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Changes in corticospinal excitability during an acute bout of resistance exercise in the elbow flexors

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Abstract

**Purpose:** Hypertrophic resistance exercise (HRE) induces central and peripheral fatigue. However, more detailed information about changes in corticospinal excitability remains to be elucidated.

**Methods:** Eleven volunteers participated in the upper arm HRE which included one repetition maximum (1 RM) control contractions and three sets of 13 RM (SET1–3). Transcranial magnetic stimulation (TMS) was applied during maximal isometric voluntary contraction (MVC) at the end of each set and during control contractions to study changes in corticospinal excitability. Electrical stimulation was used in order to measure peripheral changes.

**Results:** MVC decreased after each set when compared to control contractions. Motor evoked potential (MEP) were 138.7 ± 52.7 % (p < 0.05), 130.4 ± 44.7 % and 113.1 ± 31.4% after SET1, SET2 and SET3, respectively, when compared to pre-exercise value. A significant reduction in MEP area between SET1 and SET3 (p < 0.05) was observed while silent period (SP) duration increased (~151–165ms, p<0.05) simultaneously between these sets. TMS evoked twitch force during MVC increased significantly following each set when compared to pre-exercise value. Simultaneously a significant reduction was observed in resting twitch force over the sets.

**Conclusions:** The results of this study clearly support the existence of both central and peripheral fatigue during HRE of elbow flexors. However, changes in the MEP area and SP suggest that during HRE of the elbow flexors, the corticospinal excitability increases first, until at some point, supraspinal fatigue takes over.

Keywords: transcranial magnetic stimulation, neuromuscular responses, strength training, electromyography, fatigue

Abbreviations:

CMEP = Cervicomedullary motor evoked potentials
CV = Coefficient of variation
EMG = Electromyography
GABA\textsubscript{B} receptors = metabotropic transmembrane receptors for gamma-aminobutyric acid
HRE = Hypertrophic resistance exercise
MEP = Motor evoked potential
Mmax = Maximal M-wave
MVC = Maximal voluntary contraction
RM = Repetition maximum
RMT = Resting motor threshold
SP = Silent period
TMS = Transcranial magnetic stimulation
TWpas = passive twitch evoked by electrical stimulation
TWsup = superimposed twitch evoked by TMS
Introduction

Muscle fatigue can be defined as an exercise-induced reduction in maximal voluntary muscle force or power (Gandevia 2001; Taylor & Gandevia 2008). It develops gradually during sustained or intermittent muscle contractions (e.g. Søgaard et al. 2006; Taylor et al. 2000). Neuromuscular fatigue is not only a result of changes in intrinsic properties of a muscle, both spinal and supraspinal mechanisms can also play a major role. Thus, muscle fatigue is generally divided into peripheral fatigue which refers to processes distal to the neuromuscular junction and central fatigue which refers to more proximal neural processes (Gandevia et al. 1996). Central fatigue can be assessed by measuring the amount of force increment, which is evoked by electrical stimulation during maximal contraction (Merton 1954). Transcranial magnetic stimulation (TMS) can also be applied, not only to measure the corticospinal excitability with motor evoked potentials (MEP), but to measure the superimposed twitch responses in order to evaluate the existence of central fatigue (Gandevia 2001; Taylor & Gandevia 2008; Todd et al. 2003). Furthermore, peripheral fatigue can be demonstrated as a reduction in the peak twitch force of a passive muscle produced by supramaximal electrical stimulation of a corresponding nerve trunk or the muscle itself (e.g. Norlund et al. 2004).

It has been shown that TMS induced MEPs, which manifests as changes in corticospinal excitability, increases following different types of contractions (submaximal, maximal, repetitive or sustained) (Iguchi and Shields 2012; Sacco et al. 1997; Taylor et al. 2000). Several studies have observed increases in the MEP size following exercise-induced muscle fatigue (e.g. Hoffman et al. 2009), but not all studies are converging with the increased MEP size. For example, McNeil et al. (2011) demonstrated unaffected MEP size after sustained submaximal muscle contractions. On the other hand, sustained voluntary contractions have been shown to elicit a decrease in the MEP size after fatigue at contraction levels of 25–50% of maximal voluntary contraction (MVC). However, no changes were observed at higher contractions levels (75–100% of MVC) (Todd et al. 2003). Some studies have also indicated an increment in MEP size at the beginning of a fatiguing task, which then levels off or even seems to decrease after a certain point (Hunter et al. 2006; Taylor et al. 1996; Taylor et al. 2000). In addition, the cortical silent period, which refers to a break in the electromyographic (EMG) activity after TMS during voluntary contraction, has been observed to increase in duration during maximal and submaximal fatiguing muscle contractions (Søgaard et al. 2006; Taylor et al. 2000). Interestingly, the later component (>75 ms) of the silent period represents an intracortical inhibitory mechanism that is mediated by GABA$_B$ receptors generated within the motor cortex that leads to a failure in corticospinal drive, representing
supraspinal inhibition (Fuhr et al. 1991; Inghilleri et al. 1993; Ziemann et al. 1993).

Acute neuromuscular fatigue responses after a single hypertrophic type of resistance exercise (i.e. 6-12 repetitions per set for several sets per exercise with relatively short rest periods between the sets) have been demonstrated previously. For example, Häkkinen (1994) showed decreased EMG activity and large reductions in maximal force after hypertrophic loading (10 sets of 10 repetition maximum [RM]). Furthermore, Walker et al. (2012) showed that hypertrophic loading (5 sets of 10RM) produces neuromuscular fatigue dominated by peripheral factors, whereas fatigue induced by maximal loading (15 sets of 1RM) seems to be caused by a reduction in neural drive to the muscle. In light of this, previous studies have not provided in more detail the potential sites within the central nervous system that modulate these acute neural responses.

In long-term strength training intervention studies, increases (Kidgell et al. 2010) as well as decreases (Jensen et al. 2005) or no changes (Carroll et al. 2002; Kidgell & Pearce 2010) in MEP size have been observed following a training period. Reasons for these inconsistent findings might be variations in testing and training protocols, and in the muscles studied. However, to our knowledge, TMS has not been used to study acute neuromuscular fatigue responses during resistance exercise. Therefore, the purpose of this study was to examine muscle fatigue induced by hypertrophic type of resistance exercise of the elbow flexors. TMS was used to investigate changes in corticospinal excitability, whilst TMS-induced silent period was also monitored to examine possible changes in cortical inhibition. Furthermore, nerve and muscle stimulations were used to demonstrate the peripheral component of muscle fatigue.
Methods

Subjects

Eleven physically active young volunteers (7 males, 4 females; age = 24.5 ± 2.6 years; height = 175.1 ± 6.7 cm; weight = 71.2 ± 9.0 kg; mean ± standard deviation [SD]) participated in this study. All subjects were accustomed to strength training and reported participating in strength training at least once every second week. Subjects were informed verbally and in writing of the experimental procedures and associated risks. All subjects were with good health. Written consent was obtained from each of the participants. The recommendations contained in the Declaration of Helsinki were followed and all the procedures used in this study were approved by the university ethical committee.

Experimental protocol

Prior to the study, all subjects participated in a familiarization session. During this session, subjects practiced for proper lifting technique and the load for the hypertrophic resistance exercise (HRE) was determined. Elbow flexion was chosen to be studied, since the biceps curl is a commonly used resistance training exercise and in order to have minimal body movement during TMS. All Measurements were conducted in one session. During the measurements, subjects were seated in a custom made dynamometer (University of Jyväskylä) with their right hand fixed on the force transducer lever arm in a neutral position. To minimize body movements during the contractions, the subjects’ position was stabilized with seat belts.

Control measurement

After a warm up, which consisted of five submaximal contractions, subjects performed nine maximal voluntary unilateral 1 RM contractions (control contractions) (Fig 1A). Control contractions (elbow flexions) consisted of a concentric contraction followed by an isometric contraction both done with MVC. Stimuli (TMS and brachial plexus stimulation) were given during the isometric phase at the elbow joint angle of 90 °. Resting twitch was measured 4 seconds after three different control contractions. The order of these stimulations was randomized. Following the control
contractions, subjects then performed three maximal voluntary unilateral isometric elbow extensions at the same angle (90°) without any stimulation for the normalization of triceps brachii data (Fig 1A). There was a 2-min rest period between consecutive control contractions in order to avoid fatigue. Subjects were verbally encouraged throughout the contractions.

Resistance exercise

HRE protocol consisted of 13 elbow flexion contractions performed in three sets (SET1, SET 2 and SET 3) with a 2-minute recovery period between each set (Fig 1A). The first eight contractions in each set were executed with a free weight (i.e. dumbbell). The last five contractions were done as isokinetic apparatus. Each isokinetic contraction included an isokinetic concentric MVC ending with an isometric MVC during which the stimuli (3 xTMS and brachial plexus stimulation) were given (Fig 1B). The dumbbell was used to simulate traditional hypertrophic resistance exercise, in which MVC is not exerted in the beginning of the set. Isokinetic/isometric MVCs were used in order to have comparable contractions and the number of those contractions (5 contractions) was determined by the experimental setup and the number of stimuli given.

The first eight repetitions with dumbbell were performed with a maximum load whereby it was possible to achieve 8 repetitions in each set. If the subjects could not voluntarily complete the eight repetitions, some assistance was provided during the concentric phase of the exercise without affecting the rate of the exercise and the load was reduced for the next set. To minimize the pause between free weight movements and isokinetic contractions, the hand was fixed to the isokinetic apparatus throughout the loadings, but the isokinetic apparatus was not on during the first eight repetitions of each set. Range of motion of elbow angle was set with mechanical stops between 20 and 180° for the first eight contractions (free weight movements). Subjects were instructed to raise the dumbbell as high as possible and extend their hand as straight as possible. These free weight movements were immediately followed by five isokinetic movements. Range of motion for isokinetic movements was from 180 to 90° (180° = fully extended elbow).

During the first eight contractions, subjects were instructed to maintain a lifting tempo of 1.5 s for concentric and 1.5 s for eccentric contractions. In the following isokinetic movements, participants completed five maximal concentric contractions (speed of the movement was 60°/s), each ending with an isometric MVC performed at an elbow joint angle.
of 90°. After each isometric MVC, the isokinetic apparatus extended the arm passively between the consecutive contractions. The isokinetic movement was performed at the same speed as the free weight component. Isometric MVCs were performed for 1.2 s. TMS was applied during the second, third and fourth of the five isometric contractions, and brachial plexus stimulation was applied during the fifth contraction (Fig. 1b). Following all 13 contractions, subjects relaxed their muscles and muscle stimulation was applied 4 s after the last contraction.

Force measurements

The force measurements were conducted with an isokinetic dynamometer equipped with a strain gauge transducer (Komi et al. 2000; Linnamo et al. 2006). The dynamometer works with a strong electromotor, which provides information about the location of the lever arm and force produced against it. During the first eight repetitions of HRE the lever arm was set in a free moving state. Movement of the lever arm was programmed using Spike2-software for all isokinetic movements (Cambridge Electronics Design Limited, Cambridge, UK).

Muscle stimulation

Muscle stimulation was used for the assessment of peripheral fatigue. Stimulation was applied 4 seconds after the last MVC during SET1, SET2 and SET3. During control contractions MVC also preceded the muscle stimulation. A pair of electrical stimuli were delivered to the biceps brachii muscle to determinate the resting twitch force (constant current, DS7AH,Digitimer Ltd, Welwyn Garden City, UK). Two rectangular pulses with duration of 100µs and with an interstimulus interval of 10 ms were delivered via a cathode located above the EMG electrodes and the anode positioned over bicupital tendon (V-trodes neurostimulation electrodes, Mattler Electronics corp., USA). Stimulation intensity was increased until no further increase in twitch force was observed in relaxed muscle. During the experiment, the stimulation intensity was further increased by 20%.

Transcranial magnetic stimulation

TMS was performed using a figure-of-eight coil attached via a BiStim unit to a Magstim 200² stimulator (9-cm, Magstim, Whitland, UK). Single pulse stimulation was applied over the motor cortex of the left hemisphere to preferentially activate biceps brachii muscle. The coil was adjusted during rest to determine optimal position. Position
was marked on a tightly fit swim cap. Position and orientation was held manually. Resting motor threshold (RMT) was determined as the minimum intensity that elicited 3 out of 5 MEPs which amplitude was 50μV. Stimulation intensity was 120% of RMT.

Brachial plexus stimulation

In order to produce a maximal M-wave ($M_{\text{max}}$), a rectangular pulse of 1 ms duration was delivered to the brachial plexus at Erb’s point. The cathode was placed over the plexus and the anode over the acromion. Stimulation intensity was increased gradually until the resting M-wave in biceps brachii reached a plateau. Stimulus amplitude was then set 20% above this.

EMG

EMG data were recorded from biceps brachii, triceps brachii and brachioradialis muscles using bipolar self-adhesive Ag/AgCl electrodes (10mm diameter, Blue Sensor N, N-00-S, Ambu A/S, Denmark). Interelectrode distance was 20mm and resistance between electrodes was <2kΩ. Electrodes were attached to biceps brachii and triceps brachii (lateral head) according to SENIAM recommendations. In brachioradialis, the electrodes were attached over the muscle belly in a line with the muscle fibres. EMG signals were amplified (x1000) and filtered (10–1000Hz). EMG, force and joint angles were sampled at 2 kHz with a data-acquisition system (CED Power 1401 with Spike2 software, Cambridge Electronics Design Limited, UK).

Data analysis

MVC force was analyzed with a 500-ms window and calculated as a mean for the nine isometric MVCs during control contractions and for the five isometric MVCs during HRE protocol. EMG of each muscle was determined as a root-mean-square (rms) value over a 500 ms time window before the stimulation. EMG values during HRE were averaged for the five MVCs during each set. EMG values of the triceps brachii muscle were normalized to the maximal isometric elbow extension force measured before HRE protocol. Both peak-to-peak amplitudes and areas for MEPs and $M_{\text{max}}$ were analyzed according to Martin et al. (2006). Because the areas and the amplitudes behaved similarly, only the results for the areas are presented. Thus, MEP areas were normalized to the $M_{\text{max}}$ area in each measurement point. Silent period was
measured as an absolute silent period from the end of the MEP to the return of continuous EMG (Säisänen et al. 2008). Peak forces for the superimposed twitch evoked by TMS (TWsup) and passive twitch evoked by electrical stimulation (TWpas) were analyzed. In order to estimate possible changes in muscle activation, the ratio of the two twitch responses is calculated (TWsup/TWpas). During the HRE protocol MEPs, TWsup and silent period were calculated as an average from three MVCs, whereas Mmax and TWpas were analyzed from one measurement only.

Statistical analysis

Data are reported as means ± SD, unless stated otherwise. In order to identify the effects of the different sets on corticospinal excitability, the MEP results were calculated as a relative difference to the control value. Results were analyzed using PASW statistics 18-program. Normal distribution was determined through the Shapiro-Wilk test. Repeated measures ANOVA was performed for normally distributed variables. When significant main effects were observed, Bonferroni post hoc tests were conducted for pairwise comparisons. Non-parametric repeated measures analysis of variance (Friedmann Test with a Bonferroni correction) was performed to test changes in MEP areas and changes in EMG data for biceps brachii and triceps brachii. Significant differences were established at p ≤0.05. The coefficient of variation (CV) was calculated for individual changes in the MEP area and silent period duration during control contractions and SETs.
Results

MVC and EMG

The weight of the dumbbell was on average 7.4 ± 4.3 kg for SET1, 6.7 ± 3.8 kg for SET2 and 5.5 ± 3.1 kg for SET3. MVC was 242.0 ± 63.9 N during control contractions and decreased to 162.6 ± 44.8 N (p < 0.001) after SET1, 138.7 ± 31.0 N (p < 0.001) after SET2 and to 127.4 ± 25.5 N (p < 0.001) after SET3 (Fig. 2). Furthermore, there was a significant decline in force between SET1-SET2 (p <0.05) and SET1-SET3 (p < 0.05). Normalized EMG values for biceps brachii were 92.3 ± 27.3%, 84.0 ± 24.9% (p < 0.05) and 84.1 ± 16.6% in SET1, SET2 and SET3, respectively. Normalized EMG amplitudes for triceps brachii muscle were 83.2 ± 15.8% (p < 0.01), 82.6 ± 13.1% (p < 0.01) and 87.5 ± 17.9% (p < 0.05) and for brachioradialis 97.5 ± 24.5%, 92.3 ± 22.1% and 87.7 ± 19.1% in SET1, SET2 and SET3, respectively.

MEP size, maximal M-wave and silent period

Mean area of the MEPs were 138.7 ± 52.7 %, 130.4 ± 44.7 %, 113.1 ± 31.4% after SET1, SET2 and SET3, respectively (Fig. 3 & 4A). MEP area increased significantly in SET1 when compared to control (p<0.05) and the MEP area decreased significantly from SET1 to SET3 (p < 0.05). CVs for control, SET1, SET2 and SET3 MEP areas were 17.9%, 10.6%, 13.4% and 13.6%, respectively. Maximal M-wave areas did not differ significantly between the SETs. The mean areas were 124.7 ± 35.6% (SET1), 126.2 ± 30.0% (SET2) and 131.9 ± 37.4% (SET3). The mean duration of silent period for biceps brachii was 141.1 ± 55.5 ms during control contractions. Following SET1 silent period duration was 151.4 ± 52.0 ms, during SET2 162.3 ± 48.1 ms and during SET3 164.6 ± 50.6 ms (Fig. 4B). The increase in silent period duration was significant between SET1 and SET3 (p < 0.05). CVs for control, SET1, SET2 and SET3 silent period durations were 6.8%, 4.8%, 4.6% and 4.2% respectively.

Twitch responses

TWpas was 48.6 ± 17.5 N after control contraction and it decreased to 29.4 ± 8.2 N after SET1 (p < 0.05), 22.8 ± 7.9 N after SET2 (p < 0.05) and 18.3 ± 8.5 N after SET3 (p < 0.01) (Fig. 5A). A tendency for decreased resting twitch force was observed between SET1 and SET3 (p=0.055). TWsup was 7.5 ± 4.3 N during control contraction, and increased to
19.6 ± 7.1 N in SET1 (p < 0.001), 19.1 ± 7.8 N in SET2 (p < 0.001) and 18.0 ± 8.6 N in SET3 (p < 0.001) (Fig 5B).

TWsup/TWpas -ratio was 0.20 ± 0.18 during control measurements and it increased to 0.72 ± 0.46 during SET 1 (n.s.), 0.85 ± 0.52 during SET 2 (p<0.05) and 1.12 ± 0.80 during SET 3 (p<0.001). Even though the significance level increased during the sets, the differences between the sets were non-significant.
Discussion

The aim of this study was to investigate the neuromuscular responses to hypertrophic resistance exercise of the elbow flexors. To the best of our knowledge this was the first time that corticospinal excitability was measured during such exercise. The main findings of the current experiment were as follows: (1) TWsup/TWpas -ratio increased during the resistance exercise sets. This increase was driven by decrease in TWpas. (2) MEP size first increased during SET1, followed by decrease during SET2 and SET3, and (3) the silent period duration increased progressively from SET1 to SET3.

A considerable reduction in MVC force (32, 41 and 46 % following SET1, SET2 and SET3, respectively) was observed during the sets. Part of this impairment can be explained by peripheral fatigue, since there was a significant reduction in TWpas after SET1. Although there were no significant differences between the sets, there was a tendency for a continuous reduction from SET1 to SET3. An opposite trend could be seen when looking at the superimposed twitch amplitude (TWsup) evoked by TMS. An increased force response to external stimuli during maximal voluntary contraction is an indication of incomplete recruitment or firing frequency of motor units and thus forms a central component of muscular fatigue (Taylor et al. 2000). This interpretation is even stronger when a ratio between TWpas and TWsup was calculated. However, it should be noted that the two twitches represent different levels of stimulation intensity and most likely involves the stimulation of different motor unit populations. Intriguingly, neither central nor peripheral fatigue accumulated further during the three sets, suggesting that both central and peripheral fatigue became apparent after SET1 but remain at about the same level during SET2 and SET3. This indicates that the 2-min break between the sets was not enough for the muscle to recover, but enough to prevent further accumulation of fatigue. This is, however, slightly puzzling since it is not in line with the present findings of maximal force reduction. There was a significant reduction in MVC force between SET1–SET2 and SET1–SET3, which therefore must be a result of a net effect of these two fatigue components.

MEPs are evoked through direct or indirect corticospinal pathways, and the MEP size depends on the excitability of both cortical neurons in the motor cortex and motoneurons in the spinal cord (Gandevia 2001). Given that MEPs are influenced by both cortical and spinal mechanisms, Butler et al. (2003) used cervicomedullary motor evoked potentials (CMEPs), which stimulates the descending tract directly and is known not to be affected by presynaptic inhibition, and reported decreased CMEPs during a sustained maximal contraction. In this context, the reduction in CMEPs was due to reduced excitability of spinal motoneurons during a fatiguing task. This finding is consistent with the study of Iguchi and Shields (2012) who also reported decreased spinal excitability of the soleus muscle during intermittent maximal
contractions. In both of these studies, increased MEP size was considered to be a compensatory mechanism of the motor cortex, in an attempt to compensate for the reduction in motoneuron excitability. MEP size has also been found to increase during sustained maximal voluntary contractions or during intermittent maximal voluntary contractions (Taylor et al. 1996, 2000). In the current study, MEPs did not behave in a similar manner during fatigue compared to earlier studies that have investigated the effects of fatigue on MEP size (e.g., Taylor et al. 1996). In the present study, we initially observed an increase in the MEP size that was then followed by a subsequent decrease from SET1 to SET3. The increase in the MEP size is thought to result from increased net excitatory output evoked from the motor cortex by the magnetic stimuli (Taylor et al. 1996; Taylor and Gandevia 2008). Another explanation that the response of the motoneurons to descending input increases is not a likely one since the comparison is made to corresponding measurements during control contractions which were already executed with a maximal effort (MVC). It has been proposed that a facilitatory neural pathway increases the motor output from the motor cortex. This pathway most likely compensates at least part of the effect of supraspinal fatigue (Tanaka and Watanabe 2012; Taylor et al. 1996). In the current experiment, the decreased MEP size during the sets could be due to decreased voluntary drive caused by decreased facilitation or increased inhibition of the cortical output neurons, or inhibition of the motoneurons at the spinal level (Butler et al. 2003; Iguchi and Shields 2012). Unfortunately, cervicomedullary stimulation, which is thought to be the only valid measure for spinal sensitivity, could not be conducted in this experiment. Nevertheless, the present MEP data suggest that the hypertrophic resistance exercise first increases corticospinal excitability up to a certain point and then, subsequently, decreases it during the second and third sets. This reduction is most likely due to impaired descending voluntary drive.

Cortical silent period refers to a suppression of the ongoing EMG signal immediately after a TMS-evoked MEP response during muscle contraction (Fuhr et al. 1991). The initial portion of the silent period (50–75 ms) is primarily due to spinal inhibitory mechanism such as after-hyperpolarization and recurrent inhibition of motoneurons, whilst the later part represents cortical inhibition (Fuhr et al. 1991; Inghilleri et al. 1993; Ziemann et al. 1993). Excitability changes during the later part of the silent period are suggested to be caused by GABA-B mediated inhibition and more precisely linked to cortical glutamate levels (Lang et al. 2006; Tremblay et al. 2012). The current finding of an increase in the silent period duration is consistent with earlier reports of muscle fatigue during sustained MVC (Taylor et al. 1996) and intermittent MVC (Taylor et al. 2000). In both of these studies increased duration of silent period was linked with increased cortical inhibition. The observation that silent period duration was increased in the present study implies that the hypertrophic resistance exercise program increased the responsiveness of the intracortical inhibitory interneurons, leading to reduced net excitatory drive.
EMG analysis showed a reduction of the biceps brachii muscle activation between sets and control contraction, which is well in line with the earlier discussion about decreased voluntary drive during the sets. An interesting finding was a significant reduction in antagonist activation. This can be taken as improved muscle coordination during the sets in order to compensate at least part of the impaired force capability of the agonist muscle. It seems that the impact of impaired neuromuscular propagation was negligible, since there were no changes in the maximal M wave size during the sets.

**Conclusions**

Acute responses to resistance exercise can demonstrate which part of the neuromuscular system is stressed during the exercise. This information may assist coaches to develop targeted resistance training programs. Hypertrophic resistance exercise induces both peripheral and central fatigue. In addition, according to present study, at least part of the central fatigue has a supraspinal component. The current results show that the changes in corticospinal excitability during and following hypertrophic resistance exercise (elbow flexion) share a different fatigue profile compared with previous studies investigating muscle fatigue. The present study suggests that during the first set of the hypertrophic resistance exercise using the biceps brachii muscle, the motor cortex increases its facilitatory processes until it is no longer possible to maintain maximal voluntary drive. Since an increase in silent period duration was observed, the decrease in corticospinal excitability seems to be at least partly due to cortical inhibition. However, acute responses of other muscle groups or training protocols may have a distinct fatigue profile.

**Conflict of interest**

The authors declare that they have no conflict of interest.


Legends

Fig. 1 A) Illustration of the protocol. TMS brachial plexus and muscle signify the different stimulations used. The arrows indicate the point of the stimulation. TMS and the brachial plexus stimulation were given during the MVC, and muscle stimulation was measured 4 s after control contraction. The order of these stimulations was randomized. There was a 2-min rest period between consecutive control contractions and 10-min break between the control contractions and HRE protocol. In addition, there was a 2-min recovery period between each set during the HRE protocol. The content of each set is presented in (b). b Illustration of the resistance exercise set. Line in the picture signifies the angle of the elbow joint. The first four stimulations were delivered during the isometric MVC, and the last stimulation involved stimulating the muscle during rest. All stimulations were applied at an elbow angle of 90°. “Nerve stim.” refers to brachial plexus stimulation, and “muscle stim.” refers to motor nerve stimulation.

Fig. 2 Mean isometric MVC force as a percentage of control MVC. Data are mean forces (± SD). SET1, SET2 and SET3 refer to first, second and third set respectively. Significant difference between control and all the sets (**p<0.001) and also significant difference between SET1- SET2 and SET1- SET3 (*p<0.05)

Fig. 3 EMG and force traces from one representative subject in response to TMS from the biceps brachii during control contraction and HRE (SET1–3). On top are MEPs and subsequent silent periods and below TWsup recorded during isometric MVC

Fig. 4 A) MEP area expressed as a percentage of Mmax area (Mean ± SD). MEP area increased significantly in SET1 when compared to control (*p<0.05) and decreased significantly in SET3 when compared to SET1 (*p<0.05) B) Duration of the silent period produced by TMS during maximal isometric voluntary contraction. Data are mean durations (±SD). Significant difference between SET1- SET3 (*p<0.05)

Fig. 5 A) Increment in force evoked by electrical stimulation in rest as a percentage of control values. B) Increment in force evoked by transcranial magnetic stimulation in MVC. Data are presented as mean (±SD). Significant difference between control and sets 1–3 (*p<0.05, ** p<0.01 and ***p<0.001, respectively)
Stimuli (in randomized order)

- TMS
- Brachial plexus
- Muscle (relaxed muscle)

2 min 2 min 10 min 2 min 2 min

9 x 1 RM elbow flexion (MVC) 3 x elbow extension (MVC) Resistance exercise (HRE protocol)

Free weight movement Isokinetic + isometric part

TMS TMS TMS Nerve stim. Muscle stim.

Figure 1ab
Figure 4

A

Figure 4

B

Silent period duration (ms)

Control  Set 1  Set 2  Set 3

 MEP area (%M_{max})

Control  Set 1  Set 2  Set 3
Figure 5

A

Resting twitch force (% control)

Control  Set 1  Set 2  Set 3

B

Superimposed twitch force (% control)

Control  Set 1  Set 2  Set 3