode was taped to this site and held in place throughout the stimulation by an experimenter. The stimulus intensity was then increased in 1-mA increments until there was no further increase in the amplitude of the compound muscle action potential (M wave). To check the consistency of the arrangement between experiments, maximal muscle force was evoked by delivering a train of supramaximal stimuli at 50 Hz for 1 s. The arrangement was acceptable only if the maximal evoked forces were within 5% of each other on the 2 experimental days. When the evoked forces were out of this range, the discrepancy was corrected by making small adjustments in the position of the thumb on the transducer.

In the whole-muscle experiments, all subsequent stimuli were supramaximal (28 ± 8% higher than that which evoked a maximal M wave). For the part-muscle experiments the intensity at which the nerve was stimulated varied among subjects. Five pulses were delivered at 1 Hz at subthreshold intensity and then in increasing 0.1-mA steps. This continued until we found a stimulus intensity range over which there was no additional recruitment or derecruitment of
motor units as judged from the evoked EMG. We always used the lowest possible submaximal intensity that elicited a stable EMG recording. On average, stimuli were delivered at 34 ± 4% of the intensity that evoked a maximal M wave (threshold was 24 ± 4% of maximum).

Apart from the differences in stimulus intensity, the remainder of the protocol for the whole- and part-muscle experiments was the same. Stimuli were delivered in the following order: (1) five pulses at 1 Hz to evoke twitches; (2) two pulses 5 ms apart repeated three times at 1-s intervals to evoke doublets; (3) 50 Hz for 1 s to evoke maximal force; (4) 13 trains of stimuli (300-ms duration, at frequencies between 20 and 40 Hz using different interstimulus intervals) for purposes unrelated to the current study; and (5) after a 10-min rest, the thenar muscles were fatigued using trains of 13 pulses at 40 Hz (300-ms duration) each second, for 120 s (from Burke et al.3); (6) 50 Hz for 1 s; (7) five pulses at 1 Hz; and (8) two pulses 5 ms apart (n = 3).

**Data Acquisition and Analysis.** The proximal and distal surface EMG signals were amplified (Grass P511 Amplifiers, Astro-Med, Inc., West Warwick, RI), filtered (30–1000 Hz), and sampled (3200 Hz) to a computer using SC/Zoom software (Department of Physiology, University of Umeå, Sweden). Abduction and flexion forces were amplified (Model 2310, Measurements Group, Inc., Raleigh, NC), filtered (DC-100 Hz), and sampled on-line (400 Hz).

All data analyses were executed off-line using Zoom software. Peak and integrated forces were measured from the resultant force \[ \text{resultant force} = \sqrt{(\text{abduction force})^2 + (\text{flexion force})^2} \]. Force measurements included force peak, time to force peak, half-relaxation time (time for the force to fall to 50% of its peak value), and force–time integral (from force onset until it reached baseline again). The first five and then every fifth response during the 120-s fatigue test were measured. These same four parameters were measured for the twitch and 50-Hz responses that were evoked before and after the fatigue protocol. The doublets were excluded from analysis because the artifact from the second pulse disrupted the EMG, making it impossible to judge whether the same units were being excited throughout the part-muscle experiments.

EMG measurements made from the proximal portion of the muscles included onset latency, peak-to-peak amplitude, duration of the potential, and the integral of the first two phases defined by isoelectric crossings. The first potential of the first five and every fifth train during the fatigue protocol was measured. We found it difficult to evoke EMG of stable peak-to-peak amplitude with submaximal stimulation. The first potential in the 40 Hz fatigue protocol was therefore used to establish which twitches and 50 Hz responses were measured both pre- and postfatigue.

**Statistics.** Data are expressed as mean (± SEM). Statistical significance was set at \( P < 0.05 \). The dependent variables were M-wave amplitude and area, force peak, time to force peak, force–time integral, and half-relaxation time. Within each experimental protocol, subject and time (throughout the fatigue test) were used as independent variables. For between-experiment comparisons, two-way analyses of variance (ANOVAs) on ranks were used, with group (i.e., whole-muscle and part-muscle) and time as independent variables. If there were statistical differences, post hoc testing was done to determine where in time the groups differed. Twitch and 50-Hz parameters measured before and after fatigue were compared using paired \( t \)-tests.

**RESULTS**

In all eight experiments involving submaximal stimulation it was difficult to stimulate a constant fraction of the muscles, as judged from the peak-to-peak amplitude of the M wave (see later). The EMG data were only consistent enough for analysis in four of these experiments. Comparisons between whole- and part-muscle data were therefore done for only four subjects. There was no significant difference in the maximal thenar muscle strength (assessed by 50-Hz stimulation) of the four subjects included in the whole- and part-muscle comparisons (28.9 ± 11.3 N), and the subjects excluded (15.5 ± 4.3 N). In the successful experiments involving submaximal stimulation, an average of 3.9 ± 3.2% of the maximal muscle force produced by 50-Hz stimulation was subjected to fatigue. In one subject, only a single motor unit was stimulated. Initial 40-Hz force for the whole-muscle experiments represented 87 ± 3% of initial mean 50-Hz force.

**Force Changes.** If the units recruited by submaximal stimulation are more fatigue resistant than the average, then fatigue of these units should result in less relative force loss than that which occurs when the whole muscle is activated. This suggestion held true whether a single unit or a few motor units were activated. The force and EMG recorded from one subject at 1, 30, 60, 90, and 120 s into the fatigue protocol are shown in Figure 1. The amount of force loss and slowing was greater when the whole muscles
were fatigued compared to when only part of the muscles was excited.

At the end of the whole-muscle fatigue test, mean 40-Hz force was reduced significantly to 19 ± 3% of the initial value (25.5 ± 10.3 N to 4.5 ± 1.9 N; \( P < 0.001 \); \( n = 4 \)). After 2 min of submaximal stimulation, force was reduced to 48 ± 6% (0.4 ± 0.2 N to 0.2 ± 0.1 N; \( P < 0.001 \); Fig. 2A). Consistent with our hypothesis, the whole muscles fatigued significantly more than the few units activated during the part-muscle tests as early as 25 s into the 120-s protocol.

Similar trends were seen in the force–time integrals (Fig. 2B). The mean force–time integral produced by supramaximal stimulation was reduced to 50 ± 12% of the initial value (9.0 ± 4.2 N.s to 3.5 ± 1.3 N.s) after 2 min of stimulation (\( P < 0.001 \)). In comparison, the force–time integral was only reduced to 69 ± 3% with submaximal stimulation (0.18 ± 0.10 N.s to 0.10 ± 0.06 N.s; \( P < 0.001 \)). The decrease in the force–time integral during the whole-muscle experiments was significantly greater than that which occurred in the part-muscle experiments at 105 s (\( P < 0.001 \)).

On average, significantly more slowing in half-relaxation time was seen in the whole-muscle data compared to the part-muscle data (\( P < 0.001 \); Fig. 2C). Supramaximal stimulation resulted in more than a fourfold increase in half-relaxation time (108.8 ± 30.6 ms to 465.5 ± 126.4 ms), whereas close to a threefold increase occurred with submaximal stimulation (83.0 ± 9.0 ms to 235.4 ± 58.0 ms). This difference in slowing of force relaxation between whole- and part-muscle experiments was significant at 65 s (\( P < 0.001 \)).

Time to peak force remained relatively consistent throughout the fatigue test, for both whole-and part-muscle experiments (Fig. 2D). When the whole muscles were activated, time to force peak lengthened from 339.1 ± 4.4 ms to 354.7 ± 16.4 ms, a 5 ± 6% increase. In the part-muscle experiments, this change in the time to force peak was larger, increasing from 310.5 ± 4.7 ms to 361.9 ± 23.2 ms (17 ± 9% increase). The difference in time to peak force between the two experiments was significant at 55 s (\( P < 0.001 \)).

### Muscle Blood Flow

To address the differential effect of muscle ischemia in part- and whole-muscle contractions, we calculated a fatigue index (final/initial force) for both our part- and whole-muscle
These respective indices were then compared to the mean fatigue indices of control single motor units and control whole muscles (Thomas et al., unpublished observations) that were subjected to the same 40-Hz stimulation. The benefit of comparing the part-muscle data to the control single motor unit fatigue indices was that changes in the intramuscular circulation are minimal in both cases.

When the control and paralyzed fatigue indices were compared directly, it seemed as if the activated fraction of the paralyzed muscles performed similarly to the more fatigable single motor units from control thenar muscles (Fig. 3A). However, it is well established that paralyzed whole muscles are more fatigable than control nonparalyzed whole muscles. Thus, it may be expected that activation of any part of a paralyzed muscle would have a lower fatigue index than control single units (Fig. 3A). Therefore, we normalized the control single unit data to the mean control whole muscle fatigue index. The paralyzed muscle data from the part-

![FIGURE 2](image)
**FIGURE 2.** Mean (± SEM) force data during the 40-Hz fatigue protocol for both part- (filled squares) and whole-muscle (open squares) activation (n = 4 subjects). Data represent the first 5 s and then every fifth second throughout the 2-min fatigue protocol for peak force (A), force-time integral (B), the time to half-relaxation (C), and time to force peak (D). Data are normalized to the first response for each subject as indicated by the dotted lines.

![FIGURE 3](image)
**FIGURE 3.** Data from the current experiments on paralyzed thenar muscles compared to data collected from control (nonparalyzed) thenar muscles. (A) Fatigue index (final/initial force) for control single motor units (open circles) and whole muscle (filled circles; unpublished observations) subjected to the same 40-Hz fatigue protocol as in the present part- (open squares) and whole-muscle (filled squares) experiments. Dotted line represents no fatigue. (B) Same data normalized to the mean whole-muscle fatigue index (dotted line) for control and paralyzed muscles, respectively. Note that, after normalization, the paralyzed part muscle fatigued less than many of the control single motor units.
muscle experiments were normalized to the mean fatigue index for paralyzed whole muscles. When expressed relative to the mean whole-muscle fatigue indices, the paralyzed fraction of muscles that was activated fatigued less than many of the control single motor units (Fig. 3B).

40-Hz EMG Changes. The first EMG potentials from the stimulus trains delivered at 1, 30, 60, 90, and 120 s into the fatigue protocol are shown in Figure 1. These raw data show the typical increased slowing of the muscle action potential (M wave) seen when whole muscles rather than only part of the muscles were excited. In part-muscle experiments (n = 3), the EMG changes recorded from a small group of units were similar to the all-or-none EMG responses recorded when only a single unit was stimulated (n = 1 experiment). These data strongly suggest that the same units were activated by the submaximal stimulation throughout the part-muscle fatigue tests (Fig. 4).

The amplitude of the M wave with supramaximal stimulation decreased to 84 ± 13% of initial (6.6 ± 0.7 mV to 5.7 ± 1.3 mV), whereas the area increased 19 ± 13% (19.9 ± 3.0 µV.s to 24.9 ± 6.0 µV.s). With submaximal stimulation, M-wave amplitude increased by 37 ± 27% (0.6 ± 0.2 mV to 0.9 ± 0.4 mV; Fig. 4A) and area increased by 77 ± 8% (1.8 ± 0.6 µV.s to 3.2 ± 1.2 µV.s; Fig. 4B). Only the increases in M-wave area were significantly different between experiments (at 35 s; P < 0.001).

50-Hz Responses. Mean maximal forces produced by 50-Hz stimulation for 1 s were compared in both the whole- and part-muscle experiments prior to and after fatigue. Activation of the whole muscles elicited 28.9 ± 11.3 N force before fatigue compared to 11.9 ± 5.5 N after fatigue (38 ± 8% initial; P = 0.005). This decline in the 50-Hz force was not as strong in the part-muscle experiments, but it was still significant (0.54 N ± 0.36 N to 0.25 ± 0.14 N, 60 ± 10% initial; P = 0.003). Force–time integrals decreased significantly to 44 ± 11% initial in the whole-muscle experiments (27.6 ± 11.3 N.s to 11.0 ± 4.2 N.s, P = 0.014). For the part-muscle experiments, the force–time integrals decreased to 59 ± 9% initial, from 0.84 ± 0.77 N.s prefatigue to 0.43 ± 0.38 N.s postfatigue (n = 2). The force–time integrals could not always be measured because of interference from reflex, muscle spasm, or blood pressure responses.

With both supra- and submaximal stimulation, half-relaxation time slowed substantially. In both the whole- and part-muscle experiments half-relaxation time increased approximately threefold (from 100.7 ± 10.5 ms to 329.8 ± 89.9 ms and 86.5 ± 11.8 ms to 289.8 ± 25.5 ms, respectively). However, time to peak force for both the whole- and part-muscle experiments did not change significantly with fatigue. In whole-muscle experiments, time to peak was prolonged 3 ± 1% (from 989.2 ± 4.6 ms to 1022.4 ± 9.4 ms). In part-muscle experiments the relative increase was the same (3 ± 1%, from 1001.4 ± 6.1 ms to 1028.7 ± 6.0 ms).

Twitches. Twitches elicited prior to the fatigue protocol were compared to those evoked after fatigue. Twitch force loss with fatigue was greater when the whole muscles were activated than when only part of the muscles was excited. Initial twitch force in whole muscles was reduced significantly, reaching 42 ± 7% of the value prior to fatigue (from 1.8 ± 0.4 N to 0.8 ± 0.3 N; P = 0.004). In part-muscle experiments, twitch force was reduced to 64 ± 13% (from 0.07 ± 0.04 N to 0.06 ± 0.04 N), but this change was not significant. The twitch force–time integral in both the whole- and part-muscle experiments did not change significantly with fatigue (from 0.20 ± 0.04 N.s to 0.18 ± 0.05 N.s and from 0.01 ± 0.01 N.s to 0.01 ± 0.01 N.s, respectively).

With both the whole- and part-muscle experi-
ments, half-relaxation time and time to force peak slowed with fatigue, but these changes were not significantly different between experiments. The time required for the twitch force to reach half-relaxation in the whole muscle experiments increased from $54.4 \pm 5.5$ ms to $170.9 \pm 45.2$ ms. In part-muscle experiments the increase in half-relaxation time was from $49.5 \pm 5.2$ ms to $97.0 \pm 33.0$ ms. Whole-muscle activation resulted in a $46 \pm 16\%$ increase in time to twitch peak (from $60.6 \pm 2.6$ ms to $89.3 \pm 12.0$ ms). With part-muscle activation there was a $34 \pm 12\%$ increase (from $53.8 \pm 4.5$ ms to $71.0 \pm 4.8$ ms).

With both supramaximal and submaximal stimulation, increases were observed in the amplitude and the area of the M wave. For the whole-muscle experiments, EMG amplitude increased $22 \pm 24\%$ ($5.5 \pm 1.0$ mV to $6.3 \pm 1.0$ mV) and EMG area increased $72 \pm 40\%$ ($16.7 \pm 4.6$ µV.s to $26.3 \pm 5.3$ µV.s). In the part-muscle studies amplitude increased $27 \pm 7\%$ ($0.66 \pm 0.23$ mV to $0.89 \pm 0.32$ mV) and area increased $38 \pm 6\%$ ($2.1 \pm 0.7$ µV.s to $3.0 \pm 1.0$ µV.s). These changes in amplitude and area were significant only for the part-muscle experiments.

**Submaximal Stimulation.** Data from four experiments involving submaximal stimulation had to be excluded from analysis due to inconsistencies in the evoked M waves. Either spontaneous activity disrupted recordings ($n = 1$) or a submaximal stimulus intensity that evoked stable EMG could not be found ($n = 3$). In one subject with a maximal thenar force of only $3$ N, there were at least five different units that were spontaneously active. These units could not be silenced when the subject was asked to relax and were therefore considered involuntary (Fig. 5A). When the thenar muscles of this same subject were subjected to the 40-Hz fatigue protocol using submaximal stimulation, the spontaneous unit activity corrupted the record (Fig. 5B).

For the other three subjects, incremental increases in stimulus intensity (or the same intensity) recruited additional units or resulted in unit “drop out.” When five pulses at $1$ Hz were delivered at the same intensity, the evoked EMG and force were often inconsistent (Fig. 5C). The variability in EMG amplitude at each stimulus intensity for this same subject is shown in Figure 5D. This unpredictable recruitment and/or derecruitment of units at every submaximal stimulus intensity prevented consistent activation of the same units throughout the fatigue protocol. In these cases, comparisons between the fatigue induced with submaximal versus supramaximal stimulation were impossible.

**DISCUSSION**

This study shows that submaximal stimulation of the median nerve recruits a portion of paralyzed thenar muscles that is more fatigue resistant than the whole muscles. These data suggest that, on average, the first units recruited in these paralyzed muscles are the more fatigue-resistant ones. Furthermore, these results imply that a reversal of motor unit recruitment order during electrically evoked contractions...
cannot fully explain the extreme fatigability of paralyzed muscles.

Muscle Force. During voluntary contractions, weaker fatigue-resistant motor units are generally recruited before stronger fatigable units. In a recent study on human thenar muscles paralyzed by spinal cord injury, weaker motor units also tended to be recruited before stronger motor units with median nerve stimulation. The present study shows that, on average, those units recruited first by median nerve stimulation are also the more fatigue-resistant units. Hence, the present data and those of Thomas et al. suggest that the first-recruited motor units in paralyzed thenar muscles are both weak and fatigue resistant. The force of these few paralyzed thenar units also showed less slowing with fatigue, as found for weak units in various control muscles.

A concern with submaximal stimulation of paralyzed muscle is that the muscle could have been partly activated via H reflexes or cutaneous reflexes. H reflexes are uncommon in control thenar muscles. In our experience, they are also uncommon after cervical spinal cord injury. No late responses were present at the stimulus intensities used in three of our subjects. In the other subject, a small response at the H-reflex latency was apparent in only three of the five prefatigue twitches. However, there was no evidence of late responses during the fatigue test. With stimulation at 40 Hz, the onset of an H reflex or cutaneous response should occur about the time of onset of the next M wave. In this particular subject, the size and shape of the first M wave in each train was the same as subsequent M waves. If the M waves were being influenced by late responses, one would expect to see: (1) the reflexes either adding or subtracting from the M waves; and (2) a reflex response at the end of the train. Neither of these events occurred. Thus, our data do not show evidence of muscle activation by reflexes during submaximal stimulation. In addition, depression of any H reflexes with 40-Hz stimulation should be even greater than that seen with 10-Hz stimulation.

The greater fatigability seen in the present whole-muscle experiments compared to the part-muscle experiments may not simply reflect activation of more fatigable units. Enhanced fatigue may also result from increased muscle ischemia. Many previous studies have shown that intramuscular circulation can be compromised when there are short rest periods between submaximal, intermittent contractions. In our experiments, the initial 40-Hz force evoked by supramaximal and submaximal stimulation produced 87% and 4% of maximal muscle force, respectively. The significantly greater slowing of muscle relaxation that occurred with supramaximal nerve stimulation eventually eliminated any rest between these trains of stimuli. This probably compromised muscle blood flow to an increasing extent (Figs. 1 and 2). The relative muscle ischemia must have been greater when the whole-muscle contracted than when only part of the muscles was activated. However, as shown in Figure 3, even when differences in intramuscular circulation were at least partly corrected, those paralyzed units recruited first by electrical stimulation of the median nerve were still the more resistant to fatigue.

EMG Changes. During the part-muscle experiments a small group of units were fatigued in three subjects. In the other subject a single unit was fatigue. The unit EMG responses were all-or-none. The EMG changes during fatigue were similar regardless of whether a single unit or a small group of units was stimulated. All changes in the EMG were also gradual during fatigue, suggesting that there were no sudden changes in the recruitment or derecruitment of units. Together, these data suggest strongly that the same units were being activated throughout the part-muscle fatigue test.

Changes in the area and amplitude of the M waves did occur during fatigue of both whole-muscle and part-muscle experiments. This was not unexpected. Similar changes have been reported in many other studies of stimulated and voluntary contractions. For example, during sustained electrically evoked human biceps brachii contractions under both ischemic and nonischemic conditions, Cupido et al. showed increases in both the area and amplitude of the maximal M wave. The increases were attributed to changes in the muscle fibers and membrane properties due to enhanced electrogenic Na⁺–K⁺ pump activity. These changes would affect both submaximal and supramaximal M waves similarly, as found in the present study. In the whole-muscle but not part-muscle experiments, the M-wave amplitudes decreased toward the end of the protocol. This late decrease in M-wave amplitude is consistent with greater fatigue and muscle ischemia.

Submaximal Stimulation. These experiments also highlight the problems associated with submaximal nerve stimulation. In the subjects excluded from our analysis, we found it extremely difficult to evoke EMG potentials of consistent amplitude even when
using the same stimulus intensity. This problem may relate to a population of axons with similar electrical thresholds and/or activity-dependent changes in axonal excitability in these subjects. During both voluntary and electrically evoked contractions, there are complex changes in the excitability of motor axons.1,15,34 According to Kiernan et al.,15 repetitive activation at the interstimulus interval used in the present study (25 ms) may increase the threshold for subsequent activation of axons. If this occurs, reductions in the mean M-wave amplitude and area due to unit “drop out” would be expected. We did not observe a sudden drop out of units when we successively fatigued only part of the muscles in four subjects. Our ability to reliably excite a group of units may relate to increased innervation ratios due to motoneuron death and hence axonal loss associated with spinal cord injury.90 The remaining motor units may be recruited over wider current ranges. The activation range for different axons may also become more separate. Despite this, there is still a weak-to-strong recruitment order of reinnervated triceps brachii motor units after spinal cord injury during voluntary contractions.30 There is also appropriate reorganization of motor unit properties in animal models of partial denervation and self-reinnervation.24 Thus, reinnervation is unlikely to change our interpretation of the data.

It is noteworthy that we had to exclude half of the subjects because we were unable to find a submaximal stimulus intensity at which we were sure that a constant part of the muscle was being activated. Either new units were recruited or those units already activated dropped out, presumably due to activity-dependent changes in axonal excitability. In another excluded subject, the fatigue protocol was clearly disrupted by spontaneously active units. These potential problems make submaximal nerve stimulation a less than desirable method for meaningful measurements of muscle properties, especially when EMG is not monitored. In unavoidable circumstances, as was the case with this set of experiments, extreme care must be taken to validate outcomes.

**Functional Implications.** We have shown that the first few motor units recruited in paralyzed thenar muscles by submaximal stimulation of the median nerve are the more fatigue-resistant units. Use of submaximal stimulation during functional electrical stimulation may therefore help to reduce muscle fatigue, provided that sufficient force can be evoked to produce the desired behavior. Our data also suggest that the extreme fatigueability of paralyzed muscles during electrical stimulation cannot be explained by a reversal of motor unit recruitment alone. Hence, other factors that cause fatigue need to be looked at more closely. Synchronous versus asynchronous activation of motor units, selective motoneuron death, changes in blood flow, or even the patterns of stimulation may be more critical contributors to fatigue. Most likely, the extreme fatigability is due to altered use or disuse of the paralyzed muscles, resulting in a shift toward more fatigable muscle fiber properties.13,19,23 Studies that explore the relative importance of these factors in fatigue are therefore essential if behaviors are to be restored more effectively by electrical stimulation of nerve or muscle.

This research was funded by Australian National Health & Medical Research Council Neil Hamilton Fairley Fellowship 007148 (J.E.B.), a National Sciences & Engineering Research Council of Canada fellowship (L.G.), United States Public Health Service Grant NS-30226 (C.K.T.), and The Miami Project to Cure Paralysis.

**REFERENCES**

14. Henneman E, Somjen G, Carpenter DO. Functional signifi-


