Effects of exhaustive incremental treadmill exercise on diaphragm and quadriceps motor potentials evoked by transcranial magnetic stimulation

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Verin, Eric, Ewen Ross, Alexandre Demoule, Nicholas Hopkinson, Annabel Nickol, Brigitte Faureux, John Moxham, Thomas Similowski, and Michael I. Polkey. Effects of exhaustive incremental treadmill exercise on diaphragm and quadriceps motor potentials evoked by transcranial magnetic stimulation. J Appl Physiol 96: 253–259, 2004. First published September 5, 2003; 10.1152/japplphysiol.00325.2003.—It is unknown whether changes in corticomotor excitability follow exercise in healthy humans. We hypothesized that a fall in the diaphragm and quadriceps motor-evoked potential (MEP) amplitude elicited by transcranial magnetic stimulation of the motor cortex would occur after an incremental exercise task. In 11 healthy subjects, we measured transdiaphragmatic pressure and isometric quadriceps tension in response to supramaximal peripheral magnetic nerve stimulation. MEPs were recorded from these muscles in response to transcranial magnetic stimulation. After baseline measurements, subjects performed a period of submaximal exercise (gentle walking). Measurements were repeated 5 and 20 min after this. The subjects then exercised on a treadmill with an incremental protocol to exhaustion. Transcranial magnetic stimulation was performed at baseline and at 5, 20, 40, and 60 min after exhaustive exercise, and force measurements were obtained at baseline, 20 min, and 60 min. Mean exercise duration was 18 ± 4 min, and mean maximum heart rate was 172 ± 10 beats/min. Twitch transdiaphragmatic pressure and twitch isometric quadriceps tension were not different from baseline after exercise, but a significant decrease was observed in diaphragm MEP amplitude 5 and 20 min after exercise (60 ± 38 and 45 ± 24%, respectively, of baseline, P = 0.0001). At the same times, the mean quadriceps MEPs were 59 ± 39 and 74 ± 32% of baseline (P < 0.0001 and P < 0.01, respectively). Studies using paired stimuli confirmed a likely intracortical mechanism for this depression. Our data confirm significant depression of both diaphragm and quadriceps MEPs after incremental treadmill exercise.

When striated muscle is excessively loaded, a reversible reduction in efficiency is observed; this phenomenon is termed “fatigue” and may be present, regardless of whether or not a given task can be sustained (6). Although the mechanisms underlying fatigue can be of a peripheral nature (i.e., distal to the neuromuscular junction), central fatigue, better termed supraspinal fatigue, can also occur in humans. The evolutionary advantage of this process remains controversial, but it has been proposed as a protective mechanism, preventing irreparable exercise-induced muscle damage or exercise-induced homeostatic failure (36).

Among striated muscles, the diaphragm is unique in that it cyclically contracts throughout life to maintain ventilation. It also provides a substantial contribution to the inspiratory muscle response when the ventilatory demand increases. This is made possible by an endurance that is known to exceed that of most skeletal muscles (2, 39, 43) and biologically corresponds to a high-oxidative potential (15). As a consequence, peripheral diaphragm fatigue is not easy to produce in normal humans. Indeed, the demonstration of diaphragm fatigue requires specific inspiratory loading protocols or strenuous exercise (17). Conversely, central diaphragmatic fatigue, as studied using the twitch (Tw) interpolation technique (19), is known to develop relatively rapidly and before peripheral fatigue in normal volunteers faced with inspiratory loading (4).

As is also the case for limb muscles, the supraspinal pathways of the diaphragm can be studied in humans through the observation of their response to transcranial magnetic stimulation (TMS), applied either during inspiration (25, 33) or in relaxed conditions (38). The present study was designed to test the hypothesis that reduction of central diaphragmatic excitability would occur after a “natural” exercise task (incremental exercise leading to task failure) and whether changes observed in the diaphragm would also occur in a major locomotor muscle, the quadriceps. This secondary hypothesis was prompted by our recent observation that, when the diaphragm and the quadriceps are subjected to similar loading protocols, the degree of diaphragmatic activation could be different than that of quadriceps (16).

MATERIALS AND METHODS

Subjects

Eleven healthy subjects volunteered to participate in the study (3 women and 8 men, age 33 ± 3 yr, weight 77 ± 5 kg, height 177 ± 7 cm, body mass index 25.6 ± 1.6 kg/m2). Four of the subjects practiced sports for >2 h/wk. The study was approved by the Royal

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Measurements

Transdiaphragmatic pressure (Pdi) was measured by using a standard balloon catheter system (catheter length 110 cm; internal diameter 1.6 mm; Ackrad Laboratory, Cranford, NJ) passed through the nose after local anesthesia and placed in the esophagus and stomach to measure esophageal pressure (Pes) and gastric pressure (Pga), respectively. Pes and Pga were measured with linear differential pressure transducers (±100 cmH2O; Validyne, Northridge, CA). Pdi was calculated in real time as Pes − Pga. The Pes, Pga, and Pdi signals were visible to the subjects and the investigators throughout the study.

Quadriceps strength was studied by using a specially designed chair from which the back was removed, on which subjects laid flat with the knee flexed at 90°. Force was measured via an inextensible ankle strap connected to a transducer (Strainstall, Cowes, UK) and carrier amplifier (34).

Surface recordings of the costal diaphragm electromyographic activity were obtained by using surface electrodes [bioadhesive neonatal electrocardiogram electrodes (Ag-AgCl), MSB, Ramsbury Marlborough, Wiltshire, UK] placed in the lowest accessible intercostal space between the midclavicular line and the lateral border of the sternum (41). Surface recordings of the quadriceps electromyographic activity were obtained by using surface electrodes [bioadhesive neonatal electrocardiogram electrodes (Ag-AgCl), MSB, Ramsbury Marlborough] placed over the belly of the rectus femoris muscle. The diaphragm and the quadriceps electromyograms were recorded by using a two-channel nerve monitor at 10-kHz sampling rate and 2- to 20-kHz band-pass filtering (Neurosign 100, Magstim, Whitanull, UK).

Stimulation techniques. Phrenic nerve stimulation was achieved by using the bilateral anterior magnetic phrenic stimulation technique (BAMPS) (32). Two Magstim 200 stimulators (Magstim), equipped with 45-mm “figure-of-eight” coils, capable of a maximal output of 2.5 T, were used. All stimulations were delivered in an upright position at the end of a relaxed expiration, as judged by Pes and Pga traces, to control as precisely as possible for the potential confounding effects of lung volume and abdominal configuration on the response to phrenic stimulation (8). Femoral nerve stimulation was achieved unilaterally by using a single stimulator equipped with the same coil as above, according to the previously described technique (34). All peripheral nerve stimuli (both phrenic and femoral nerves) were given at 100% of stimulator output. TMS was achieved by using a single Magstim 200 stimulator equipped with a cone-shaped figure-of-eight coil (maximal output: 2.5 T) positioned over the vertex with handle in the sagittal plane. The head was secured in position by using a head strap. The position of the coil relative to the scalp was optimized in terms of the amplitude of the diaphragm and quadriceps motor potentials evoked in conditions of relaxation with the stimulator output set at 100%. The scalp landmarks were then marked by using an indelible pen to ensure reproducibility of the stimulation conditions throughout the experiments. Subsequently, to standardize the intensity of TMS among subjects, we gave TMS at 20% of output greater than threshold (for the diaphragm). We chose to standardize around the threshold for the diaphragm rather than the quadriceps, because, in pilot studies, we found that this threshold was generally higher than that of the quadriceps. In brief, the method used to establish threshold was that the stimulator output was decreased from 100% by 5% steps until the diaphragmatic response disappeared (present in less than one-half of at least 7 stimuli). The responses of the two muscles to the same TMS shock were studied simultaneously, and the analysis was conducted in each subject, on the dominant side.

Exercise protocol. The subjects exercised on a treadmill (Powerjog EG 10, Sports Instruments, Birmingham, UK), according to an incremental design [Bruce protocol (30)]. Transcutaneous oxygen satura-

![Fig. 1. Design of the protocol. Subjects were first studied at rest, then after gentle walk, and after exercise test. Peripheral and transcranial magnetic stimulation (TMS) of the quadriceps and of the diaphragm were performed.](https://jap.physiology.org/doi/10.1152/jappl.2002.96.1.254/figure1)
replacing single-shock TMS by paired TMS, according to the procedure originally described by Kujirai et al. (20), in which the first stimulus of the pair acts as a conditioning stimulus. Paired TMS were obtained by using two Magstim 200 stimulators linked by a clocking device set (BiStim, The Magstim, Whitland, Dyfed, UK) at a 15-ms interstimulus interval that is likely to provoke intracortical facilitation (20). Paired TMS were made at baseline, 5 min after submaximal exercise, and 5, 10, 20, 30, 45, and 60 min after a Bruce protocol exhaustive exercise test. The purpose of this study was to address whether the main observation could be explained by intracortical mechanisms.

Additional study 2. In three subjects from the original set, the experimental paradigm was reproduced (except 20 min after submaximal exercise), with single TMS shock, but using multichannel esophageal diaphragmatic electrodes (Gaeltec, Dunvegan, Isle of Skye, UK) and diaphragmatic surface electrodes. In this additional experiment, the amplitudes were expressed in microvolts. The purpose of this study was to provide independent confirmation that our observations were indeed representative of the diaphragm motor area.

Additional study 3. In three subjects, we tested the variability of MEP amplitude for the costal diaphragm and quadriceps at rest during 1 h. These subjects underwent single TMS shock at baseline and 5, 20, 40, and 60 min after baseline. Amplitudes were expressed in microvolts.

RESULTS

Single TMS and Peripheral Stimulation

Exercise. All of the subjects exercised until exhaustion, with the mean duration of the test being 18 ± 4 min. Their maximum heart rate was 172 ± 10 beats/min, and the transcutaneous oxygen saturation at the end of the exercise was 96 ± 1%.

Responses to phrenic and femoral nerve stimulation. In the 11 subjects, at baseline, mean Tw Pdi was 23.4 ± 5.2 cmH_{2}O, and the mean Tw Q was 12.1 ± 2.6 kg, on average. After exercise, whatever the time, these values were respectively 23.3 ± 5.1 cmH_{2}O and 11.7 ± 4.7 kg (no significant difference), indicating the absence of peripheral contractile fatigue. Three subjects exhibited marked decreases in the amplitude more than of the diaphragm mass action potentials in response to BAMPS, probably because of changes in the recording conditions induced by exercise (for example, changes in skin conductance). The data from these subjects were discarded from analysis of the responses to TMS (Table 1).

Responses to TMS. Both a diaphragm and a quadriceps response to TMS delivered at the maximal stimulator intensity were observed in all subjects. The lowest stimulation intensity at which a diaphragm response was present was 75 ± 10%. The lowest stimulation intensity at which a quadriceps response was present was 50 ± 10% (Table 2).

Figure 2 depicts the evolution of the amplitude of the diaphragm MEP with time. No significant change was induced by the submaximal exercise run, whereas a significant decrease was observed after the maximal exercise run. This decrease was present 5 min after the end of the exercise and reached a nadir at 20 min (respectively, 60 ± 38%, P = 0.0001; 45 ± 24%, P < 0.0001). At 40 and 60 min, the amplitude of the diaphragm MEPs had partly recovered, but remained significantly lower than the baseline value.

As a consequence of this difference in pattern, the reduction in diaphragm MEP amplitude was significantly more marked than the reduction in quadriceps MEP amplitude at 20 min (quadriceps and diaphragm: 74 ± 32 vs. 45 ± 24%; P < 0.001) (Fig. 2).

The average latency of the diaphragm MEP was 17.7 ± 1.0 ms at baseline. There was no significant change after the submaximal exercise run, but it was significantly shorter than
at baseline 5 min after the real exercise test (17.2 ± 1.1 ms; \( P < 0.05 \), as well as at 40 and 60 min (17.2 ± 0.9 ms, \( P < 0.01 \) and 17.0 ± 0.8 ms, \( P < 0.0001 \), respectively). The latencies of the quadriceps MEP were unchanged after the submaximal exercise and after the actual exercise.

Additional Experiments

Double TMS: cortical facilitation and inhibition. A diaphragm and a quadriceps response to paired TMS were observed in all cases and evidenced intracortical facilitation. The evolution with time of the amplitude of the MEP obtained after intracortical facilitation is depicted for the diaphragm and the quadriceps in Fig. 3. The patterns were similar to those observed with single TMS.

*Esophageal diaphragmatic electrode.* The diaphragmatic esophageal electrode recorded shorter MEPs compared with surface electrodes (16.2 ± 0.8 vs. 17.1 ± 1.0 ms, \( P < 0.05 \)) with the same amplitude (220 ± 173 vs. 225 ± 139 μV). The behavior was the same for the esophageal and the surface electrodes, as illustrated in Fig. 4.

There was a maximum amplitude decrease 20 min after the exercise test (\( P < 0.01 \)) with a beginning of recovery afterward. In these three subjects, there was no change in the MEP amplitudes obtained after peripheral phrenic nerve stimulation.

**Single TMS at rest.** There was no change in diaphragmatic or quadriceps MEPs amplitude over a 60-min period at rest in the three subjects, as shown in Fig. 5. In this experiment, one subject had a low-cortical excitability, which also did not change with time.

**DISCUSSION**

Our data show that the MEPs elicited from the diaphragm and quadriceps muscle by TMS decrease after exhaustive treadmill exercise in healthy humans. Because peripheral contractile fatigues was excluded, this suggests a supraspinal process and generates the hypothesis that central fatigue may have a mechanistic role in task failure. Moreover, comparison of the time course and magnitude of changes in the diaphragm and the quadriceps MEP shows that this process tends to be more pronounced and slower to recover in the diaphragm.

**Methodological Issues**

Two factors are crucial to the validity of our results: the reproducibility of the stimulus and the validity of the chest surface signal as a measure of diaphragm activity.

The position of the stimulating coil in space, the position of the body and of the head of the subjects, and the position of the
coil relative to the head were carefully controlled for by the use of ink marks on the scalp and the head strap. The stability of the MEP amplitudes in both the diaphragm and the quadriceps before and after the submaximal exercise makes us confident about our ability to reproduce a reasonably consistent stimulation from one series of measurements to another. Similarly, the stability of CMAP amplitudes in response to peripheral stimulation confirms stability of the recording electrodes for both diaphragm and quadriceps.

Data for study 1 were obtained by using surface electrodes, which record the sum of the activity of the various muscle layers that lie beneath them and are also liable to record activity from distant muscle through volume conduction. TMS cannot specifically activate the cortical area governing the contraction of the diaphragm, and thus the coactivation of several muscles is unavoidable. Therefore, there is a significant risk of signal contamination at the level of chest electrodes, which may complicate the interpretation of changes in MEP. To limit this phenomenon, we placed our “diaphragm” electrodes in a way that has been shown to minimize the risk of signal contamination (9, 41). As a result, in the three subjects in whom surface and esophageal recordings were directly compared, MEPs recorded with esophageal and surface electrodes were well matched in term of latency, tending to be slightly (<1 ms) shorter from the esophageal site, as noted previously by our laboratory and others (22, 29). In these subjects, the effect of exercise on the esophageal and surface-recorded MEP was similar, suggesting that our main data set was indeed recorded from the diaphragm. In addition, an additional argument supports our view that the surface signals are of diaphragmatic origin: specifically, we report depressed rather than increased MEP after exercise. Signal contamination, if present from nonrespiratory muscle, would lead to an underestimation of the extent of the MEP depression. Conversely, if our signals were from extra diaphragmatic respiratory muscle, the finding of exercise-induced MEP depression would still be of scientific interest.

An exercise-induced depression could occur at any site from the cortex to the muscle. Although we believe that we excluded peripheral transmission failure as a cause of our data by measuring the CMAP, our data do not clearly distinguish between various candidate supraspinal sites. However, despite minor protocol differences from the main study, our paired stimulation studies demonstrated a comparable reduction in the facilitated MEP, and this leads us to postulate an intracortical mechanism.

Exercise-induced Contractile Fatigue

The level of pressure developed by the diaphragm in response to BAMPS and the level of force developed by the quadriceps in response to femoral nerve stimulations were not diminished by the exercise protocol performed by the subjects. Regarding the quadriceps, there do not seem to be fatigue data after treadmill exercise in healthy young volunteers, although low-frequency fatigue may be induced by a “stepping exercise” (12) and by cycle exercise (23). For the diaphragm, the occurrence of peripheral low-frequency fatigue after exercise is more controversial. Johnson et al. (19) showed, in 12 healthy volunteers exercising at 85 and 95% of their maximum oxygen uptake, that Tw Pdi was reduced at all lung volumes after task failure. In that study, the contribution of the diaphragm to the respiratory motor output tended to decrease with the duration of the effort, and the authors concluded that “significant diaphragmatic fatigue is caused by the ventilatory requirements imposed by heavy endurance in healthy persons.” These results were confirmed in another study by the same team (1), which also suggested that the mechanism of diaphragm fatigue induced by whole body exercise was a conjunction of blood flow redistribution toward limb muscle reducing diaphragm perfusion and of the diaphragmatic effort. Similarly, Mador et al. (24) also found diaphragm fatigue associated with task failure in sedentary subjects cycling at 80% of their maximal work capacity. However, other data support our premise that diaphragm fatigue is difficult to elicit in healthy subjects; for example, Mador et al. (23) did not find diaphragm fatigue after exhaustive cycling exercise in healthy elderly subjects. Similarly, Levine and Henson (21) found it impossible to elicit low-frequency diaphragm technique in young adults using treadmill exercise alone; indeed, even when an inspiratory resistance was used with treadmill exercise, fatigue was seen in only 5 of 10 subjects. Some of these discrepancies may be due to the difference between cycling and treadmill exercise. In particular, treadmill exercise conducted with the Bruce-type protocol implies a very rapid increase in the effort intensity and may induce dyspnea more intensely and more rapidly than other protocols.

Taken together, these data suggest that task failure associated with contractile diaphragm fatigue during exercise only occurs with the use of very specific protocols rather than as a common occurrence. In our subjects, the combination of an absence of change in diaphragm and quadriceps Tw output with a reduction in the amplitude of the MEP makes it logical to assume that the neuromuscular contribution to task failure, if any, was predominantly central.

Exercise-induced Central Fatigue

A central component to skeletal muscle fatigue can be demonstrated by using the Tw interpolation technique (31) (for review, see Ref. 13). In brief, this technique assesses the degree of voluntary activation of a given muscle by superimposing a supramaximal stimulation of its parent nerve onto voluntary contraction. With this technique, central fatigue has been shown to develop in the quadriceps during sustained maximal voluntary contractions (5) and in other limb muscles (see

Fig. 5. Evolution, in 3 subjects, of diaphragmatic (a) and quadricipital (●) MEP amplitude after TMS at rest, without any exercise. It can be seen that amplitude did not change with time. Values are means ± SD.
review in Ref. 13). Regarding the diaphragm, it has been shown that the inability of healthy subjects to voluntarily sustain a target Pdi amounting to 75% of the maximal possible value is largely, although not solely, due to a central component of fatigue (4, 28). Guleria et al. (16) have suggested that one explanation for the relative difficulty generating low-frequency fatigue in the diaphragm compared with nonrespiratory muscles could be due to such a phenomenon. Consistent with the present data, that study showed that normal subjects could achieve greater activation of the quadriceps (87.5%) than of the diaphragm (70%) during similar loading protocols and that, consequently, there was a lesser reduction in Tw tension in the diaphragm compared with the quadriceps after the protocol (6 vs. 41%).

Another way to assess central fatigue is to study the response of the muscle of interest to transcranial electrical or magnetic stimulation (see review in Ref. 13). However, the changes in the response to TMS that occur during and after a fatiguing task are complex. During the fatiguing effort itself, both excitatory and inhibitory mechanisms take place. The size of MEP increases (40, 44), and the poststimulation cortical silent period lengthens (40). Whereas nonfatiguing tasks induce postexercise facilitation (3, 37), prolonged fatiguing tasks induce postexercise depression (35), although this is not constantly observed (27) and may depend on individual variations of the baseline cortical excitability (44). The depression of the MEP after a fatiguing exercise, first described by Brasil-Neto et al. (7) in the flexor carpi radialis, has been subsequently evidenced in a range of muscles. It can reach 50% of the baseline values, with a variable but progressive recovery of amplitude, which takes place over ≥30 min (7). It is accompanied by a lengthening of the post-TMS silent period (36). The source of the reduction in the corticospinal output is mainly cortical (42), but it may depend on the experimental paradigm. Sacco et al. (36), from the abolition of the postexercise depression in resting MEP by a weak tonic contraction, have shown that decreases in excitability at the spinal level could contribute to the reduced corticomotor excitability that is observed after a fatiguing exercise. The exercise-induced depression in MEP is specific to the muscle engaged in the fatiguing task (27, 37) as is also the case for the postexercise lengthening of the cortical silent period (26). Hollge et al. (18) are seemingly the only investigators to have studied the response to TMS of various muscles after different types of whole body exercise. They showed that predominantly anaerobic exercises (press-ups, 400-m runs) induced a marked postexercise depression in MEP without change in peripheral responses to stimulation and without changes in latency. Conversely, predominantly aerobic prolonged exercises, such as jogging, were not associated with postexercise changes in the MEP amplitude. With intense short bouts of exercise-generating high-mechanical forces being a source of muscle damage (11), these observations support the concept of central fatigue as a protective mechanism (13).

**Postexercise Depression of the Diaphragmatic Corticomotor Output**

Our study, by showing postexercise depression of the response to TMS after an exhaustive bout of whole body exercise, is in line with the literature. It is, however, seemingly the first to describe this phenomenon in the diaphragm. We observed a reduced diaphragmatic response not only to single-shock TMS, but also to double-shock TMS performed with a 15-ms interstimulus interval that is known to produce intracortical facilitation in skeletal muscle (20), including the diaphragm (10). Therefore, it is likely that intracortical facilitation of the diaphragm response to TMS was decreased in our subjects, which is an argument in favor of a cortical site for the reduction in the corticomotor output. Excluding subjects with decreased electromyographic responses to phrenic nerve and femoral nerve stimulation from the analysis allows us to rule out a peripheral site. However, we did not use specific approaches to discriminate between a cortical and a spinal site of inhibition (35, 42).

As in other studies, the latency of the quadriceps MEP did not change after exercise in our subjects. This was not the case in the diaphragm, where a reduction in MEP latency was present. This result is surprising, because a shortened diaphragm MEP latency is generally associated with facilitation of the response to TMS (38) rather than with inhibition. However, although sufficiently consistent to reach statistical significance, the shortening in latency was of small magnitude. Hollge et al. (18) observed shortened MEP latencies after whole body exercise of the aerobic type.

The pattern of MEP depression and recovery that we observed in the quadriceps, with an average 35% reduction in size compared with baseline and rapid recovery, resembles that previously observed in hand muscles during focal fatiguing tasks and in limb muscles after whole body exercise (18). In the diaphragm, postexercise depression took longer to reach a nadir than for the quadriceps, reaching a maximum 20 min after the end of exercise, and recovering at a slower pace. There was no major difference in behavior among the subjects, although, anecdotally, the most sedentary among them tended to exhibit an even more marked and more prolonged diaphragmatic depression. The number of subjects involved in this study is, however, too small to allow us to draw any conclusion from this finding, but it would be interesting to test this hypothesis prospectively in larger groups of subjects with different states of fitness and to study the effects of training on this pattern.

The tendency to observe a more profound and more durable postexercise corticomotor inhibition in the diaphragm than in a locomotor muscle after a “natural” exercise task has various implications. Simply put, this difference could reflect evolutionary development of a tendency for early central diaphragm fatigue, perhaps to protect the organism from overt contractile failure of the diaphragm. This explanation is plausible and would be consistent with early observations that the inspiratory muscles are better able to sustain activity under load (14). However, it ignores the observation that overt diaphragm fatigue does not, even at peak exercise, result in impaired ventilation (19). An alternative explanation is that it is the cortical control of the quadriceps that has undergone evolutionary development to prevent early termination of locomotor tasks, which might include escaping predators or catching animals for food. Study of these and other muscle groups during various tasks relevant to daily life might resolve this issue.

In summary, our data confirm significant depression of both diaphragm and quadriceps MEP after incremental treadmill exercise, suggesting a role for central fatigue in task failure with this protocol. The use of paired stimuli suggests that an
intracortical mechanism is at least partially responsible for this observation. The depression tended to be more pronounced for the diaphragm motor area than the quadriceps motor area, suggesting that regions of the motor cortex have a range of susceptibilities to central fatigue, which may reflect evolutionary-ary pressures.

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