Vertex transcranial magnetic stimulation (TMS) elicited tibialis anterior motor evoked potentials (MEPs) and silent periods (SPs) that were recorded during and following isometric maximal volitional contraction (MVC). During MVC in 6 healthy subjects, MEP amplitudes in the exercised muscle showed an increasing trend from an initial value of 4539 ± 809 μV (mean ± SE) to 550 ± 908 μV ($P < 0.13$) while force and EMG decreased ($P < 0.01$). Also, SP duration increased from 165 ± 37 ms to 231 ± 32 ms ($P < 0.01$). Thus, during a fatiguing MVC both excitatory and inhibitory TMS-induced responses increased. TMS delivered during repeated brief 10% MVC contractions before and after a fatiguing MVC in 5 subjects, showed no change in MEP amplitude but SP duration was prolonged after MVC. This SP prolongation was focal to the exercised muscle. Silent periods recorded after pyramidal tract stimulation were unchanged following the MVC. These results suggest that MEP and SP might have common sources of facilitation during an MVC and that inhibitory mechanisms remain focally augmented following a fatiguing MVC. © 1996 John Wiley & Sons, Inc.
Key words: MEP • silent period • motor cortex • transcranial magnetic stimulation • fatigue

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EFFECT OF FATIGUING MAXIMAL VOLUNTARY CONTRACTION ON EXCITATORY AND INHIBITORY RESPONSES ELICITED BY TRANSCRANIAL MAGNETIC MOTOR CORTEX STIMULATION

W. BARRY McKAY, BS, DOBRIVOJE S. STOKIC, MD, ARTHUR M. SHERWOOD, PhD, GERTA VRBOVA, MD, and MILAN R. DIMITRIJEVIC, MD, DSc

Transcranial electrical stimulation (TES), introduced by Merton and Morton in 1980,[32] provided a technique for external excitation of the motor cortex in intact human subjects. In 1985, Barker et al.[2] reported a more comfortable, although less focal method, for depolarizing cortical cells using transcranial magnetic stimulation (TMS). Transcranial stimulation of the motor cortex is reported to excite pyramidal cells directly or indirectly through intracortical connections to elicit corticospinally mediated motor evoked potentials (MEPs).[1,9] It is well known that MEP amplitudes are dependent upon the level of volitional activation that exists prior to stimulus delivery.[3,22] When TES was applied during sustained maximal voluntary contraction (MVC), Merton et al.[21] reported that MEP amplitudes remained unchanged throughout the contraction, even though muscle power declined progressively. However, when voluntary effort has ended, the amplitudes of TMS-induced MEPs recorded in relaxation have been shown to decrease to below pre-exercise values.[5,6,29] This depression was also found to persist for a relatively long time after exercise, up to 20 min.[30]

Transcranial motor cortex stimulation also induces a silent period (SP) when delivered during a voluntary contraction.[23,28,32] This SP can be elicited at lower TMS intensity than the MEP[47] and it increases in duration with increasing stimulus strength.[46] The early portion of the SP can be explained by segmental

From the Baylor College of Medicine, Restorative Neurology and Human Neurobiology, Houston, Texas (Mr. McKay, Drs. Stokic, Sherwood, and Dimitrijevic); and University College London, Department of Anatomy and Developmental Biology, London, UK (Dr. Vrbova).

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Address reprint requests to W. Barry McKay, BS, Baylor College of Medicine, Division of Restorative Neurology and Human Neurobiology, One Baylor Plaza, S809, Houston, TX 77030.

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mechanisms, but the remainder of the SP is thought to be of intracortical origin.[8,15,24,40,41,43,45,46]

In a previous study of voluntary activation of ipsi- and contralateral muscle groups during MVC, we showed that with increasing effort to maintain an isolated contraction of ankle dorsiflexors, a consistent pattern of muscle coactivation develops, probably spread via cortical and spinal connectivity.[12] This spread of excitation would suggest that, during a fatiguing motor task, in the attempt to maintain a target force, supraspinal excitatory drive does not decrease but probably increases. Therefore, in the current study, we used TMS of the motor cortex to elicit MEP responses and to measure changes in motor cortex excitability brought about by an MVC. Also, we measured TMS-induced silent periods to monitor the effects of MVC on inhibitory activity. Further, we stimulated descending spinal tracts at the level of the pyramidal decussation and the peripheral nerve to determine to what extent segmental mechanisms play a role in modifying TMS-induced excitatory and inhibitory responses.

MATERIALS AND METHODS

Eight healthy subjects were studied under two paradigms after having given informed consent. First, TMS test stimuli were delivered over the motor cortex during an MVC. Second, TMS was delivered, in separate sessions, during low level volitional contractions of ankle dorsiflexor muscles before and after an MVC. In both paradigms, subjects were seated upright in a specially constructed chair equipped with transducers to measure isometric dorsiflexion forces.[12] Surface EMG electrodes were placed 3 cm apart, oriented parallel to the long axis of the muscle, and centered over the muscle bellies of both tibialis anterior muscles. EMG signals were amplified with a gain of 5000, a filter bandpass of 30–1000 Hz, digitized at 2000 samples per second with a 12-bit resolution, and stored for computer-assisted analysis of MEP latency, amplitude, and duration along with the duration of the silent periods. A Novametrix Magstim 200 with research grade dual cone coil (9.6-cm diameter, type 9902) was used for TMS. The coil was held by the examiner and centered over the scalp vertex. Current flow through the coils was clockwise over the left hemisphere and counterclockwise over the right. Peroneal nerve stimulation was delivered percutaneously through a bipolar probe placed over the nerve at the fibular head with an intensity that elicited, in relaxation, a supramaximal M-wave from the tibialis anterior muscle to be exercised.

For both paradigms, the average amplitude of integrated EMG and its median frequency (30–500 Hz) were measured during the 500 ms immediately prior to TMS delivery. The duration of the SP was measured from the onset latency of the MEP, determined in relaxation, to the return of recognizable EMG activity.[40,47] Peak amplitudes were used for MEP and M-wave measurements. Net twitch forces produced by peroneal nerve stimulation were measured as an increase from the prestimulus force during the MVC. One- and two-way repeated measures analyses of variance (ANOVA) were used to evaluate the data, and a probability level of $P < 0.05$ was considered significant.

Paradigm 1—MEP and SP Changes during Sustained MVC. In 6 healthy male subjects, ranging in age from 28 to 49 years, TMS beginning 2 s after the onset of MVC was repeated at 15-s intervals while MVC of right ankle dorsiflexor muscles was maintained for 2 min (eight stimuli). Initial force developed by the MVC, 440.3 ± 50.8 N (mean ± SE), decreased within 87 ± 9 s to 50%, and by the end of 2 min it measured 186.7 ± 10.6 N. Thresholds for MEP elicitation at rest were between 40% and 50% of stimulator output. TMS stimulus strength of 80% of stimulator output was empirically determined to elicit MEPs that could be easily differentiated from background EMG during the MVC. EMG in the contralateral tibialis anterior muscle was monitored to detect coactivation.

Fatiguing MVC Effects on Motor Cortex Excitability. TMS-induced SPs were measured following all eight test stimuli in the exercised tibialis anterior (ExTA) and in the nonexercised, contralateral tibialis anterior (CTA) after it was coactivated which occurred for test stimuli 4 through 8 in 5 of the 6 subjects. Supramaximal peroneal nerve stimulation (48–85 mA) was delivered 5 s after each TMS.

Paradigm II—MEP and SP Changes Following MVC. Five healthy subjects, 4 male and 1 female, ranging in age from 28 to 62 years, were studied to assess the effect of MVC on TMS-induced MEPs and silent periods during low level voluntary contractions. TMS strength was adjusted to 10% of stimulator output above the threshold for MEP (45–55% of stimulator output) in relaxed tibialis anterior muscles. Transcranial stimuli were delivered during brief, 5-s-long, volitional contractions at 10% of MVC force and were repeated every 15 s for 5 min before and after a fatiguing MVC. In this group of subjects, force declined from 476 ± 17 N to 194 ± 7 N in 62.8 ± 7.1 s. Three subjects performed 10% MVC contractions of ankle dorsiflexors bilaterally but only the right performed the fatiguing MVC. The subjects

were provided with dorsiflexion force feedback displayed on an oscilloscope before and after but not during the fatiguing MVC. In separate sessions, in 2 of the 5 subjects, TMS was replaced with supramaximal peroneal nerve stimulation that elicited mixed nerve silent periods in the exercised TA. Further recordings, in these same 2 subjects, consisted of electrical stimulation delivered over the mastoid bones to activate the axons of the pyramidal tract at the level of the pyramidal decussation[44] using 100-μs pulses at 300–375 mA. These stimuli were alternated with TMS delivered at 10% above threshold for MEP. As indicated previously, stimuli were delivered every 15 s during brief 10% MVCs for 5 min before and after the fatiguing MVC.

RESULTS

Paradigm I—MEP and SP Changes during Sustained MVC. In the 6 subjects studied, MVC of the right ankle dorsiflexor muscles occurred with the peak force and a short plateau lasting a few seconds followed by a long-lasting progressive decline in force. During these 2 min of MVC, as force decreased by approximately 60%, average EMG amplitude decreased from 371 ± 48 μV to 185 ± 21 μV ($P < 0.01$) in the ExTA muscle (Fig. 1). The average median frequency of the ExTA EMG decreased from 107 ± 10 Hz to 88 ± 11 Hz ($P < 0.01$). ExTA M-wave mean peak amplitudes were not significantly different, beginning at 4903 ± 724 μV and ending at 6032 ± 768 μV. ExTA M-wave net twitch forces remained unchanged throughout the MVC, beginning at 21.5 ± 1.5 N and ending at 17.1 ± 5.3 N.

Prior to the unilateral MVC, mean MEP amplitudes recorded in relaxation from both tibialis anterior muscles were rather asymmetrical (1785 ± 263 μV in the right and 1935 ± 217 μV in the left). Throughout the course of the MVC, mean peak MEP amplitudes in the ExTA appeared to increase from 4539 ± 809 μV (initial test stimulus) to 5501 ± 908 μV (eighth test stimulus) but this increase did not reach statistical significance (ANOVA $P < 0.13$) (Fig. 1). MEP durations in the ExTA were prolonged by an average of 11.5 ms (from 46.8 ± 3.1 ms to 58.3 ± 3.5 ms) during the MVC ($P < 0.01$). MEPs recorded simultaneously in the nonexercised contralateral tibialis anterior muscle were lower in amplitude than those in the ExTA during MVC. CTA MEP amplitudes rose from 2552 ± 384 μV to 3934 ± 226 μV during the ExTA MVC, an increase that was statistically significant ($P < 0.01$). To summarize, while ExTA EMG amplitude, frequency composition, and force of MVC decreased, M-wave amplitude and twitch force were unchanged. MEP amplitude recorded from the same muscle showed an increasing trend growing by approximately 20% by the end of the MVC. Moreover, CTA MEP amplitudes increased significantly, beginning well before the onset of EMG activity.

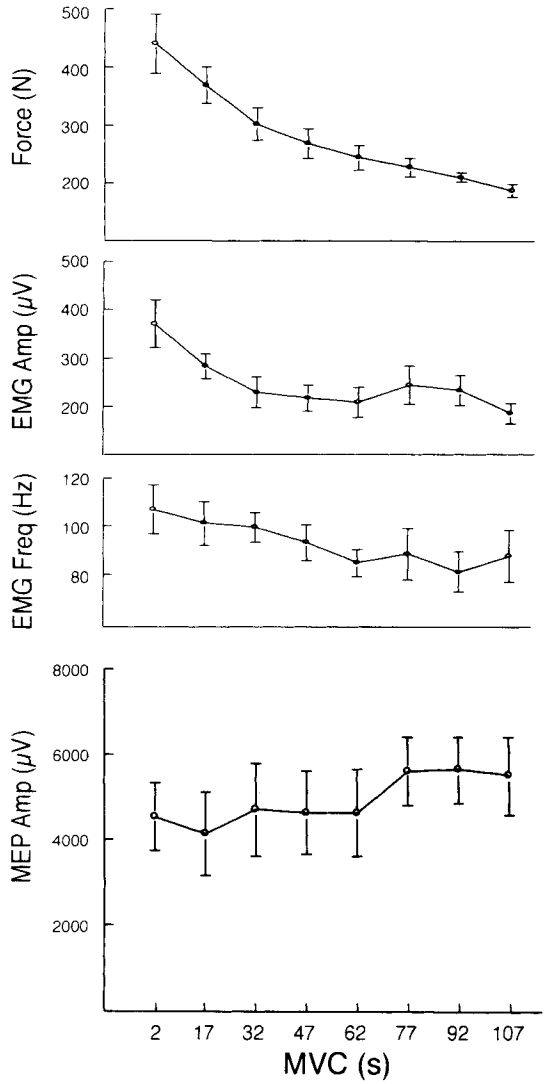

FIGURE 1. Tibialis anterior, group mean (± SE) force, EMG amplitude and median frequency, transcranial magnetic stimulation (TMS)-induced motor evoked potentials (MEPs) measured at 15-s intervals during maximal voluntary contraction ($n = 6$). Although the MEP amplitude increase was not statistically significant ($P < 0.13$), it occurred while dorsiflexion force and average EMG amplitude and frequency decreased ($P < 0.01$).

In addition to the MEPs, TMS-induced silent periods were clearly present in the ExTA. SP durations progressively increased by about 21% throughout the exercise period, from 165 ± 37 ms to 231 ± 32 ms ($P < 0.01$) (Fig. 2). ExTA mixed nerve silent periods following supramaximal peroneal stimuli were unrecognizable throughout the MVC. As ExTA MVC con-

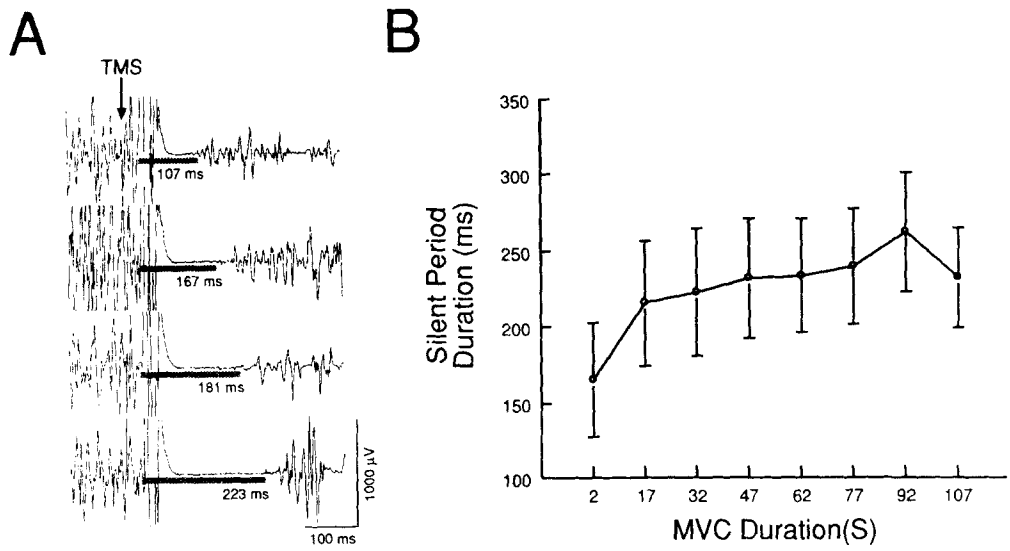

FIGURE 2. (A) TMS-induced silent periods recorded from the tibialis anterior of a representative subject illustrates the steady increase for the first four of eight trials recorded at 15-s intervals during an MVC. **(B)** Group mean (n = 6) silent period duration increase during 2 min of MVC.

tinued, the CTA muscle began to coactivate in 5 of the 6 subjects by the fourth test stimulus. This coactivation of the CTA provided sufficient background activity to measure the SP which progressively increased for the last five test stimuli, from 143 ± 13 ms in the fourth test stimulus to 165 ± 24 ms in the eighth test stimulus ($P < 0.08$). Interestingly, SP prolongation occurred in a similar rate in the two muscles. Therefore, ExTA and CTA TMS-induced SP durations, although of different lengths in the two muscles, increased in parallel for the last five test stimuli.

Paradigm II—MEP and SP Changes following MVC. All 5 subjects were able to produce brief isometric dorsiflexion contractions at 10% of MVC force for the series of 20 test stimuli preceding and following the fatiguing unilateral MVC. There was no change in average EMG amplitude or median frequency within these contractions. TMS delivered during these brief contractions, elicited MEPs in the ExTA with mean peak amplitudes that were similar before (2140 ± 85 μV) and after (2270 ± 83 μV) the fatiguing MVC. However, mean SP duration in the exercised muscle increased by 30%, from 134.7 ± 15.3 ms before MVC, to 168.6 ± 13.2 ms afterwards ($P < 0.05$) (Fig. 3).

In 3 of these 5 subjects, the 10% of MVC test series were performed simultaneously by both tibialis anterior muscles but the exercise MVC was carried out only on the right. The ExTA mean SP duration increased from 135.8 ± 3.6 ms to 183.1 ± 4.6 ms ($P < 0.01$). The mean SP duration in the CTA remained unchanged (134.7 ± 4.7 ms before, 134.9 ± 6.1 ms after ExTA MVC). There was no change during the 10% MVC test series in CTA MEP mean peak amplitudes which were 1420 ± 80 μV before ExTA MVC and 1435 ± 103 μV after MVC. This shows that prolongation of the TMS-induced silent period is present after cessation of the MVC but only in the exercised muscle with no change in the MEP.

Stimulation of the long descending tracts at the pyramidal decussation elicited silent periods, in 2 subjects, that were unchanged after MVC (55.8 ± 9.2 ms before MVC and after MVC of 48.9 ± 8.0 ms). During these same trials, TMS was alternated with long tract stimulation, inducing silent periods that increased significantly, from 151.4 ± 17.7 ms 182.0 ± 17.0 ms following MVC ($P < 0.05$). Electrical stimulation of the peroneal nerve in 2 subjects elicited mixed nerve silent periods, measured from stimulus to return of EMG activity, that were 113.6 ± 1.6 ms and 121.9 ± 2.0 ms before MVC and 117.6 ± 1.2 ms and 128.3 ms ± 3.1 ms, after MVC, respectively. The difference was not statistically significant.

DISCUSSION

In the present study, EMG amplitude and force output decreased significantly during 2 min of MVC (Fig. 1). M-wave responses in paradigm I showed no changes in amplitude or duration as a result of the MVC. Milner-Brown and Miller[34] showed that ankle dorsiflexors were less fatigable than other muscles and that muscle fiber membrane excitability was unchanged following MVCs of up to 2 min.[35] Our find-

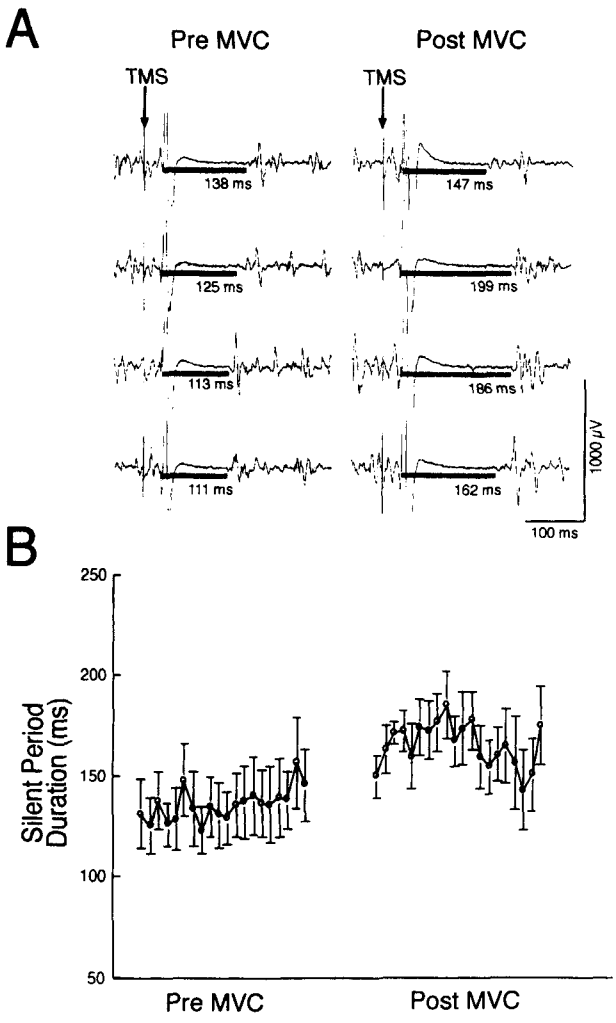

FIGURE 3. (A) Example of TMS-induced tibialis anterior silent periods recorded during brief 10% MVC contractions at 15-s intervals, the last four consecutive trials prior to (left) and the first four consecutive trials after MVC (right). **(B)** Mean silent period duration for 20 trials (5 min) before and after MVC ($n = 5$). Note the increased silent period duration post-MVC ($P < 0.01$).

ings support their observation and suggest that transmission of an action potential down the motor axon, through the motor endplate and along the muscle membrane, is not compromised under the recording conditions reported here. Therefore, such a reduction in force likely results from failures of excitation—contraction coupling, contractile mechanics, metabolic capacity, and a reduction of motor unit firing. It has been postulated that the reduction of spinal motor neuron activation that occurs during MVC is the result of reflex disfacilitation and active reflex inhibition.[4,18,19,21,26] More direct evidence has been provided by Macefield et al.[27] who, using microneurographic recording, monitored motor unit firing rates before and after anesthetic block of tibialis anterior muscle afferents. They showed that, during a sustained MVC, a decrease in firing rate such as occurs in a normally innervated muscle is absent as a result of this acute deafferentation. However, they stated that a decline in motor neuron firing rate within the first 30 s of MVC may reflect a decrease in the volitional drive, one which subjects could overcome by increasing their effort as described by Gandevia et al.[17] in a 1993 report.

The amplitude of MEPs in the ExTA tended to increase and those in the nonexercised CTA significantly increased, indicating that the excitability of the corticospinal system increases as, presumably, does its excitatory influence on spinal motor structures. Merton et al.[31] reported similar findings showing that TES-induced MEPs recorded at 10-s intervals from the adductor pollicis muscle remained steady throughout 4 min of MVC while contraction force decreased by approximately 25%. They concluded that motor cortex excitability and the state of fast conducting motor pathways were not affected by the fatiguing contraction, but stressed that this applies only to those muscle fibers and their central connections that are excited by the cortical stimulus. More recently, Gandevia et al.,[16] using TMS, reported that with visual feedback of force, MEPs from elbow flexors increased significantly during MVC as contraction force decreased. These findings suggest that the excitability of the motor cortex is not only maintained but actually increases during a sustained volitional contraction. This facilitation could come with increasing effort to maintain MVC from continuously increasing cortical and subcortical activation of the motor cortex. Moreover, the increasing amplitude of MEPs recorded from the nonexercised CTA appears from the beginning of the ExTA MVC. This would imply that the relatively organized coactivation of other muscles observed during an MVC might, in part, result from increasing excitability which spreads to motor cortex regions representing those muscles.[12,17] Similar increases in central drive have been reported by Duchateau and Hainaut[13] in studies of long loop reflexes in hand muscles which showed an increase in amplitude not only in the exercised muscle but also in nearby muscles during the fatiguing contraction. They proposed that descending excitatory drive increases in an effort to compensate for decreasing excitation coming from peripheral afferents. Our MEP results support such a conclusion regarding excitation mediated via the corticospinal system.

We report here that the duration of the TMS-induced silent period progressively increased by approximately 21% during the MVC (Fig. 2) and re-

mained prolonged after MVC had ended (Fig. 3). Inhibitory effects of TMS on human cerebral cortex are well reported and include: (1) delayed initiation of movement;[10,36,40,42] (2) activation of intracortical inhibitory circuits;[7,8,14] (3) interhemispheric inhibitory interactions;[33,39] and (4) ipsilateral motor cortex inhibition.[25,39] The TMS-induced silent period, which represents interruption of ongoing volitional activity, has certain characteristics that imply its organization. For example, H-reflexes recovered by 50% of unconditioned values within the first 60–90 ms of the 170–215-ms TMS-induced silent period in the flexor carpi radialis muscle.[15] It is thought that this early part is due to segmental inhibition and that the latter portion of the TMS-induced SP is of suprasegmental origin.[24,45,46] Therefore, it would be reasonable to think that any exercise-induced prolongation of the TMS-induced SP would involve suprasegmental mechanisms. Also, the results presented here show an increase in TMS-induced SP duration that occurred at the same rate in both the exercised and coactivating tibialis anterior muscles during a fatiguing MVC. Since the motor neuron firing rate in the ExTA is progressively declining and that of the coactivating CTA is increasing with additional motor units being recruited, it is likely that the progressive prolongation of the TMS-induced SP, common to both muscles, is due to suprasegmental mechanisms.

Electrical stimulation of the pyramidal tract at the pyramidal decussation or cervicomedullary junction can elicit silent periods during volitional activation but they are of much shorter duration than those produced by TMS.[24,44] In the current study, during brief low level volitional contractions, silent periods produced by electrical stimulation of the long descending tracts at the pyramidal decussation were well defined. Unlike the TMS-induced SP, which was prolonged after the MVC, silent periods elicited by descending tract stimulation failed to show any increase in duration. This would suggest that the mechanisms of exercise elicited increases in the duration of the TMS-induced SP involve structures located above the pyramidal decussation.

Although the latter portion of the TMS-induced silent period is considered to be the result of intracortical inhibition of the motor cortex, changes in the activity of other central nervous system structures might play a role. For example, TMS-induced SP duration in the tibialis anterior was prolonged in patients with lesions in the parietal lobe or thalamus.[20] Also, the TMS-induced SP duration is increased in patients with cerebellar degeneration.[11] Furthermore, pharmacologically induced modification of activity within subcortical–cortical loops has been reported in normal subjects and in patients with Parkinson's disease where prolongation of the silent period occurred after dopaminergic and anticholinergic therapy.[37] Another source of TMS-induced SP duration increase could be in the cortical and subcortical GABAergic systems. Priori et al.[38] showed that hyperventilation significantly reduces the duration of the TMS-induced silent period and proposed that changes in pH, occurring during hyperventilation, may effect GABA-mediated inhibition. These reports suggest that inhibitory mechanisms, in structures other than the motor cortex, could be involved in the generation and prolongation of the TMS-induced silent period.

During a sustained unilateral MVC, TMS-induced MEP and SP increase in both exercised and nonexercised tibialis anterior muscles. Such a concurrent increase in excitatory and inhibitory responses suggests that facilitation of their two different generating mechanisms might come from common or related sources; e.g., limbic system, basal ganglia, or premotor cortex structures. During brief, low level volitional contractions following MVC, we found that the TMS-induced SP was prolonged but that the postexercise MEP was unchanged. Therefore, it appears that facilitation brought by volitional activation probably maintains the excitability of pyramidal cells within the motor cortex at a target level. In the absence of such voluntary activation, however, the MEP would be depressed as previously reported.[30] Also, it is important to note that postexercise prolongation of the TMS-induced SP is focal to the exercised muscle, much as was postexercise depression of the MEP, in the relaxed muscle following MVC. The mechanisms for the observed postexercise increase in TMS-induced SP are less clear; however, such an increase would imply that inhibitory mechanisms remain focally augmented following a fatiguing MVC. Taken together, these findings may lead to the establishment of neurophysiological parameters for the examination of the reduced motor capacity or endurance reported by patients who suffer from a variety of neurologic disorders. However, further study is needed to determine to what extent structures that provide descending excitation via pathways other than those of the direct corticospinal system are affected by a fatiguing contraction.

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