*J Appl Physiol*
89: 305–313, 2000.

# Supraspinal fatigue during intermittent maximal voluntary contractions of the human elbow flexors

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Received 7 November 1999; accepted in final form 11 February 2000

**Taylor, Janet L., Gabrielle M. Allen, Jane E. Butler, and S. C. Gandevia.** Supraspinal fatigue during intermittent maximal voluntary contractions of the human elbow flexors. *J Appl Physiol* 89: 305–313, 2000.—Responses to transcranial magnetic stimulation in human subjects ($n = 9$) were studied during series of intermittent isometric maximal voluntary contractions (MVCs) of the elbow. Stimuli were given during MVCs in four fatigue protocols with different duty cycles. As maximal voluntary torque fell during each protocol, the torque increment evoked by cortical stimulation increased from ~1.5 to 7% of ongoing torque. Thus "supraspinal" fatigue developed in each protocol. The motor evoked potential (MEP) and silent period in the elbow flexor muscles also changed. The silent period lengthened by 20–75 ms (lowest to highest duty cycle protocol) and recovered significantly with a 5-s rest. The MEP increased in area by >50% in all protocols and recovered significantly with 10 s, but not 5 s, of rest. These changes are similar to those during sustained MVC. The central fatigue demonstrated by the torque increments evoked by the stimuli did not parallel the changes in the electromyogram responses. This suggests that part of the fatigue developed during intermittent exercise is "upstream" of the motor cortex.

transcranial magnetic stimulation; central fatigue; motor cortex; exercise

IN HUMAN EXERCISE, FATIGUE is a decrease in the maximal voluntary force produced by a muscle or muscle group. Although much of fatigue is due to changes in the muscle fibers, some loss of force occurs through inadequate activation of motoneurons. This is known as central fatigue (for review, see Ref. 9). Central fatigue varies between muscles and with different tasks (17, 19). During prolonged isometric maximal voluntary contractions (MVCs) of the elbow flexors lasting 2–3 min, activation of the motor cortex by transcranial magnetic stimulation can evoke extra force from the muscle despite maximal voluntary activation (10). Thus at least some of the inadequate activation of motoneurons can be attributed to suboptimal descending drive from the motor cortex.

At the same time, during a sustained MVC, there are changes in the electromyogram (EMG) responses to transcranial magnetic stimulation. The short-latency excitatory response (motor evoked potential; MEP) grows in size, and the subsequent profound inhibition of ongoing EMG, known as the silent period, is prolonged (18, 21, 25). It is likely that changes in the motor cortex contribute to both phenomena. The latter part of the silent period after cortical stimulation depends on intracortical inhibition of descending drive (13, 22, 24). Thus the prolongation of the silent period with sustained contractions suggests a net increase in inhibition to corticospinal neurons. The size of the MEP depends not only on the excitability of corticospinal neurons but also on the motoneurons and the muscle fiber membrane. Comparison of MEPs and the responses to subcortical stimulation of descending tract axons during a sustained MVC indicates that some of the increase in the size of MEPs is due to an increase in net excitatory output evoked from the cortex (25). Although suboptimal output from the motor cortex (central fatigue) occurs together with the prolongation of the silent period and the growth of the MEP during a 2-min MVC, these changes can be dissociated under some conditions (10). Thus, although changes in the EMG responses to transcranial magnetic stimulation accompany fatigue, they may not be causally related to the loss of voluntary force.

Fatigue induced by periods of submaximal isometric exercise may have a greater central component than fatigue induced by prolonged maximal efforts (16, 17). Throughout a sustained MVC, high intramuscular pressure prevents blood flow to the contracting muscles. This maintained muscle ischemia does not allow recovery of muscle fibers during the contraction and maximizes the fatigue occurring within the muscle. During weak or intermittent exercise, muscle fibers will fatigue more slowly, and this may allow changes within the central nervous system to play a greater role in the overall loss of force production. Hence, this study was designed to examine whether the development of the supraspinal component of central fatigue was similar during exercise protocols with differing levels of activity. Because central fatigue can only be measured during maximal contractions, the level of exercise was varied by changing the duty cycle of the

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exercise rather than by varying the strength of contractions. The periods of contraction and rest were also chosen to examine the time course of the changes in the EMG responses to transcranial magnetic stimulation that occur during maximal efforts and their relationship to the supraspinal component of central fatigue. From previous studies on sustained MVCs, we expected that central fatigue due to suboptimal output from the motor cortex would not parallel the changes in either of the cortically evoked EMG responses. Results from the study have been published in abstract form (4).

## METHODS

*Setup.* Nine normal subjects (25–46 yr old; 4 women) took part in experiments to examine responses to transcranial magnetic stimulation during fatiguing contractions of the elbow flexors. All procedures were undertaken with the informed consent of the subject and the approval of the local ethics committee. Subjects sat with the right arm flexed to 90° in an isometric myograph that measured flexion torque exerted about the elbow (transducer linear to 2 kN, Xtran, Melbourne, Australia; see Ref. 1 for details). The arm was positioned with the forearm vertical and supinated and strapped to the myograph at the wrist (Fig. 1*A*). Feedback of flexion torque was provided to the subject by an LED display. Subjects were encouraged verbally throughout all contractions.

Transcranial magnetic stimuli were delivered via a round coil (13-cm OD) over the vertex (stimulus intensities 75–100% output, Magstim 200, maximal output 2.0 Tesla). The coil was oriented to stimulate the left hemisphere preferentially. Stimulus intensity was adjusted for each subject so that a silent period of 180–200 ms followed the MEP in contracting muscles when subjects were instructed to regain maximal torque as fast as possible after the stimulus. For up to 100 ms after an MEP evoked by magnetic stimulation of the motor cortex, spinal motoneurons can show inhibition as a result of afferent input and recurrent inhibition. This inhibition can result in a period of EMG silence and must contribute to the initial part of the silent period after magnetic stimulation (13, 25). Thus, so that the duration of the silent period that we measured reflected intracortical inhibition of motor output and not an effect at a segmental level, we chose to elicit silent periods that lasted longer than any known inhibition at the motoneuron pool.

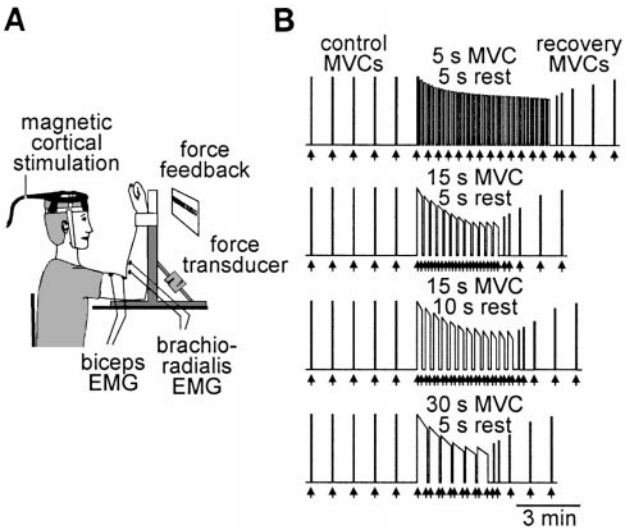


Fig. 1. *A*: experimental setup. Note that the schematic does not show that the axis of the myograph was aligned with the center of the elbow joint (see Ref. 1 for details). *B*: contraction protocols performed in 4 separate experiments. Each protocol comprises a total of 3 min of maximal voluntary contraction (MVC). Arrows represent magnetic cortical stimuli. Stimuli were given near the start and end of each 15-s and 30-s contraction. One stimulus was given during each third 5-s contraction. EMG, electromyogram.

*Protocol.* Each subject ($n$ = 9) took part in four sessions, each performed on a different day. In each session, subjects initially performed five brief (1- to 2-s) maximal voluntary isometric elbow flexions separated by rests of at least 1 min. A series of longer fatiguing MVCs followed. The duration of these MVCs and the intervals of rest between them varied between protocols, but each series included a total of at least 3 min of maximal effort (see Fig. 1*B*). The durations of contractions and rests were chosen to enable examination of the time course of the development and recovery of the changes in EMG responses to cortical stimulation. Previous studies showed that the MEP and silent period had altered after 15 s of continuous MVC and had recovered with 15 s of rest. The patterns used were 5-s MVC and 5-s rest (50% duty cycle) continuing for 7.5 min, 15-s MVC and 10-s rest (12 contractions, 60% duty cycle), 15-s MVC and 5-s rest (12 contractions, 75% duty cycle), and 30-s MVC and 5-s rest (6 contractions, 86% duty cycle). Finally, subjects performed a series of brief MVCs at 15 s, 30 s, and 1, 2, and 3 min after the series of fatiguing contractions. During each brief contraction, a single transcranial magnetic stimulus was given. In the 5-s MVC and 5-s rest series, stimuli were given every 30-s (in the middle of each third 5-s MVC). In the other series, stimuli were given ~2 s after the start and ~2 s before the end of each MVC. Stimulus intensity for each subject was constant in all sessions. When the stimulus was delivered during the contractions, an EMG "silence" followed the MEP, and, as a result, torque dropped. Subjects were instructed repeatedly to regain their maximal torque as fast as possible. EMG was recorded from biceps brachii and brachioradialis through surface electrodes (9-mm diameter Ag/AgCl electrodes fixed over the muscle belly and tendon). EMG signals were amplified (53 Hz to 1 kHz; Digitimer amplifier D150) and sampled with the torque signal at 5 kHz from 50 ms before to 500 ms after each stimulus. Data were recorded on disk for off-line analysis (1401 interface, Cambridge Electronic Design).

*Data analysis.* The increment in torque elicited by the magnetic cortical stimulus was calculated as the difference between the peak torque after the stimulus and the mean voluntary torque over the 50 ms preceding the stimulus (see Fig. 2*A*). To estimate the relative levels of voluntary drive, the torque increment was expressed as a percentage of the mean prestimulus torque. Because all contractions were MVCs, prestimulus torque was always an estimate of the ongoing maximal voluntary torque. Thus an increase in this percentage represents a decrease in voluntary activation and is termed central fatigue.

The area of MEPs was measured automatically between cursors that encompassed the potentials evoked by all stimuli in each experiment (see Fig. 2*B*). Peak-to-peak amplitude of each MEP was also measured. For each protocol for each subject, the area and amplitude of MEPs were normalized to the mean area and amplitude of the five MEPs evoked during brief control MVCs. The duration of the silent period was measured by cursor and was taken as the interval from the

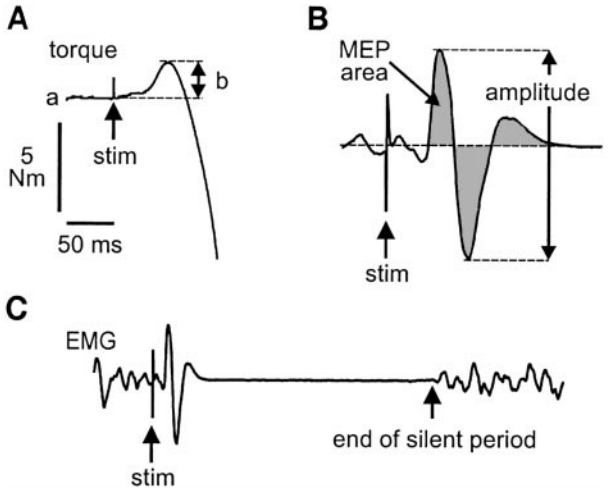


Fig. 2. Schematic representations of measurements of torque and EMG responses after a transcranial magnetic stimulus. Arrows on each trace point to the stimulus artifact. *A*: the torque trace shows the prestimulus level of ongoing maximal torque (*a*) and the increment (*b*) evoked by the stimulus. *B*: this EMG trace shows a motor evoked potential (MEP). The measured area of the MEP is shaded. Amplitude was measured peak to peak. *C*: EMG on a slower time base shows the MEP and subsequent silent period. The duration of the silent period was measured from the stimulus artifact to the return of EMG, as indicated by the arrow.

stimulus to the return of continuous EMG (see Fig. 2*C* and traces in Fig. 5).

Group data are expressed as means ± SD unless otherwise stated. For each contraction protocol, each data set (MEP area, silent period duration) was analyzed by use of a repeated-measures two-way ANOVA (factors: muscle and time). To compare data at the starts and ends of contractions, *t*-tests were performed on reduced data sets that excluded control and recovery data. Comparisons between contraction protocols were made by using one-way repeated-measures ANOVA. Differences between means were identified by post hoc testing (Student-Newman-Keuls). Significance was set at the 5% level.

## RESULTS

During series of intermittent isometric MVCs, maximal voluntary torque decreased, and the increment in torque evoked by cortical stimulation increased (Figs. 3 and 4). This increase in evoked torque demonstrates the development of central fatigue. The EMG responses to transcranial magnetic stimulation were also affected (Fig. 5). The silent period lengthened, and the MEP increased in size. These findings extend the observation of similar changes in 2-min sustained fatiguing contractions (10, 25). However, different contraction protocols dissociated changes in central fatigue and silent period duration and also dissociated changes in silent period duration and MEP size.

*Torque.* With duty cycles of 50, 60, 75, and 86%, all the tasks were fatiguing. By the end of the total of 3 min of contraction, maximal voluntary torque dropped to 60 ± 11.5% of its initial value in the 5-s MVC and 5-s rest (50% duty cycle) task and to ~40% in the other three protocols. Figure 4 shows that ~80% of the drop in torque occurred over the first half of each task. Over the last half of the protocols, torque showed some recovery over each period of rest so that torque measured near the beginning of each contraction was greater than that measured near the end of the previous contraction. More recovery occurred with 10-s rest between contractions [9.1 ± 8.9% (mean ± SD) of initial MVC; Fig. 4*B*] than with 5-s rest (Fig. 4, *C* and *D*; 6.0 ± 7.4% and 4.9 ± 10.9%; $P < 0.05$, one-way ANOVA and post hoc Student-Newman-Keuls). Over each final contraction, torque went from 59 ± 14.4% to 42 ± 15.5% of initial MVC during the 15-s MVC and 10-s rest task, but from 53 ± 6.4% to 42 ± 5.3% with 15-s MVC and 5-s rest and from 51 ± 6.2% to 40 ± 10.4% with 30-s MVC and 5-s rest. With 3 min of rest after the end of the fatiguing protocols, maximal voluntary torque recovered to 70 ± 10.7% (5-s MVC and 5-s rest), 72 ± 12.2% (15-s MVC and 10-s rest), 73 ± 9.6% (15-s MVC and 5-s rest), and 81 ± 8.7% (30-s MVC and 5-s rest) of its initial value.

When data for all subjects were pooled, voluntary activation decreased in all protocols. Figure 3 shows examples of torque increments evoked by cortical stimulation during the 60% duty cycle task in one subject. On average, during the brief control MVCs, the cortical stimulus evoked an increment of 1.4 ± 1.0% of the prestimulus torque. Although there was variability between subjects, this increment in prestimulus torque increased throughout each protocol (Fig. 4, □). On average, torque increments evoked over the last third of each task were larger than those evoked in the first third (*t*-tests; $P < 0.05$, 5-s MVC and 5-s rest; $P < 0.005$, 15-s MVC and 10-s rest; $P < 0.001$, 15-s MVC and 5-s rest; $P < 0.005$, 30-s MVC and 5-s rest). The mean increments observed in the last third of each

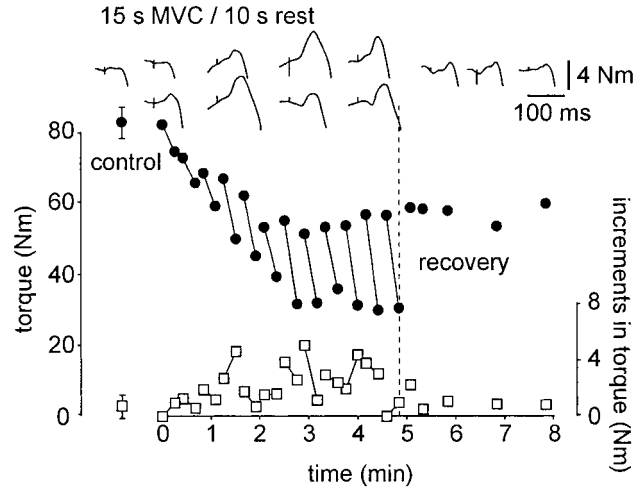


Fig. 3. Torque data from the 15-s MVC and 10-s rest protocol in one subject. At *top* are traces showing examples of the increments in elbow flexion torque that were elicited by cortical stimulation. The initial trace was recorded during a control MVC, the pairs of traces near the start and end of *contractions 1*, *4*, *8*, and *11* of the fatiguing series, and the final 3 traces at 1, 2 and 3 min into the recovery period. A stimulus artifact indicates the moment of stimulation on most traces. □, Right axis: increment in torque evoked by each stimulus. ●, Left axis: fall in ongoing maximal voluntary torque, with data from the start and end of each 15-s MVC joined by a line.

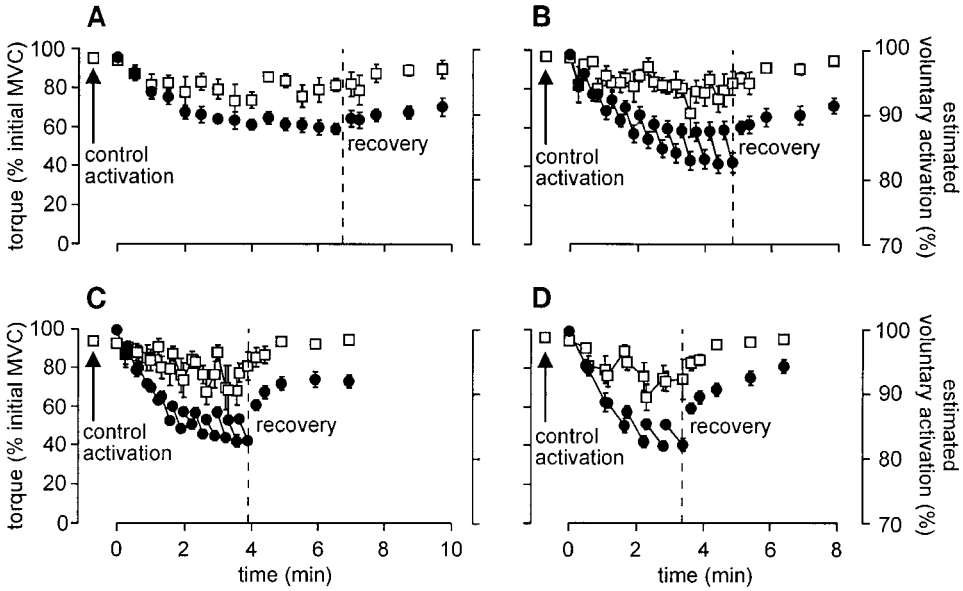


Fig. 4. Maximal voluntary torque and voluntary activation in each contraction protocol. Group data (means ± SE; $n = 9$) show the fall in maximal voluntary torque (●) in each fatiguing series of contractions. The protocol with the lowest duty cycle (5-s MVC and 5-s rest; *A*) shows maximal voluntary torque before delivery of the stimulus in every third contraction. In the protocols with 15-s MVC and 10-s rest (*B*), 15-s MVC and 5-s rest (*C*), and 30-s MVC and 5-s rest (*D*), 2 stimuli were given during each contraction, and the 2 torques recorded near the start and end of each contraction are joined with a line. The vertical dashed line marks the end of the fatiguing contractions in each protocol. The values for voluntary activation (□) can be read from the right-hand *y*-axis. The increment in torque evoked by a cortical stimulus has been expressed as a percentage of the maximal voluntary torque before the stimulus and has been subtracted from 100% to estimate voluntary activation.

protocol were 6.0 ± 4.3% of prestimulus torque in the 5-s MVC and 5-s rest protocol, 6.4 ± 6.4% in the 15-s MVC and 10-s rest protocol, 7.7 ± 6.8% in the 15-s MVC and 5-s rest protocol, and 8.5 ± 6.5% in the 30-s MVC and 5-s rest protocol. Voluntary activation was not more affected by any one of the contraction protocols. During the fatigue protocols, voluntary activation was lower than 80% in 2–3% of observations in each protocol. Cortical stimulation evoked some increments of more than 25% of ongoing torque in some subjects.

After the end of each fatiguing protocol, recovery of voluntary activation occurred over the first minute. Grouped data from all protocols showed that the increments in ongoing torque evoked by cortical stimulation remained significantly greater than in control trials after 15 and 30 s of the recovery period but had returned to control levels by 1 min. Consistent with this relatively slow recovery, voluntary activation was similar near the beginnings and ends of the intermittent contractions during each of the protocols (*t*-tests for each protocol, $P > 0.05$). Even rest intervals of 10 s did not allow significant recovery of activation (Figs. 3 and Fig. 4*B*).

*Silent period.* In control trials, the duration of the silent period did not vary significantly between different sessions. For biceps brachii, the mean duration for all subjects was 192 ± 26 ms and for brachioradialis 193 ± 29 ms. With all four fatiguing protocols, the duration of the silent period increased, although the extent and time course of the prolongation differed between protocols (Fig. 6). Data from brachioradialis are not shown but resembled those from biceps brachii. At the end of the fatiguing protocol after a total 3 min of contraction, the prolongation of the silent period varied between ~20 ms with the 50% duty cycle (5-s MVC and 5-s rest; biceps brachii, 21 ± 14 ms; brachioradialis, 18 ± 16 ms) and >75 ms with the 30-s MVC and 5-s rest protocol (biceps brachii, 75 ± 43 ms; brachioradialis, 83 ± 40 ms). Figure 6*A* shows the change in the silent period in the 5-s MVC and 5-s rest protocol. A single stimulus was delivered during each contraction, and there was a small, gradual increase in duration of the silent period over the 6 min of the protocol. In the other protocols, which involved 15-s or 30-s MVCs, two stimuli were delivered during each contraction so that a silent period near the beginning and end of each MVC could be observed.

Figure 6*B* shows changes in the duration of the silent period in the 15-s MVC and 10-s rest series (60% duty cycle). In both biceps brachii and brachioradialis, the duration of the silent period increased with each 15-s contraction but recovered to close to control duration with each 10-s interval of rest. The duration of the silent period at the start of each MVC did not change significantly throughout the protocol, but the duration at the end of the MVCs increased through the first 2 min of contraction (the initial 8 MVCs). This increase in duration of the silent period was significant by the end of the second MVC.

In the 15-s MVC and 5-s protocol (75% duty cycle), the silent period again increased in duration in both elbow flexor muscles during each MVC and showed

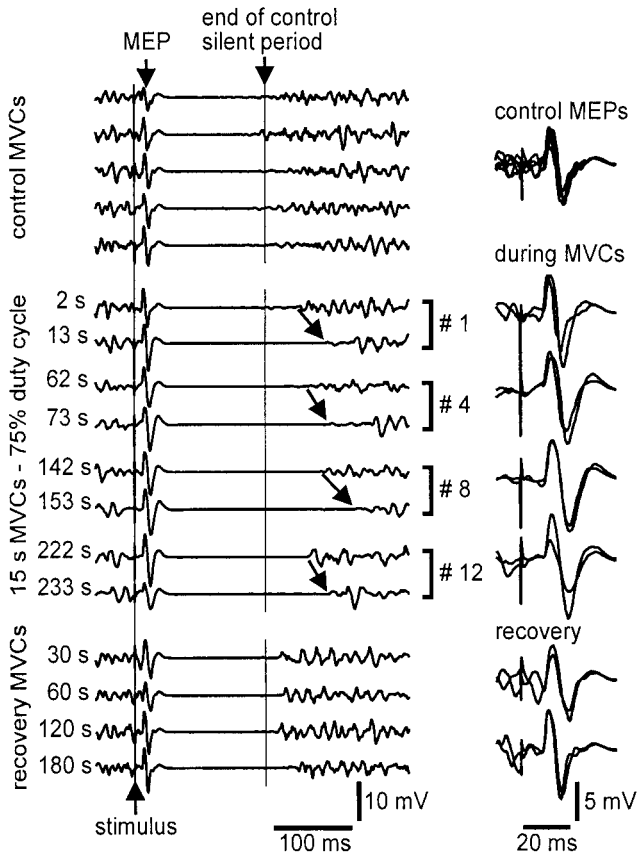


Fig. 5. EMG traces from biceps brachii in a single subject in one protocol (15-s MVC and 5-s rest). *Left*: traces recorded over 400 ms. Five traces at *top* were recorded during brief control MVCs. The magnetic cortical stimulus (left vertical line) is followed by a short-latency excitatory response (i.e., MEP) and then a period of EMG silence (silent period) before voluntary EMG resumes. The right-hand vertical line marks the mean duration of the silent period in the 5 control trials. The next group of 8 traces was recorded during the 1st, 4th, 8th, and 12th contractions in the series of 12 fatiguing 15-s MVCs. Each pair of traces was recorded near the start and end of a contraction. The silent period increases in duration during each MVC and recovers partially during 5-s rest. Four traces at *bottom* were recorded during brief MVCs in the recovery period. The MEPs from all the traces are shown expanded on the right side of the figure. MEPs during the fatiguing MVCs are larger than during the brief control or recovery MVCs.

some recovery toward control duration with rest. Figure 5 shows this prolongation and recovery in single traces recorded from biceps brachii in one subject. At the beginning of each contraction, the silent period is shorter than at the end of the preceding MVC, but the 5-s intervals of rest are insufficient to allow complete recovery (Fig. 6*C*). The silent periods at the beginning of the MVCs increased significantly in duration by the fifth MVC, whereas the silent periods elicited near the end of each MVC were prolonged significantly from the initial contraction and continued to increase in duration over the ensuing 3 MVCs (~1 min total MVC).

Finally, during the 30-s MVC and 5-s rest protocol (86% duty cycle, Fig. 6*D*), the silent period showed a similar pattern of change. It was significantly prolonged by the end of the second MVC and did not lengthen further after the third MVC. The duration of the silent period recovered partially during each 5-s rest but was significantly increased by the beginning of the fourth MVC. In all of the protocols, the silent period had returned to control length when tested during a brief MVC at 15 s after the end of the fatiguing contractions.

*MEP.* The MEP increased in area in all contraction protocols (Fig. 7; see also Fig. 5). The growth of the MEP did not differ significantly between the different protocols, with a maximal mean growth in biceps of 56 ± 36% with 5-s MVC and 5-s rest, 76 ± 46% with 15-s MVC and 10-s rest, 72 ± 68% with 15-s MVC and 5-s rest, and 78 ± 45% with 30-s MVC and 5-s rest. Similar growth was seen in brachioradialis (56 ± 28%, 63 ± 56%, 76 ± 46%, and 65 ± 39%, respectively). Like its area, the amplitude of the MEP also increased in all protocols. However, the extent of this increase was about half that of the increase in area and was less consistent.

In all contraction protocols, MEPs behaved similarly in biceps brachii and brachioradialis. Data from biceps brachii are illustrated. In the 5-s MVC and 5-s rest protocol (Fig. 7*A*), the MEPs grew quickly in contrast to the gradual prolongation of the silent period. The MEPs increased in area by the fourth 5-s contraction and then grew no further. In the 15-s MVC and 10-s rest protocol, the MEPs grew during the first contraction (Fig. 7*B*). During the 10-s rest periods, the MEPs tended to decrease in size so that, overall, MEPs evoked near the starts of the contractions were smaller than those evoked at the ends (*t*-test, $P < 0.001$). That is, the MEPs showed some recovery during each 10-s rest. With the 15-s MVC and 5-s rest protocol, shown in Fig. 7*C* (see also Fig. 5), MEPs were not different in size at the start and end of each contraction but grew at the beginning of the fatiguing protocol and remained large until the recovery period. The 5-s rest was not long enough to allow significant recovery. A similar pattern of increase in the size of the MEP occurred with the 30-s MVC and 5-s rest protocol (Fig. 7*D*). In all of the contraction protocols, the MEP had recovered to its control size when elicited during a brief MVC 15-s after the end of the fatiguing contractions.

## DISCUSSION

*Failure of voluntary activation and development of central fatigue.* As maximal voluntary torque fell in each contraction protocol, increments in elbow flexor torque were elicited by transcranial magnetic stimulation. Subjects became unable to activate the elbow flexor muscles fully with continuing maximal voluntary efforts. The increments in torque were larger than during brief control contractions and increased relative to ongoing maximal torque with the total time of contraction. This progressive failure of voluntary activation demonstrated central fatigue during each of the contraction protocols. Furthermore, suboptimal output from the motor cortex contributed to the failure of voluntary activation. To evoke extra force from the muscle, stimulation of the motor cortex elicited extra

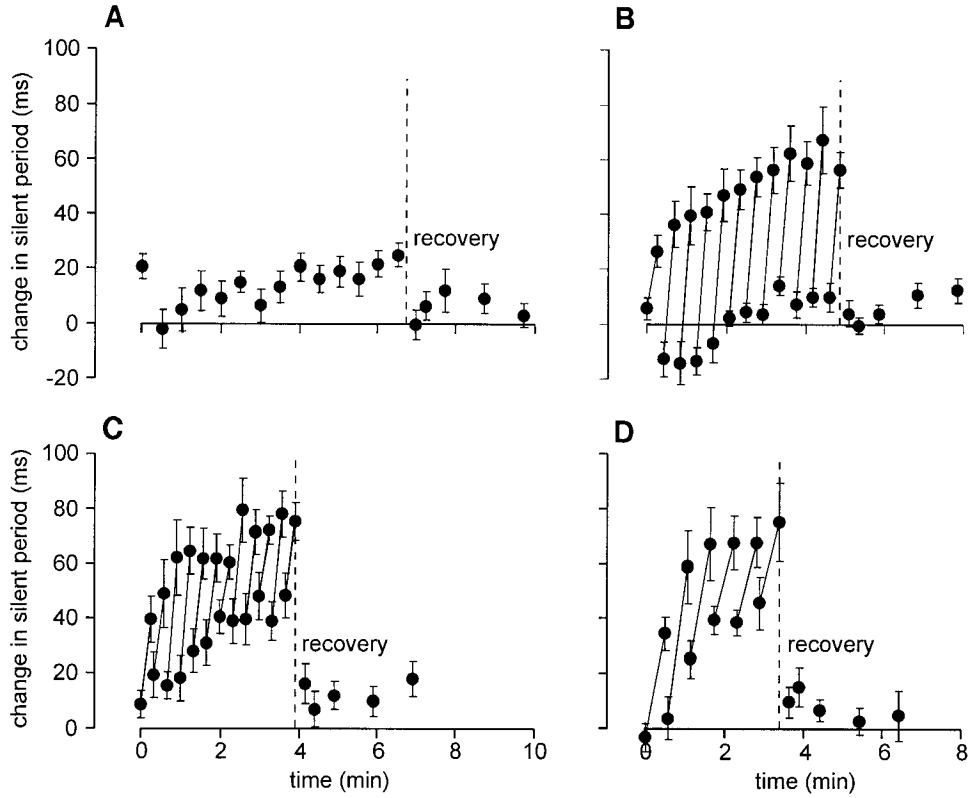


Fig. 6. Change in the duration of the silent period in the 4 protocols. Group data (means ± SE; $n = 9$) for biceps brachii (●) are shown for each of the four contraction protocols. With the 5-s MVC and 5-s rest protocol (*A*), the duty cycle is lowest (50%), and the silent period is not prolonged much over control duration. With 15-s MVC and 10-s rest (*B*), the silent period duration increases during each contraction, with almost complete recovery during 10-s rest. In 15-s MVC and 5-s rest (C) and 30-s MVC and 5-s rest (*D*), both tasks show partial recovery of the silent period with 5-s rest. Data for the start and end of contractions are joined by lines.

output from the cortex, and this extra output recruited additional motoneurons. This implies that maximal voluntary effort did not generate maximal descending drive and that the descending drive that it did generate was insufficient to activate the motoneuron pool optimally. Thus the central fatigue demonstrated here did not occur because the motoneurons were impossible to activate but occurred at a supraspinal level.

Central fatigue, as tested by cortical stimulation, was similar in all the exercise protocols (50–86% duty cycle), even though overall fatigue, shown by the drop in maximal voluntary torque, was less with the lowest duty cycle. A similar progressive failure of motor cortical output to optimally drive motoneurons also occurs during sustained MVCs (10). The increment in torque at the end of a sustained 2-min MVC of the elbow

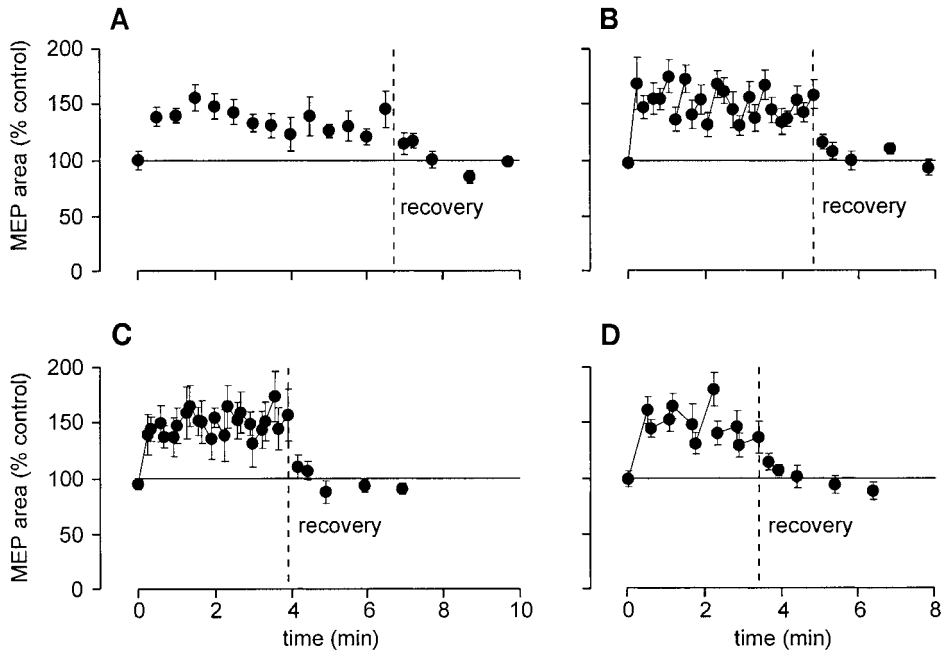


Fig. 7. Change in the area of the MEP in the 4 protocols. Group data (means ± SE; $n = 9$) for biceps brachii (●) are shown for each of the 4 contraction protocols. The area of the MEP is normalized for each protocol in each subject to the mean area of the MEPs elicited during brief control MVCs. MEPs in biceps brachii and brachioradialis (not shown) behave similarly. In each protocol, the MEPs become larger than their control size. *A*: 5-s MVC and 5-s rest; *B*: 15-s MVC and 10-s rest; *C*: 15-s MVC and 5-s rest; *D*: 30-s MVC and 5-s rest.

flexors was 9.8 ± 8.3%. This is not different from the mean increments between 5.2 ± 6.0% and 7.9 ± 3.8% seen at the end of the first 2 min of contraction in the intermittent protocols. Although we failed to demonstrate differences in supraspinal fatigue with the protocols in the present study, such differences might become apparent in exercise of longer duration or with submaximal contractions. However, no differences in central fatigue were found in exercise that consisted of intermittent maximal contractions at low-to-medium duty cycles (5–50%; 20).

Although increments in torque elicited by magnetic cortical stimulation during a maximal effort reflect failure of voluntary activation, it is not possible to compare these quantitatively with the measurements of voluntary activation [derived by comparing the twitch resulting from supramaximal stimulation of a muscle nerve during a maximal effort with that evoked in the relaxed muscle ("twitch interpolation"; e.g., Refs. 1, 2, 3)]. There are a number of problems associated with cortical stimulation used to measure central fatigue. *1*) The twitch in the relaxed muscle cannot be used as a control. Cortical stimuli do not evoke maximal twitches in the relaxed muscle, and the changes in cortical and spinal motoneuron excitability during a voluntary contraction mean that, for any submaximal stimulus, more motor units are recruited during contraction than during relaxation (12, 26, 29). The evoked increment in torque can be normalized to the ongoing maximal voluntary torque to account for fatigue in the muscle fiber, but this is not ideal (see Ref. 10). *2*) Even during a strong voluntary contraction, the cortical stimulus may not recruit all motor units and thus may underestimate failure of voluntary activation. *3*) The cortical stimulus does not recruit only the corticospinal neurons and motoneurons that activate the muscles of interest. The stimulus can evoke twitches in many muscles, including antagonists to the action being investigated (11). Thus, at some joints, the twitch of the antagonists can "counteract" that of the agonists, especially after the agonists are fatigued. Again, central fatigue will be underestimated. Hence, an increment in torque evoked by magnetic cortical stimulation during a maximal effort reveals suboptimal voluntary activation, but lack of an increment in torque is not a reliable indicator of complete activation. Magnetic cortical stimulation most reliably shows suboptimal activation when the target muscle group is stronger and more easily activated than its antagonists. At the elbow, the flexors are nearly twice as strong as the extensors (6) and have a stronger short-latency facilitatory response to magnetic stimulation (23).

*Fatigue and changes in EMG responses to transcranial magnetic stimulation.* Changes in the EMG responses to transcranial magnetic stimulation occur with fatiguing intermittent contractions as previously shown for sustained voluntary contractions. The silent period is prolonged, and the MEP grows in size. However, the different exercise protocols demonstrate that the development and the recovery of the changes in the inhibitory and excitatory responses have different time courses. The increase in size of the MEP occurs more quickly and recovers more slowly than the prolongation of the silent period. As a consequence, the changes in silent period duration were quite different in the different contraction protocols, whereas the MEP grew similarly in each protocol.

The silent period is a period of EMG silence that immediately follows the excitatory response to magnetic cortical stimulation. Initially, there is a decrease in excitability of spinal motoneurons (shown by a decreased H-reflex), but this recovers after ~100 ms (8, 28). The continued inhibition of voluntary EMG after recovery of motoneurons is attributed to inhibition of corticospinal neurons within the cortex (13, 22, 24). Long-lasting inhibitory postsynaptic potentials (IPSPs) can be evoked in pyramidal neurons by electrical stimulation of the cortex (14, 15), and this is likely to involve GABAergic interneurons (22).

The duration of the silent period increases with the intensity of the magnetic stimulus and decreases with the voluntary effort that the subject exerts to regain torque output after the stimulus (5, 30). The duration of the silent period may reflect a balance between excitatory and inhibitory inputs to the output neurons of the motor cortex. With fatiguing contractions, the silent period lengthens when the subject's effort becomes near maximal. Either the magnetic stimulus becomes more effective at generating IPSPs, or the subject's voluntary drive to the motor cortex decreases. The behavior of the silent period in the different protocols in this study demonstrates an effect that builds up over 30–45 s of continuous maximal effort, that starts to recover quickly, and that approaches complete recovery after a 10-s rest. The very slow lengthening of the silent period with repeated 5-s MVCs separated by 5-s rest periods indicates that whatever change underlies the prolongation of the silent period starts to occur within a 5-s MVC, even though the silent period itself is not yet detectably prolonged. Furthermore, in each protocol, the effect is cumulative if additional exercise is undertaken before complete recovery.

The change in the silent period was not inevitably associated with central fatigue. In the 50% duty cycle task, the increments in torque elicited by the cortical stimuli increased although the prolongation of the silent period was small, and, after the end of each fatiguing protocol, when silent-period duration recovered in 15 s, subjects continued to be unable to activate the motor cortex optimally. These instances of dissociation of the ability to drive the motor cortex and the lengthening of the silent period confirm that the suboptimal drive to the motoneurons from the motor cortex is not due to the motor cortical changes represented by the prolongation of the silent period. Furthermore, the observation that the silent period is not necessarily increased in duration when the motor cortex is activated suboptimally suggests that the fatigue-induced prolongation of the silent period is not due to inadequate drive to the motor cortex.

The size of the short-latency excitatory response to transcranial magnetic stimulation (i.e., MEP) depends

on the descending volleys evoked from the cortex, on the response of the motoneuron pool to the volleys, and on the individual muscle fiber action potentials. Hence, change in the excitability of the motor cortex or of the motoneuron pool or any change in the muscle fiber action potential can alter the size of the MEP. In a sustained MVC of the elbow flexors, the MEP grows in size. This results, in part, from an increase in size of the muscle fiber action potentials due to hyperpolarization of the muscle fiber membrane by increased activation of the electrogenic $Na^+/K^+$ pump (7). Other factors, including changes in pH and temperature, might also act in the muscle to change the size of the muscle action potential, but their overall effect is difficult to predict. However, on the basis of studies using supramaximal stimulation of the brachial plexus, some of the increase in size of the MEP cannot be accounted for by changes in the periphery and is probably due to increased net excitatory output evoked from the motor cortex by the magnetic stimulus (27). In the present study, the MEP grew similarly during all intermittent MVC protocols. Overall, it increased more quickly than the duration of the silent period and recovered more slowly. However, recovery of the MEP occurred more quickly than recovery of voluntary activation. The MEP recovered partially in 10 s and fully in 15 s, whereas voluntary activation did not recover with 10-s rest and took ~1 min to recover. Thus the increased increment in torque elicited by cortical stimulation near the end of the fatiguing protocols does not depend solely on the greater recruitment of motor units that might be represented by the larger MEP. A failure of voluntary activation remained despite reduction of the MEP to its control size.

The seemingly parallel changes in the size of the MEP and duration of the silent period during sustained MVCs has led to the suggestion that a common source may facilitate both excitatory and inhibitory elements within the cortex (18). In the present study, different time courses for the development of the growth of the MEP and prolongation of the silent period were clear in the lowest duty cycle task. Furthermore, the silent period recovered fully with 10-s rest, but the MEP did not. These differences argue against a common source for the changes.

*Change in evoked EMG responses and central fatigue.* Recovery of voluntary activation occurred more slowly than recovery of the silent period or the MEP but faster than recovery from muscle fatigue. Whereas the EMG responses to cortical stimulation recovered in 15-s or less, the elicited increments in torque returned to control levels over 1 min, and maximal voluntary torque recovered to only 70–80% of control levels with 3-min rest. The temporal disparity between recovery of the EMG changes and recovery from central fatigue is consistent with our previous study of sustained MVCs. In that study, descending drive from the motor cortex remained suboptimal if the fatigued muscle was held ischemic at the end of the contraction (10). During this maintained ischemia, the silent period and MEP recovered fully. This suggests that neural signals related to the fatigued state of the muscle contributed to central fatigue but that this fatigue was somehow "upstream" of the motor cortex.

In summary, the current study demonstrates a supraspinal component to the central fatigue produced by a series of intermittent MVCs. The loss of voluntary torque represented by this central fatigue is on average ~7% but can be substantial (>25% of ongoing maximal voluntary torque) in individual trials in individual subjects. Changes in the EMG responses to transcranial magnetic stimulation resemble those seen during sustained MVCs and demonstrate net changes in the motor pathway from the motor cortex to the muscle fiber. However, the changes demonstrated by these altered EMG responses cannot fully account for the failure of voluntary activation.

We thank Dr. Brenda Bigland-Ritchie for reading the manuscript.

This work was supported by the National Health and Medical Research Council of Australia.

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