Fatigue of intermittent submaximal voluntary contractions: central and peripheral factors

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Central and peripheral factors were studied in fatigue of submaximal intermittent isometric contractions of the human quadriceps and soleus muscles. Subjects made repeated 6-s, 50% maximal voluntary contractions (MVC) followed by 4-s rest until the limit of endurance (Tlim). Periodically, a fatigue test was performed. This included a brief MVC, either a single shock or 8 pulses at 50 Hz during a rest period and a shock superimposed on a target force voluntary contraction. At Tlim, the MVC force had declined by 50%, usually in parallel with the force from stimulation at 50 Hz. The twitches superimposed on the target forces declined more rapidly, disappearing entirely at Tlim. In similar experiments on adductor pollicis, no reduction of the evoked M wave was seen. The results suggest that, during fatigue of quadriceps and adductor pollicis induced by this protocol, no central fatigue was apparent, but some was seen in soleus. Thus the reduced force-generating capacity could result mainly or entirely from failure of the muscle contractile apparatus.

Methods

Subjects. Ten healthy adult subjects (male and female, ages 18–50) were studied during experiments on the
quadriiceps and soleus muscles. Three others performed the experiments on adductor pollicis. All were familiar with the procedures and gave their informed consent.

**Protocol**

*Control values.* Each subject made a series of brief (3–5 s) MVCs with 3 min of rest between contractions. Stimulating pulses were delivered once per second before, during, and after each MVC. Those superimposed on the contraction tested the maximality of each MVC while the five shocks delivered before and after the MVC allowed comparison of twitch amplitudes in an unpotentiated vs. a potentiated condition. The MVC force was determined, and 50% of this force was marked as the target force on the monitor oscilloscope in front of the subject. After 5 min of rest, the subject generated two constant, target force contractions, holding each for 6 s with a 4 s rest between (0.6 duty cycle). Stimulating pulses were delivered once per second during this control run to measure the amplitudes of the superimposed twitches. This was followed by two brief trains of 50 Hz stimulation (8 pulses/train) delivered to the unfatigued relaxed muscle to determine control responses to the high-frequency stimulation. For adductor pollicis the control MVC was also compared with the force from more prolonged 50 Hz stimulation.

*Fatiguing exercise.* Following a 10-min rest, the subject generated a continuous pattern of 6 s contractions followed by 4 s rest until after the target force could no longer be maintained. At intervals (every 1 or 5 min depending on the muscle employed and its estimated endurance time), a fatigue test was carried out over a span of two contractions. The test consisted of a brief MVC with superimposed shock generated during the last 3 s of a target force contraction, a stimulus superimposed on a target force contraction, and either a single shock or 8 pulses at 50 Hz during a rest period. A typical record is shown in Fig. 1.

*Influence of the fatigue test procedure.* The interpretation of these experiments depends on the relationship between the changes of force in response to maximum voluntary effort compared with those to transcutaneous muscle stimulation. The experiments on soleus sometimes lasted up to 60 min. It might be argued that either the fraction of the muscle stimulated declined with time and/or that the test procedure contributed to the muscle contractile failure. For the latter reason, the 50 Hz stimulation was restricted to only 8 pulses. To examine these possibilities, the fatigue test protocol was also applied to the otherwise rested muscle once every 5 min for 60 min when no fatiguing target force voluntary contractions were performed between them.

*Force recording.* Quadriceps force was measured using a strain gauge dynamometer described previously (19). The knee was held at an angle slightly <90° with the strap from the strain gauge securely anchored just above the malleolus. The leg in this position produced a resting tension on the strain gauge of from 2 to 5% of the MVC force. The subject was strapped at the waist to maintain muscle length and prevent substantial use of the hip extensors.

The force from the triceps surae (mainly soleus) was measured using a dynamometer similar to that described by Lippold et al. (14) and by Belanger and McComas (1) but modified for isometric contractions (20). The subject sat with the knee securely clamped at an angle of 90° to prevent heel rise during contraction. In this position, with the gastrocnemius slack, most of the force on the foot plate secured at the base of the dynamometer was generated by the soleus muscle (18).

The forces from the adductor pollicis contractions were measured using the method based on that of Merton (16) and described in detail previously (6). The hand was fixed in a supinated position with the fingers slightly flexed. The thumb was attached to the strain gauge through a chain with a looped strap fastened just proximal to the first phalangeal joint. The muscle was slightly stretched to give a resting tension of 5–10% of the MVC force.

*Muscle stimulation.* The quadriceps muscle was stimulated transcutaneously using a pair of 5 × 22 cm pad electrodes soaked in saline. These were applied transversely to the proximal and distal surfaces of the anterolateral thigh. The pads were then covered with plastic to minimize evaporation and bandaged in place.

Soleus was also stimulated transcutaneously using a pair of 4 × 8 cm saline-soaked pad electrodes placed horizontally; one just distal to the lower border of the gastrocnemius and the other over the Achilles’ tendon at the level of the malleolus. These were also covered with plastic and bandaged in place.

For adductor pollicis, a cathode button was strapped to the wrist and carefully positioned over the ulnar nerve. This position was continuously readjusted throughout each experiment while monitoring the evoked M wave to ensure that stimulus maximality was maintained. An anode plate was secured under the same strap and located on the lateral surface of the wrist.

The quadriceps and soleus muscles were stimulated with square-wave pulses of 100–μs duration and 130 V (the maximum most subjects were willing to tolerate). Trains of 8 pulses at 50 Hz then produced ~30 and 50% of the subject’s MVC force for soleus and quadriceps.
respective, without intolerable pain (Fig. 1). For adductor pollicis, the pulses were of 50-μs duration and 80–120 V, adjusted to be substantially supramaximal (7). Pulses were delivered as either single shocks or as brief trains of either 8 pulses or 1–2 s at 50 Hz.

Electromyogram recording. One surface disk electrode was applied to the belly of vastus lateralis, with an indifferent electrode 18–20 cm away over the lateral epicondyle of the femur. For soleus, one electrode was located over the distal belly of the muscle with the indifferent electrode 16–18 cm away over the lateral malleolus. Similarly, for the hand, one electrode was located over the center of adductor pollicis muscle and one over the metacarpophalangeal joint of the thumb. The subjects were grounded.

Data analysis. All signals were recorded on tape and also on a chart recorder. The surface electromyogram (EMG) signals were differentially amplified (10 Hz–10 kHz), rectified, and integrated over 1-s periods (Fig. 5). The force was displayed on an oscilloscope screen in front of the subject. Stimulus pulses were also put on tape to help detect the location of superimposed twitches when these became small. This detection was also aided by the presence of the stimulus artifact on the EMG channel. The superimposed twitches were then further amplified before measurement.

RESULTS

Quadriiceps and soleus: control values. With practice, each subject was able to make maximal contractions of both muscles on which no superimposed twitch could be detected. This showed that, in the absence of fatigue, it is possible to maximally activate all motor units by voluntary effort. Control values were obtained for the forces generated by an MVC, 50 Hz stimulation, and single shocks both at rest and superimposed on the target force (mean ± SD, n = 3–5 for each experiment). These values are shown in Table 1. For both muscles, the amplitude of the resting twitches was potentiated following either voluntary contractions or repetitive stimulation. Maximum potentiation was generally seen following the second MVC, with little change thereafter. For quadriceps, twitch potentiation averaged 1.6 ± 0.4 times the unpotentiated twitch amplitude. Similar potentiation was observed in the twitches superimposed on the target force contractions. This made it difficult to select suitable control values with which to compare the changes during fatigue. The values following maximum unfa-
same level (60% MVC) at the beginning and end of this period. Under both conditions the force from 8 pulses at 50 Hz generated 70% of that seen during more prolonged, 1- to 2-s stimulation. These results show that 1) transcutaneous stimulation when applied over prolonged periods continues to activate the same constant fraction of the whole muscle and 2) that the fatigue testing procedure itself induces negligible muscle contractile failure.

Quadriceps fatigue. In six experiments on four subjects, the sequence of contractions illustrated in Fig. 1 was repeated until after the target force could no longer be attained (i.e., beyond the limit of endurance, $T_{lim}$). At this time, despite maximum voluntary effort the MVC had declined by >50%. The mean target force actually exerted during this time varied only slightly between experiments (48 ± 2% MVC, $n = 7$), but the endurance times were remarkably constant, averaging 4.4 ± 0.6 min.

The force of the periodic brief MVC declined linearly throughout the exercise until, at the limit of endurance, they only just reached the target force (Fig. 3). In well-motivated subjects, no twitches were seen when superimposed on these MVCs. The responses to 50 Hz stimulation between contractions also declined linearly with time. Paired t tests showed no statistical difference between the percent changes in the MVC and those of 50 Hz stimulation recorded after equal periods of fatigue. Thus for this muscle the decline in force-generating capacity could be completely accounted for by muscle contractile failure. The mean values from all experiments are shown in Fig. 4A.

Figure 4A also shows the percent changes in amplitude of the twitches superimposed on the target force voluntary contractions ($T_{WS}$) compared with their prepotentiated control values. These remained relatively constant in amplitude for the first 60 s and then declined rapidly. It seems likely that during the first 60 s of contraction, the decline in the superimposed twitch amplitude was masked by some further twitch potentiation thus delaying the onset of rapid changes. At the limit of endurance no superimposed twitches could be detected; nor were they seen at any time throughout the experiment when superimposed on the periodic brief maximal efforts, despite up to a 50% loss of force-generating capacity. These observations again suggest that throughout fatigue of 5-min duration induced by 50% MVC intermittent submaximal contractions, voluntary effort can still fully activate all motor units, and fatigue is not due to inadequate motor drive.

**Surface IEMG.** The surface integrated EMG (IEMG) recorded during target force contractions increased progressively throughout the exercise period. At the limit of endurance when a maximal effort was required to just reach the target force and when the superimposed twitches disappeared, these maximal EMG values were never less than those recorded during prefatigue control maximal contractions (Fig. 4B). At this time the target force IEMG was not significantly different from that recorded during the periodic brief maximal contractions. These observations provide further support, indicating that force generation was not limited by inadequate muscle excitation or peripheral failure of electrical trans-
mission.

**Soleus fatigue.** The mean target force exerted in these experiments was 50.2 ± 2.0% MVC. However, as expected, this predominantly type I muscle proved to be highly fatigue resistant. Endurance times were more variable than for quadriceps, averaging 35.1 ± 15.7 min compared with 4.4 ± 0.6 min for quadriceps using the same fatiguing protocol. The wider variation in the rate of force loss made it difficult to compare data from different subjects as a function of time. The pooled data were therefore compared at various percents of the total endurance times observed in each experiment. Because of the longer endurance times, the fatigue tests were only given every 5 min.

Figure 5A shows the pooled data from seven experiments on four subjects. As in the quadriceps experiments, the forces during the brief MVC contractions and those in response to 50 Hz stimulation declined linearly with time, whereas the superimposed twitches almost disappeared. However, the MVC forces declined more quickly so that when only 50% of the initial MVC could be generated by voluntary effort (Tlim), the average response to 50 Hz stimulation was still 70.0 ± 14.0% of that obtained from the unfatigued muscle. Paired t tests showed these differences in percent force loss to be significant at P < 0.01.

**Surface IEMG.** The surface IEMG recorded during target force contractions again increased slowly throughout the exercise period. However, there was a significant decline in the surface IEMG recorded during the brief MVCs. At the limit of endurance, this averaged ~60% of the initial prefatigue value. The time when the target force IEMG first matched that from the MVC once more coincided with the endurance time estimated from the MVC force measurements (Fig. 5D). These results are thus compatible with some failure of central motor drive.

**Adductor pollicis experiments.** With transcutaneous stimulation only part of the quadriceps and soleus could be activated, and the muscle mass action potentials (M waves) could not be monitored. A few experiments were therefore carried out on the adductor pollicis using supramaximal stimulation of the ulnar nerve and M wave measurements. The experimental protocol was otherwise identical, and the results were similar to those obtained from quadriceps. Typical records obtained before fatigue and at Tlim are illustrated in Fig. 6, which also shows the corresponding changes in the IEMG, the evoked M waves, and the responses to more prolonged 50 Hz stimulation.

Maintaining stimulus maximality was difficult, but as in previous experiments (6, 7, 13) whenever a decline in M wave amplitude was observed it could be restored by repositioning the stimulating cathode and/or increasing the stimulus intensity. When this was done, no decline was seen in the amplitude of the evoked M wave, but its duration increased by ~20% (Fig. 6B), presumably as a result of slowing of muscle conduction velocity. Thus, for fatigue of the adductor pollicis muscle induced by similar intermittent submaximal contractions, no evidence for failure of peripheral electrical transmission was apparent.

**Low-frequency fatigue.** Figure 7 shows the % changes in the response of the quadriceps (A) and soleus (B) muscles to single shocks periodically delivered to the relaxed muscle between contractions (Tw). For both muscles the twitch amplitudes declined more rapidly than the force from 50 Hz stimulation. However, the differences between these two were more marked during fatigue of the quadriceps than for soleus. At the limit of endurance the quadriceps twitch amplitudes had declined by 75% compared with a 54% decline for the 50-Hz responses. The corresponding values for soleus were 40 and 30%, respectively.
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Figure 6. Adductor pollicis. A: Force and integrated EMG (IEMG) records from the unfatigued muscle and at limit of endurance. MVC and target force voluntary contractions are compared with those from supramaximal single shocks, 8 pulses at 50 Hz, and more prolonged 50 Hz stimulation. B: M waves recorded in same experiment during control period (A) and at limit of endurance (B) from relaxed muscle, during tetanic stimulation, and superimposed on target force contractions.

Figure 7 also shows the corresponding rates of MVC decline. For soleus these were similar to those of the twitches elicited between contractions. Thus, had these alone been used for comparison with the MVC responses, we would have concluded that for soleus, like quadriceps, no central component of fatigue could be detected. This illustrates again that twitch responses do not necessarily provide a reliable index of muscle contractile failure.

Discussion

These results suggest that, during fatigue of the quadriceps muscle induced by intermittent medium-intensity isometric exercise, the central nervous system remains capable of full muscle activation, and that in well-motivated subjects the reduced force in response to maximal voluntary effort can result only from failure of the muscle contractile apparatus. This conclusion is based on the finding that 1) the force from periodic brief MVCs declined in parallel with that from short trains of tetanic stimulation, 2) throughout the experiment no superimposed twitches could be detected when single shocks were delivered during the MVCs, and 3) the twitches superimposed on the target force contractions declined more rapidly, becoming undetectable at the limit of endurance when maximal efforts were required to meet the target force.

For fatigue of the soleus muscle, the results are less clear. In each experiment the MVC force declined somewhat more quickly than that in response to 50 Hz stimulation. At the limit of endurance the ratio of the MVC force to that from 50 Hz stimulation indicated that the muscle was then only ~77% activated by maximum voluntary effort. This conclusion is at variance with the absence of twitches on the periodic MVCs and the disappearance of the superimposed twitches from target-force contractions at and beyond T\text{lim}. However, at that time the twitches elicited from the relaxed muscle between contractions had declined from 9.4 to ~5.6% of the MVC. Thus, when 77% activated by maximum voluntary effort, any superimposed twitch would be <1.3% MVC, a value probably too small to be distinguished from the tremor generated by fatigue when contractions are continued for this period of time.

A reduced capacity to fully activate the soleus muscle may also be indicated by the behavior of the surface EMG. Whereas the quadriceps EMG during the brief MVCs increased as fatigue progressed, that from the
soleus muscle declined (Fig. 5B). However, a reduction in the surface EMG is normally seen in fatigue of sustained maximal contractions. It can be accounted for by a concomitant decline in motor neuron firing rates, without any reduction in the degree of muscle activation (6, 8). Whether a similar reduction in MVC firing rates also occurs in fatigue of submaximal intermittent contractions remains to be established. This cannot be inferred from the behavior of the surface EMG alone, since this may be influenced by other factors such as changes in conduction velocity and synchronization.

An inability to continue full voluntary activation of the soleus muscle during fatigue would not be surprising, since Belanger and McComas (1) found that many of their subjects were unable to activate it maximally even in the unfatigued state. Moreover, in fatigue of the diaphragm induced by the same contraction protocol, Bellemare and Bigland-Ritchie (2) concluded that about 50% of the reduced force-generating capacity was due to reduced motor drive. Possibly in both these types of exercise, the central component apparent in fatigue could be overcome with additional practice by the subjects and/or more “persuasive” encouragement.

It can be argued that the force decline during both voluntary and stimulated contractions of both the leg muscles may have resulted from progressive failure of neuromuscular transmission, for with transcutaneous stimulation it is likely that the muscle is excited via intramuscular nerve endings. But monitoring of the M waves was not feasible. However, for quadriceps the progressive increase in the target force IEMG to the initial control MVC values make this unlikely. The similar experiments on adductor pollicis proved to be extremely difficult because of an overwhelming urge by most subjects to substitute increasing activation of synergists to generate the target force as fatigue progressed. However, in the few successful experiments, where the MVC continued to match that from 50 Hz stimulation of the ulnar nerve (Fig. 6), the results were identical to those of quadriceps. Here no decline in the evoked M wave amplitude was seen even when the MVC force had declined well below the target force. Again, the target force surface IEMG increased linearly, the final level exceeding that seen in the initial control maximal contractions. It therefore seems unlikely that electrical transmission failure contributed to the force loss seen in any of the muscles. This possibility, however, cannot be ruled out.

Assessment of the relative degree of muscle activation by twitch occlusion has been well documented for submaximal voluntary contractions in the unfatigued muscle (1, 3, 4, 16). This method has not previously been used to determine changes in the degree of muscle activation during fatigue. For the unfatigued quadriceps muscle there is a near-linear relation between the amplitude of the superimposed twitch and the voluntary force on which it was superimposed. This relationship was independent of the degree of twitch potentiation. Comparable relationships were also obtained for both muscles after fatigue.

During fatigue both the superimposed twitch and that from the relaxed muscle declined. This made it difficult to detect extremely small superimposed twitches particularly in the presence of marked tremor. This, together with the curvature of the soleus-twitch occlusion relationship at high forces and the small initial-twitch amplitude, probably accounts for no superimposed twitches being seen on the soleus MVCs at the time when a comparison of the MVC and 50-Hz forces suggests incomplete voluntary muscle activation. For quadriceps, however, superimposed twitches of small amplitude could still be detected up to shortly before the limit of endurance, and their disappearance coincided with the time that a maximal effort was required to reach the target. Thus, despite these problems, their amplitude provides a reliable index of changes in the degree of muscle activation during fatigue.

Continued full muscle activation by the central nervous system has been demonstrated during fatigue from 60 s sustained MVCs of the adductor pollicis (8) and...
quadiceps (5) muscles. This was done by comparing the voluntary force to that from supramaximal tetanic nerve stimulation. In the quadiceps experiments, however, it was demonstrated that the same results could be obtained by comparing the force of an MVC to that from transcutaneous stimulation of only a fraction of the total muscle (5, 10); the method used in the present experiments. However, here we also limited the tetanic stimulation to trains of 8 pulses to reduce the chance that the testing procedure might influence the rate at which fatigue developed. Prolonged high-frequency stimulation might also have induced failure of peripheral neuromuscular transmission to which the muscle becomes increasingly sensitive with fatigue (6, 13). The trains of 8 pulses at 50 Hz only developed 70% of that produced by longer, 1- to 2-s trains; but this proportion remained quite constant over 60 min when tested in “sham” experiments and appeared to provide a reliable index of muscle contractile strength. This test procedure did not have any detectable effect on the MVC force produced. The results during fatigue of the quadiceps muscle were identical with those from the adductor pollicis illustrated in Fig. 7 when prolonged maximal stimulation of the ulnar nerve matched the MVC before and immediately following the limit of endurance.

Calculation of the relative changes in twitch amplitude during fatigue was complicated by potentiation. The twitches recorded between contractions were expressed as a percentage of those following maximum potentiation in the unfatigued state. These potentiated control values were more difficult to obtain for the superimposed twitches recorded between contractions were expressed as a percentage of those following maximum potentiation in the unfatigued state. These potentiated control values were more difficult to obtain for the superimposed twitches. Therefore, during the early part of the exercise, further twitch potentiation probably tended to conceal muscle contractile failure, so that little change in amplitude was seen. The continued presence of twitch potentiation throughout the contraction protocol was demonstrated by the even lower twitch amplitudes recorded when shocks were sometimes given within the first few minutes of recovery as the effects of potentiation wore off.

The greater decline in the response to single shocks between contractions compared with those to brief trains of 50-Hz stimulation shows the progressive development of “low-frequency fatigue.” A greater relative decline in the force from low- compared with high-frequency stimulation has been observed following many forms of exercise (11). It has been attributed to impaired Ca$^{2+}$ release per impulse, which may be one of the components of muscle contractile failure. When trains of impulses arrive in quick succession, the Ca$^{2+}$ is thought to accumulate in the sarcoplasm so that full cross-bridge interaction can once more take place. In the present experiments the time course of low-frequency fatigue development was measured. It developed more quickly and to a considerably greater extent during fatigue of the quadiceps than for soleus, despite the much shorter exercise duration. This suggests that the type II muscle fibers in quadiceps may perhaps be more susceptible to this type of excitation-contraction coupling failure than are the type I fibers that predominate in soleus. However, it is clear that any fatigue experiments measuring only changes in the amplitude of the responses to single shocks would overestimate the contractile failure occurring during fatigue of voluntary contractions.

Two main conclusions can be drawn from these experiments. First, the difference between the fatigue resistance of these two muscles is striking. The endurance times of soleus were about seven times longer than for quadiceps when the same contraction protocol was used. Even at the limit of endurance after 30–40 min of exercise, the response of soleus to 50 Hz stimulation revealed only 30% actual muscle contractile failure, compared with 50% after only 4.4 min for quadiceps. Second, during fatigue induced by prolonged intermittent submaximal contractions the central nervous system seems to remain capable of full muscle activation, at least for the quadiceps and adductor pollicis muscles. Whether, after additional practice, subjects could also learn to do this more completely with soleus is not clear.

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