

Evidence for a supraspinal contribution to human muscle fatigue

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Summary

1. Muscle fatigue can be defined as any exercise-induced loss of ability to produce force with a muscle or muscle group. It involves processes at all levels of the motor pathway between the brain and the muscle. Central fatigue represents the failure of the nervous system to drive the muscle maximally. It is defined as a progressive exercise-induced reduction in voluntary activation or neural drive to the muscle. Supraspinal fatigue is a component of central fatigue. It can be defined as an exercise-induced decline in force due to suboptimal output from the motor cortex.

2. When stimulus intensity is set appropriately, transcranial magnetic stimulation (TMS) over the motor cortex during an isometric maximal voluntary contraction (MVC) of the elbow flexors commonly evokes a small twitch-like increment in flexion force. This increment indicates that, despite the subject's maximal effort, motor cortical output at the moment of stimulation was not maximal and was not sufficient to drive the motoneurons to produce maximal force from the muscle. An exercise-induced increase in this increment demonstrates supraspinal fatigue.

3. Supraspinal fatigue has been demonstrated during fatiguing sustained and intermittent maximal and submaximal contractions of the elbow flexors where it accounts for about one-quarter of the loss of force of fatigue. It is linked to activity and the development of fatigue in the tested muscles, and is little influenced by exercise performed by other muscles.

4. The mechanisms of supraspinal fatigue are unclear. Although changes in the behaviour of cortical neurones and spinal motoneurons occur during fatigue, they can be dissociated from supraspinal fatigue. One factor that may contribute to supraspinal fatigue is the firing of fatigue-sensitive muscle afferents which may act to impair voluntary descending drive.

Introduction

Voluntary contraction of a muscle to produce force or movement involves a series of events which start in the brain and end in the muscle. Processes which lead to muscle fatigue begin at every level whenever people make

repetitive or sustained muscle contractions. Muscle fatigue can be defined as any exercise-induced loss of ability to produce force or power with a muscle or muscle group^{1,2}. In practical terms, this means that muscle fatigue is best measured in human subjects by asking them to perform some kind of maximal task and looking for a decrement in performance. Such tasks include isometric contractions to test maximal force, isotonic contractions to test maximal velocity, or contractions against a load to test maximal power. In submaximal tasks, fatigue is indicated by changes in the relationship between EMG and force but is difficult to quantify. In the past, muscle fatigue has been divided into two components, peripheral fatigue and central fatigue^{e.g. 3,4}. Peripheral fatigue is defined as the loss of force due to processes occurring at or distal to the neuromuscular junction. It can be thought of as fatigue within the muscle itself and is responsible for much of the loss of force of fatigue. However, some loss of force occurs because of the failure of the nervous system to drive the muscle maximally. This is known as central fatigue, a progressive exercise-induced reduction in voluntary activation or neural drive to the muscle. Under some conditions, central fatigue is responsible for 20-25% of the loss of force of fatigue. More recently, supraspinal fatigue has been identified as a component of central fatigue^{5,6}. It can be defined as a loss of force due to suboptimal output from the motor cortex. The following paragraphs describe the measurement of supraspinal fatigue and its contribution to central fatigue, give examples of exercise in which supraspinal fatigue occurs, and discuss evidence for mechanisms which could underlie supraspinal fatigue.

Measurement of supraspinal fatigue

Voluntary activation is a measure of how well subjects can drive a muscle to produce maximal force. It is commonly measured by stimulating the motor nerve to a muscle while the subject performs an isometric maximal voluntary contraction (MVC)^{7,8}, for review². If a twitch-like increment in force (superimposed twitch) is evoked by the stimulus, voluntary activation is less than 100%. Despite the subject's maximal effort, some motor units were either not recruited or were not firing fast enough to drive the muscle fibres to generate all their force. An increase in the superimposed twitch with exercise indicates impairment of voluntary activation and thus, central fatigue^{e.g. 3,5,9,10}. Such a decrease in the ability to activate the muscle maximally can be attributed to processes occurring upstream of the site of stimulation at the motor axons, that is, to something

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happening in the central nervous system.

Transcranial magnetic stimulation (TMS) can activate neurones in the motor cortex in human subjects to evoke short-latency excitatory responses in many muscles^{11,12}. Thus, TMS can also be used to measure voluntary activation in some circumstances^{5,6,13,14}. If stimulation of the motor cortex during an isometric MVC produces a twitch-like increment in force from the contracting muscles then voluntary activation is less than 100%. However, voluntary activation measured with motor cortical stimulation reveals something different from voluntary activation measured with motor nerve stimulation. If motor cortical stimulation evokes a superimposed twitch, then motor cortical output was not maximal and was not sufficient to drive the motoneurons maximally. In turn, motoneurone firing was not maximal or sufficient to drive the muscle maximally. That is, despite subjects' maximal efforts, no site in the motor pathway from the motor cortex to the muscle was working maximally at the moment of stimulation. If the superimposed twitch evoked by TMS during an MVC increases during exercise, then the motor cortex has become less able to drive the muscle fully although extra output from the motor cortex remains available. This indicates the development of supraspinal fatigue, which can be attributed to suboptimal output from the motor cortex.

Measurement of voluntary activation using motor nerve stimulation is confined to muscles which can be stimulated to evoke a maximal twitch with little spread of the stimulus to an antagonist or other muscles. The use of TMS to measure voluntary activation is even more restricted because of the lack of precision in stimulating one muscle or muscle group from the motor cortex. As yet, TMS has only been used successfully to measure activation of the elbow flexor muscles^{5,13} although it has also been attempted for adductor pollicis and triceps brachii^{15,16}. The technique works for the elbow flexor muscles because i) the elbow flexors have stronger excitatory connections from the motor cortex than the antagonist extensors; ii) contracting muscles are more easily activated than relaxed muscles by TMS; iii) the elbow flexors are about twice as strong as the extensors. Together these factors mean that during strong elbow flexion contractions, stimulus intensity can be adjusted so that TMS can evoke a near-maximal excitatory response in the elbow flexors (as seen by the evoked EMG responses in biceps and brachioradialis) with only a small response in the elbow extensors (triceps), and that the evoked extension force is small compared to flexion forces. Although the presence of any extensor twitch implies that voluntary activation will be overestimated, subjects are rarely able to achieve 100% activation even when unfatigued¹³ (see Fig. 2A control). Hence, this measure is sensitive to failure of voluntary activation. As the development of peripheral fatigue means that exercising muscles become weaker, the relative contribution of the non-exercising antagonist should become greater during fatigue. Thus, this technique is likely to underestimate supraspinal fatigue.

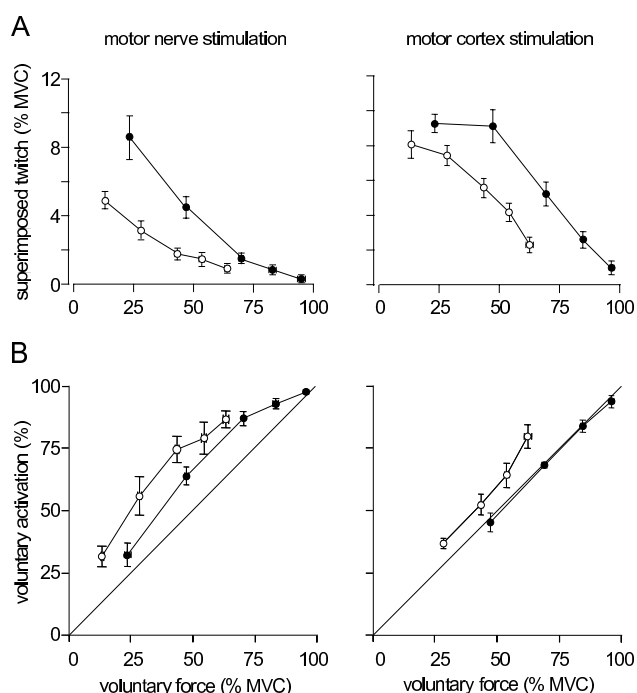


Figure 1. A. Superimposed twitches evoked during voluntary contractions of different strengths by motor nerve stimulation or motor cortex stimulation. Subjects performed brief isometric voluntary contractions of the elbow flexors to maximal and submaximal target forces with unfatigued muscles (filled circles) or with the muscles fatigued to reduce maximal force to 60% of its initial value (open circles). Motor nerve stimulation was delivered during some contractions (left panel) and motor cortex stimulation during others (right panel). The amplitude of the superimposed twitches is plotted against contraction strength. Both are expressed as a percentage of the unfatigued maximal voluntary force (MVC). For motor cortex stimulation, the relationship is linear for contractions >50% MVC.

B. Voluntary activation calculated from the superimposed twitches plotted in A. In the fatigued muscle (open circles), maximal efforts produced forces of ~60% of the initial MVC. Voluntary activation calculated from motor nerve stimulation during maximal efforts dropped from 97% in the unfatigued muscle to 87% with fatigue. By comparison, voluntary activation calculated from motor cortex stimulation dropped from 94% to 80%. Adapted from Figs. 4 and 6 of Todd et al., 2003¹³.

Quantitative comparison of central fatigue and supraspinal fatigue is problematic because voluntary activation measured with motor nerve stimulation does not equate to voluntary activation measured with TMS. For elbow flexion, central fatigue is commonly measured by stimulation over the motor point of biceps to activate biceps and brachialis. At high contraction strengths the relationship of the superimposed twitch to voluntary force becomes non-linear, so that there is little change in superimposed twitch size for changes in voluntary force^{13,17} (see Fig. 1A left panel). This non-linearity could represent differential activation among the elbow flexors, with

stronger activation of the tested muscles than the non-tested ones¹⁷. In contrast, the superimposed twitch evoked by TMS, which tests all the elbow flexor muscles, decreases linearly with strong contractions¹³(Fig. 1A right panel). Antagonist stimulation or muscle lengthening at the moment of stimulation could also be factors in the non-linearity in the superimposed twitch evoked by motor nerve stimulation^{17,18}. Whatever the cause, the different relationships of superimposed twitch to voluntary force for the two stimuli makes direct comparison difficult. Notionally, it is impossible for voluntary activation of a given muscle measured with TMS to be worse than voluntary activation measured with motor nerve stimulation as descending input from the motor cortex is a subset of drive to the motoneurons. Similarly, supraspinal fatigue is a subset of central fatigue.

When does supraspinal fatigue occur?

Supraspinal fatigue has been demonstrated in the elbow flexors in a number of different exercise paradigms. These have included maximal and submaximal isometric contractions, as well as concentric and eccentric exercise^{5,6,13,19,20,21,22}. Over a 2-min sustained isometric maximal voluntary contraction (MVC) of the elbow flexors, voluntary force drops by approximately 60%. At the start of such a contraction, the increment in force evoked by stimulation of the motor nerve to biceps and brachialis evokes a superimposed twitch of about 0.2% MVC. Over the course of the contraction this twitch grows by 50-100%. By comparison, the superimposed twitch evoked by TMS is ~1% MVC in the fresh muscle (which equates to ~95% activation) and grows to 3-4 times its original size^{5,23}. Such changes are clear evidence that central and supraspinal fatigue have developed. In fresh muscle, a TMS-evoked superimposed twitch of 3-4% MVC represents voluntary activation of ~75-81%¹³ (compare Fig. 1A with 1B). Because peripheral fatigue has also occurred, increases in the size of the superimposed twitch are greater relative to the muscle's capacity for force production than is evident from the absolute increase. For example, Fig 1 (open circles) shows that when the muscle is fatigued such that the MVC has fallen to 60% of its original value a superimposed twitch of 3-4% MVC represents voluntary activation of ~70-75%. When maximal voluntary force falls to ~40% of its initial value during a 2-min sustained MVC, the superimposed twitch of 3-4% MVC can be calculated to represent ~66-72% activation. If subjects' predicted force output with a voluntary activation of 95% is compared to their actual fatigued MVC, the loss of force due to decreased voluntary activation can be estimated. Thus, we calculate that supraspinal fatigue probably accounts for between 22 and 30% of the loss of force by the end of 2 minutes of sustained maximal effort.

An increase in the superimposed twitch evoked by TMS has also been demonstrated in intermittent isometric MVCs with various contraction durations and rest intervals⁶ (5s MVC / 5s rest; 15s MVC / 5 s rest; 15 s MVC / 10 s rest; 30 s MVC / 5 s rest). By the time maximal voluntary

force had fallen by 40% in each paradigm, the superimposed twitch had more than doubled. This change equates to voluntary activation of the fatigued muscle of ~80%. If subjects' voluntary activation had remained high (95%) then instead of falling to 60% of the initial maximum, voluntary force would have fallen only to ~71%. This difference suggests that a little over a quarter of the 40% loss of force results from supraspinal fatigue. It seems that under such circumstances, supraspinal fatigue tends to contribute the same proportion of the decline in voluntary force with each protocol despite the different time course of the development of fatigue.

Supraspinal fatigue does not only occur when subjects make maximal contractions, in which corticospinal neurones are likely to be firing at high rates. It can also be demonstrated during fatigue produced by relatively weak submaximal contractions if these are sufficiently prolonged. Subjects held an isometric elbow flexion of 15% of their maximal force and fatigue was monitored with a brief maximal effort every 3 mins¹⁹. The MVC force had fallen by 10% after the first minute of sustained weak contraction and then fell steadily to ~65% of its initial value by 30 mins. At the same time, the superimposed twitch evoked by TMS during the brief MVCs doubled (Fig 2). Thus, supraspinal fatigue developed although the ongoing contraction remained less than 25% of maximum and presumably did not require anywhere near maximal output from the motor cortex. Despite continued, more frequent, brief MVCs, voluntary activation recovered when subjects stopped performing the sustained weak contraction. Hence, the occasional maximal efforts did not cause the supraspinal fatigue.

Exercise which involves non-isometric voluntary contractions and is therefore repetitive rather than sustained can also produce supraspinal fatigue. Subjects performed repeated elbow flexions and extensions against a hydraulic (viscous) load²². Each contraction took about 2 s, with force peaking at ~30% of isometric maximum. Maximal isometric flexion force and voluntary activation was tested after each 30 s of exercise. After a solenoid-operated brake was applied to the arm bar, TMS was given over the subject's motor cortex during a brief maximal flexion effort. Exercise resumed as quickly as possible. During this exercise, maximal voluntary force dropped by ~35% over about 3 minutes, and then remained relatively steady until the end of the exercise (5 mins). The superimposed twitch produced by TMS increased from ~1% to ~2% MVC and also changed little over the remaining exercise. Thus, supraspinal fatigue again developed along with overall muscle fatigue. In this exercise, although the elbow flexors were active for half of the total exercise time, the elbow extensors were active in the intervening period. Hence, subjects had to make an effort continuously although only part of it was directed to the elbow flexors. As the level of supraspinal fatigue demonstrated in the elbow flexors was similar to that induced by other paradigms in which other muscles were not deliberately contracted, this suggests that supraspinal fatigue is linked to the use of particular a muscle group and not to the overall activity of the motor

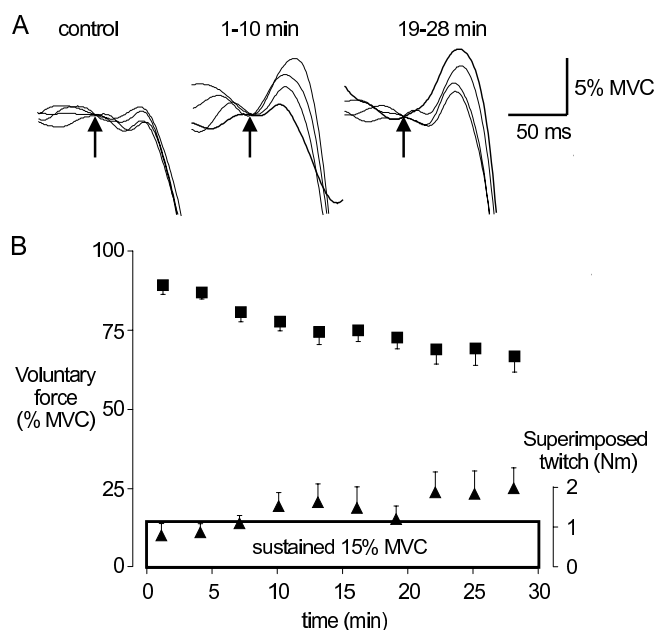


Figure 2. A. Superimposed twitches evoked by motor cortex stimulation during occasional brief maximal efforts during a sustained weak contraction. Three sets of 4 overlaid traces from one subject are shown. Ongoing force has been offset to allow comparison of the twitches. On the left (control) are superimposed twitches evoked during brief maximal efforts prior to the start of the sustained weak contraction. The middle set of traces were elicited during the first 10 minutes of the weak contraction. The smallest twitch (thick line) was evoked after 1 minute. The right hand set of traces were elicited after 19-28 minutes of sustained weak contraction. The largest twitch (thick line) was evoked after 28 minutes. The arrow indicates the time of motor cortex stimulation.

B. Maximal voluntary force and amplitude of superimposed twitches in brief maximal efforts during a sustained 15% maximum isometric contraction of the elbow flexors. Subjects ($n=8$) made a sustained weak isometric elbow flexion. At 3 minute intervals, they performed a brief maximal effort and TMS was delivered. Force (filled squares) measured during the maximal efforts is shown as a percentage of subjects' initial maximal force (left axis). Its fall over the course of the sustained weak contraction shows the development of fatigue. An increase in the amplitude of the superimposed twitch (filled triangles; right axis) shows the development of supraspinal fatigue.

cortex.

Finally, superimposed twitches evoked by TMS have been demonstrated during maximal concentric and eccentric isokinetic contractions²⁰. Twitches were larger during eccentric than during concentric MVCs (~4% and 2% MVC respectively). This suggests that voluntary activation is lower during eccentric exercise even though more force is generated. However, the measurement of twitches when the muscle is shortening or lengthening is complicated by the muscles' force-velocity characteristics.

With fatigue, voluntary forces decreased to about 45% of their initial maxima and the superimposed twitches increased in size by 50-100% for both concentric and eccentric MVCs. Thus, supraspinal fatigue could be demonstrated in both shortening and lengthening contractions.

Mechanisms of supraspinal fatigue

Although supraspinal fatigue can be attributed to suboptimal output from the motor cortex (in that extra output is available while ongoing output is insufficient to produce maximal force), the mechanisms that underlie the apparent increasing failure to use all cortical output are not clear. Two categories of possible mechanisms can be postulated: i) mechanisms which reduce descending output from the motor cortex; and ii) mechanisms which reduce the efficacy of output from the motor cortex in generating force. The first category might include changes in the properties of corticospinal neurones or input to corticospinal neurones. The second category might include changes in motoneurone behaviour which make the motoneurones less responsive to descending input and changes in muscle contractile properties which increase the motor unit firing rates needed to produce fused contraction. However, whether cortical output becomes inadequate during fatigue because it decreases or because it becomes less effective, demonstration of supraspinal fatigue requires that extra effective output from the cortex can be evoked by stimulation.

The behaviour of cortical neurones does change during fatiguing contractions. When TMS is used to activate cortical neurones during a voluntary contraction, both excitatory and inhibitory responses can be recorded in the EMG. The motor evoked potentials (MEPs) are short-latency excitatory responses that are recorded as compound muscle action potentials. They are evoked through direct and synaptic activation of corticospinal neurones so that their size depends on the excitability of these cortical neurones as well as on the excitability of motoneurones in the spinal cord^{24,25,26,27} for review. After the MEP, there is a silent period in the ongoing voluntary EMG. The duration of this silent period is thought to depend on inhibition of voluntary descending output from the motor cortex through the actions of intracortical inhibitory interneurones. Both the MEP and the silent period change during a sustained MVC^{28,29,30} (Fig. 3). The MEP gets larger. This suggests increased excitability of the cortical neurones. At the same time, the silent period gets longer. This suggests an increase in the effectiveness of intracortical inhibition. However, neither of these changes in the cortex appears to be critical to the occurrence of supraspinal fatigue as the impairment of voluntary activation can sometimes be demonstrated when the changes are not present^{5,6} (Fig. 3).

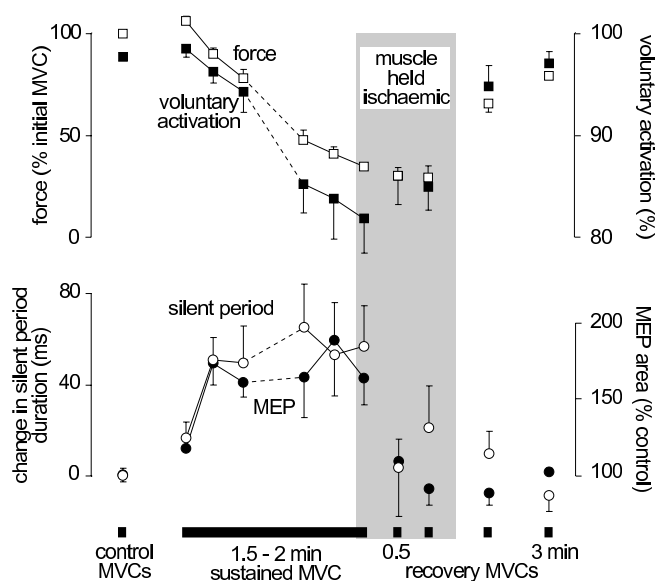


Figure 3. Maximal voluntary force, voluntary activation and the EMG responses evoked by transcranial magnetic stimulation (TMS) during a sustained maximal contraction with a subsequent period of muscle ischaemia. Subjects performed a 1.5 to 2 min sustained isometric maximal voluntary contraction (MVC) of the elbow flexor muscles. At the end of the MVC, before relaxation, a blood pressure cuff was inflated around the upper arm to maintain muscle ischaemia (shaded box). Brief MVCs were performed before the sustained MVC, during the 2 minutes of ischaemia, and then after the cuff was released. TMS was delivered during the brief and sustained MVCs. The upper panel shows that maximal voluntary force (open squares, left axis) fell by ~60% during the sustained MVC and did not recover while the muscle was held ischaemic. The fall in voluntary activation (filled squares, right axis) calculated from the superimposed twitch evoked by TMS indicates the development of supraspinal fatigue during the sustained MVC. Voluntary activation also remained low while the muscle was ischaemic. The lower panel shows that the EMG responses to TMS recorded from brachioradialis (an elbow flexor distal to the cuff) also change during a fatiguing sustained MVC. The motor evoked potential (MEP, filled circles, right axis) increased in size during the sustained contraction and the silent period (open circles, left axis) increased in duration. After the sustained MVC, both responses recovered to control values despite the maintained muscle ischaemia. Adapted from Fig. 3 of Gandevia et al., 1996⁵.

Motoneurons are also affected during fatiguing contractions. Firing rates decrease during sustained maximal contractions^{31,32,33}, and in biceps, the EMG responses to stimulation of the corticospinal tract at a subcortical level (cervicomedullary stimulation) decrease in size³⁴. As these responses have a large monosynaptic component, the decrease suggests that motoneurons have become less responsive to synaptic input. This is consistent with inhibition of the motoneuron pool or with changes in the intrinsic membrane properties of the motoneurons due

to repetitive activation. In terms of subjects' ability to drive the muscle maximally, the motoneurons' decreased response to a constant input suggests that extra descending drive might be required to maintain activation. That is, the same cortical output might be adequate for near maximal activation near the start of a sustained MVC but become less effective later in the contractions. However, such changes do not fully explain supraspinal fatigue which can only be demonstrated if some cortical output is untapped by voluntary effort but can be activated by TMS. The question as to why cortical output is not fully utilised despite maximal effort remains.

As suggested previously, supraspinal fatigue demonstrated for a particular muscle appears to be closely linked to prior activity and fatigue of that muscle so that extra activity in the form of voluntary contraction of another muscle makes little difference. TMS during sustained 1-min MVCs of the elbow flexors of one arm demonstrated the development of supraspinal fatigue. Subjects performed 2 such MVCs separated either by a 1-min rest or by a maximal effort with the other arm. Although superimposed twitches in each set of elbow flexors became 2-3 times as big during the sustained maximal efforts of those muscles, there was minimal crossover of supraspinal fatigue between the two arms²¹. Similarly, alternating activity of elbow flexors and extensors does not seem to produce supraspinal fatigue out of proportion to peripheral fatigue in the elbow flexors, although the effect of altering extensor activity was not formally tested. Central fatigue (tested with motor nerve stimulation) also seems to be largely muscle specific with little crossover between homologous muscles on the two sides of the body³⁵.

The association between peripheral muscle fatigue and supraspinal fatigue has been demonstrated most clearly by preventing the recovery of fatigued muscle by holding the muscle ischaemic at the end of a fatiguing voluntary contraction⁵. When the voluntary contraction is stopped, any changes due to repetitive activity within the motor pathway can recover while the lack of blood flow to the muscle prevents recovery of muscle force and maintains firing of group III and IV muscle afferents which are sensitive to the metabolic products of fatigue. If brief maximal efforts are performed under these conditions, motor unit firing rates and voluntary activation tested with motor nerve stimulation, often remain low³³. That is, central fatigue continues while peripheral fatigue of the muscle is maintained. Similarly, testing voluntary activation using TMS shows that the supraspinal component of fatigue also does not recover while the muscle is ischaemic⁵ (Fig.3). In contrast, the size of the MEP and duration of the silent period do return to control values. Furthermore, responses to cervicomedullary (corticospinal) stimulation, which are reduced at the end of a sustained MVC, also return to control values³⁴. Thus, although neurones in the pathway from motor cortex to the muscle appear to have recovered from the fatiguing contraction, output from motor cortex is still inadequate to activate the muscle fully. This suggests that something to do with the

maintained fatigued state of the muscle acts to impair its voluntary activation, but this does not occur at the motoneurons or at the level of motor cortical output. One possibility is that firing of fatigue-sensitive muscle afferents acts upstream of the motor cortex to impair voluntary descending drive.

Conclusions

TMS over the motor cortex usually evokes twitch-like increments in force from the elbow flexors muscle despite subjects' maximal voluntary effort. These increments increase during exercise and demonstrate that some of the loss of force of fatigue occurs because of inadequate drive from the motor cortex. This supraspinal fatigue is seen during sustained and intermittent maximal and submaximal contractions. It appears to be linked to activity and the development of fatigue in the tested muscles. Although changes in the behaviour of spinal motoneurons and cortical neurons also occur during fatigue they can be dissociated from supraspinal fatigue. In contrast, afferent firing that is associated with maintaining the muscle in a fatigued state may contribute to the suboptimal output from the motor cortex.

Acknowledgements

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