Supraspinal fatigue does not explain the sex difference in muscle fatigue of maximal contractions

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Young women are less fatigueable than young men for maximal and submaximal contractions, but the contribution of supraspinal fatigue to the sex difference is not known. This study used cortical stimulation to compare the magnitude of supraspinal fatigue during sustained isometric maximal voluntary contractions (MVCs) performed with the elbow flexor muscles of young men and women. Eight women (25.6 ± 3.6 yr, mean ± SD) and 9 men (25.4 ± 3.8 yr) performed six sustained MVCs (22-s duration each, separated by 10 s). Before the fatiguing contractions, the men were stronger than the women (75.9 ± 9.2 vs. 42.7 ± 8.0 N·m; P < 0.05) in control MVCs. Voluntary activation measured with cortical stimulation before fatigue was similar for the men and women during the final control MVC (95.7 ± 3.0 vs. 93.3 ± 3.6%; P > 0.05) and at the start of the fatiguing task (P > 0.05). By the end of the six sustained fatigue MVCs, the men exhibited greater absolute and relative reductions in torque (∼5% vs. ∼3% of initial MVC) than the women (52 ± 9%; P < 0.05). The increments in torque (superimposed twitch) generated by motor cortex stimulation during each 22-s maximal effort increased with fatigue (P < 0.05). Superimposed twitches were similar for men and women throughout the fatiguing task (5.5 ± 4.1 vs. 7.3 ± 4.7%; P > 0.05), as well as in the last sustained contraction (7.8 ± 5.9 vs. 10.5 ± 5.5%) and in brief recovery MVCs. Voluntary activation determined using an estimated control twitch was similar for the men and women at the start of the sustained maximal contractions (91.4 ± 7.4 vs. 90.4 ± 6.8%, n = 13) and end of the sixth contraction (77.2 ± 13.3% vs. 73.1 ± 19.6%, n = 10). The increase in the area of the motor-evoked potential and duration of the silent period did not differ for men and women during the fatiguing task. However, estimated resting twitch amplitude and the peak rates of muscle relaxation showed greater relative reductions at the end of the fatiguing task for the men than the women. These results indicate that the sex difference in fatigue of the elbow flexor muscles is not explained by a difference in supraspinal fatigue in men and women but is largely due to a sex difference of mechanisms located within the elbow flexor muscles.

transcranial magnetic stimulation; central fatigue; voluntary activation; gender; elbow flexor muscles

WOMEN ARE LESS FATIGABLE THAN MEN when sustaining a contraction at the same relative intensity (11) for various upper and lower limb muscle groups and contraction types (6, 14, 15, 20, 22, 26, 38). For example, when sustaining the same relative low- to moderate-intensity contraction with the elbow flexor muscles, young women had a longer time to failure than young men who were stronger (12, 14, 15). The differences appear related to the task but may be underpinned by the absolute strength exerted and differences in oxidative metabolism (13–15, 26). Differences in the neural drive to the muscle may also contribute. During the performance of intermittent isometric maximal contractions with the dorsiflexor muscles, young men experienced greater deficits in maximal force and voluntary activation of the muscle than young women (26). It was proposed that the greater failure of voluntary activation in men was due to increased firing of fatigue-sensitive small-diameter muscles afferents that are activated by metabolites. In that study, voluntary activation was quantified through stimulation of the motor nerve during maximal contraction (26), and the observed increases in the increment in force evoked by such stimulation imply a failure of voluntary drive at one or more sites proximal to the motor nerve.

A failure in voluntary activation during maximal efforts means that the level of neural drive to the muscle is less than optimal (8). The extra force evoked by the superimposed stimulus to the axons indicates either that the motor units were not all recruited voluntarily or that they were discharging at rates that were not high enough to produce full fusion of force (1, 10, 21). This progressive impairment of voluntary activation is known as central fatigue and is due to failure at a site within the central nervous system (8). Stimulation of the motor cortex can also be used to estimate voluntary activation and can further localize the site of failure of voluntary drive to or above the level of the motor cortical output (9, 31, 34, 35). Supraspinal fatigue is a component of central fatigue and is attributable to suboptimal output from the motor cortex (8). It is seen as an exercise-related fall in voluntary activation measured with cortical stimulation. It is unknown whether the greater central fatigue that develops in men compared with the women (26) is due to failure at sites proximal or distal to the motor cortex, although previous studies have suggested that small-diameter muscle afferents may impair voluntary drive at a supraspinal level (4, 9). Therefore, this study used stimulation of the motor cortex to further define the sites of failure during performance of an intermittent fatiguing contraction in men and women.

The purpose of this study was to compare the supraspinal fatigue measured with transcranial magnetic stimulation (TMS) of the motor cortex during sustained isometric maximal voluntary contractions (MVCs) of the elbow flexor muscles of women to men.
young men and women. We hypothesized that men would experience greater reductions in maximal force than women and that this would be due to greater deficits in the voluntary supraspinal drive that generates the output from the motor cortex. We also determined whether the changes in voluntary drive during isometric exercise were accompanied by changes in motor cortex "excitability," which we assessed by the short-latency excitatory electromyograph (EMG) response to the motor cortex stimulation and the length of the subsequent EMG silence ("silent period").

METHODS

Eight women (25.6 ± 3.6 yr) and 9 men (25.4 ± 3.8 yr) volunteered to participate in the study, which involved one experimental session with the elbow flexor muscles. All subjects were healthy with no known neurological or cardiovascular diseases and were naive to the protocol. Before participation in the study, each subject provided informed consent. All of the experimental procedures were approved by the institutional ethics committee and conducted according to the Declaration of Helsinki at the Prince of Wales Medical Research Institute, Sydney, Australia.

The physical activity level for each subject was assessed with a questionnaire (18) that estimated the relative kilocalorie expenditure of energy per week. The day of the menstrual cycle on which the experimental protocol was performed was recorded for each female participant. The first day of menstruation was considered as day 1 of the cycle.

Recordings

Subjects were seated upright in an adjustable chair with the dominant arm held firmly at the wrist via a secure strap in an isometric myograph that measured elbow flexion torque (Fig. 1A). Subjects were positioned with the dominant shoulder and the elbow flexed at 90° with the forearm vertical and fully supinated. Isometric elbow flexion torque was measured using a linear strain gauge (XTran, Melbourne, Australia; linear to 2 kN). EMG signals were recorded with bipolar surface electrodes (Ag-AgCl, 10-mm diameter) that were placed over the muscle belly and tendon of biceps brachii and triceps brachii. Care was taken to standardize electrode locations. A large self-adhesive ground electrode was fixed on the upper arm. EMG signals were amplified (×100–300) and band-pass filtered (16–1,000 Hz). Force (1,000 samples/s) and EMG (2,000 samples/s) signals were recorded to computer using a 1401 A-D converter and Spike2 software (CED, Cambridge, UK).

Stimulation

Two forms of stimulation were used during each experiment: stimulation of the brachial plexus and TMS.

Fig. 1. Experimental setup, fatiguing protocol, and superimposed twitch torques during the fatiguing protocol. A: experimental apparatus and setup. B: representative torque data of a man who performed the fatiguing protocol. Arrows at the bottom of the panel show the timing of cortical stimuli (Stim). C: superimposed twitches evoked by cortical stimulation for the same subject as in B. Twitches evoked during the control maximal voluntary contraction (MVC) trials (overlayed) and at the start (a) and end (b) of each of the 6 22-s sustained MVCs are shown. The superimposed twitch torque increased with fatigue.
Stimulation of the brachial plexus. The brachial plexus was stimulated to produce a maximal compound muscle action potential (Mmax) of the biceps brachii and triceps brachii muscles while the subject was at rest. Single stimuli (100-μs duration) were delivered to the brachial plexus with a cathode in the supravacular fossa and an anode on the acromion using a constant-current stimulator (model DS7AH, Digitimer, Welwyn Garden City, Hertfordshire, UK). The stimulation intensity ranged between 60 and 180 mA. The average amplitude of the resting Mmax was 19.5 ± 4.7 mV for the biceps and 12.2 ± 3.9 mV for the triceps.

TMS. Transcranial magnetic stimuli were delivered via a round coil (13.5-cm outside diameter) over the vertex (Magstim 200, Magstim, Whitland, UK) to evoke motor-evoked potentials (MEPs) in biceps and triceps muscles. The direction of current flow in the coil preferentially activated the motor cortex in the hemisphere, which innervated the dominant arm. A single pulse was delivered over the motor cortex at an intensity (50–90% of maximum stimulator output) that produced a large MEP in the agonist biceps muscle (minimum amplitude of 50–60% of Mmax) during a brief MVC of the elbow flexor muscles but only a small MEP in the antagonist triceps muscle (amplitude <15% of Mmax) (36). TMS was delivered during voluntary contractions only.

Experimental Protocol

Each subject visited the laboratory for one experimental session to assess voluntary activation during brief MVCs and during performance of fatiguing intermittent isometric maximal contractions performed with the elbow flexor muscles over a period of 182 s. The intermittent contractions included 6 22-s maximal contractions with a 10-s interval between each sustained MVC. The motor cortex was stimulated using TMS to elicit MEPs in the biceps brachii and twitches of the elbow flexor muscles to assess voluntary activation at the start and end of each 22-s contraction. TMS was also delivered to the cortex during brief nonfatiguing maximal contractions before and after the fatiguing task.

The protocol comprised:

1) Measurement of Mmax at rest using electrical stimulation of the brachial plexus.

2) Performance of five sets of brief control contractions (2–3 s) separated by at least 1 min of rest to minimize fatigue. Each set involved performance of a MVC followed by contractions of 60% MVC and 80% MVC. The submaximal target contractions were calculated from the preceding MVC and displayed on a light-emitting diode visual feedback device. Within a set, the start of each contraction was separated by 5 s, and TMS was delivered during each contraction.

3) Each subject performed a set of six sustained 22-s MVCs separated by 10 s of rest (Fig. 1B). After each MVC, brief contractions were performed at 60% and 80% MVC. These target torques were calculated from the torque just before cessation of the 22-s sustained MVC. TMS was delivered to the cortex at the start (after 2 s of contraction) and end (2 s before the end of the contraction) of each sustained MVC and during each submaximal contraction. Immediately before the first sustained MVC, a 60% and 80% MVC were performed. The target values for these contractions were calculated from the last brief control MVC.

4) Recovery was monitored for ~10 min by performance of a series of brief contraction sets similar to those performed before the fatiguing contractions. Sets of contractions consisted of a brief MVC followed by a contraction at 60% and 80% of the MVC just performed. Ten sets of contractions were performed at the following times after termination of the sustained MVCs: 15 s, 45 s, 1 min 15 s, 2 min 15 s, 3 min 15 s, 4 min 15 s, 5 min 15 s, 6 min 15 s, 8 min 15 s, and 10 min 15 s.

Data Analysis

Voluntary activation was quantified by measurement of the torque responses to stimulation of the motor cortex (35, 36). Any increment in elbow flexion torque evoked during a contraction (superimposed twitch) was expressed as a fraction of the torque before the stimulation (9, 31). The superimposed twitch was also expressed as a fraction of the estimated amplitude of the response evoked by the same stimulus at rest (resting twitch). The estimation of the resting twitch was achieved for each subject by linear regression analysis of the amplitude of the superimposed twitch vs. the voluntary torque during the brief maximal and submaximal contractions (60 and 80% MVC). One regression analysis was performed for each set of brief contractions. During the fatigue task, the regression was calculated using the brief 60 and 80% MVCs and the nearest cortical stimulus during a sustained MVC. Thus each superimposed twitch was compared with an estimated resting twitch measured when the muscle was in a similar state of fatigue. For example, the brief submaximal contractions performed during the 10-s interval after the cessation of a 22-s contraction were used as a reference for the superimposed twitches elicited at the end of the previous sustained contraction and at the start of the next sustained contraction. The y-intercept was taken as the estimated amplitude of the resting twitch evoked by motor cortex stimulation (Fig. 2). The amplitude of the estimated resting twitch can be calculated to be 12.5 N·m through extrapolation of a linear regression (r² = 0.997) (35, 36) B: 9 sets of brief contractions and their corresponding linear regressions from 1 male subject. Each set of contractions is represented by a different symbol. Five sets of brief contractions (filled symbols) were performed before the fatigue protocol and were used to calculate the control value for the estimated resting twitch. The other 4 sets of contractions illustrated (open symbols) are the final 4 in the fatigue protocol and are from the beginning and end of the 5th and 6th sustained MVCs in the same subject. Note the fall in voluntary torque and the estimated resting twitch (y-intercept of linear regression) with fatigue.

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be accurately determined from three data points, when the contractions are above 50% MVC (35). The amplitude of the resting twitch was estimated rather than measured directly because motor cortical and spinal cord excitability increase with activity (25). All of the elbow flexor muscles activated by TMS contribute to the amplitude of the estimated resting twitch.

The estimated resting twitch torque was used to calculate voluntary activation with the following formula: voluntary activation = (1 − superimposed twitch/estimated resting twitch) × 100 (35, 36). Although the regression of voluntary torque and the superimposed twitch torque evoked during the contractions was always linear during control contractions, it was not linear (r < 0.9) in one-third of the contraction sets during the fatigue protocol. This is likely due to the speed of torque recovery or large triceps MEPs. Consequently, these estimations of voluntary activation and the predicted twitch amplitude were excluded from the statistical analysis. Because the poor estimates of the resting twitch were concentrated in particular subjects, and in the middle of the fatigue protocol, four subjects (2 men and 2 women) were excluded from analysis in the fatigue and recovery period. Estimates for the end of the third sustained MVC and beginning and end of the fourth sustained MVC were also excluded.

The contractile properties of the muscle were also assessed. The amplitude of the estimated resting twitch was used as an index of the force-generating capacity of the muscle and the fall of torque after a cortical stimulus was used to determine the peak relaxation rate of muscle fibers (33). The peak relaxation rate of muscle was calculated during each MVC by measurement of the steepest rate of torque decline during the period of EMG silence immediately after motor cortex stimulation. The steepest rate of torque decline was normalized to the total torque (voluntary plus evoked) before the silent period. This measure reflects the peak relaxation rate of elbow flexor muscle fibers.

The amplitude and areas of MEPs and M_{max} were measured between sets of cursor set at the start and end of the waveform for the biceps and triceps muscles. Because amplitude and area showed similar changes, only areas are reported. The area of each MEP was between sets of cursors set at the start and end of the waveform for the contractile properties of the muscle were also assessed. The amplitude of the estimated resting twitch was used as an index of the force-generating capacity of the muscle and the fall of torque after a cortical stimulus was used to determine the peak relaxation rate of muscle fibers (33). The peak relaxation rate of muscle was calculated during each MVC by measurement of the steepest rate of torque decline during the period of EMG silence immediately after motor cortex stimulation. The steepest rate of torque decline was normalized to the total torque (voluntary plus evoked) before the silent period. This measure reflects the peak relaxation rate of elbow flexor muscle fibers.

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Voluntary torque was quantified by calculation of the mean torque over a 100-s period immediately before the stimulus.

Statistical Analysis

Data are reported as means ± SD within the text and are displayed as means ± SE in the figures. Two-way, repeated-measures ANOVAs were used to compare the following variables between men and women across time: voluntary torque, percent decline in MVC torque, voluntary activation measures, MEP area, silent period duration, estimated resting twitch amplitude, and peak rate of relaxation after cortical stimulation. Post hoc analyses (t-tests) were used to test for differences among pairs when appropriate. A significance level of P < 0.05 was used to identify statistical significance.

RESULTS

The men and women were similar in age (25.4 ± 3.8 vs. 25.6 ± 3.6 yr; P > 0.05) but differed in height (176 ± 6 vs. 164 ± 7 cm; P < 0.05) and mass (76.5 ± 9 vs. 58.1 ± 7 kg; P < 0.05). The estimated physical activity levels were similar for the men (26.7 ± 19.4 metabolic equivalents·h/wk) and women (22.6 ± 17.8 metabolic equivalents·h/wk; P > 0.05).

MVC Torque and Voluntary Activation

Control trials. The men were stronger than the women for the five brief MVCs that were performed before the sustained fatiguing contractions (75.9 ± 9.2 vs. 42.7 ± 8.0 N·m; P < 0.05). The mean voluntary activation measured with cortical stimulation during these contractions was calculated with the estimated resting twitch and was greater for the men (96.5 ± 2.8%) than the women (93.0 ± 5.2%; P = 0.04) when the five control MVCs were pooled. However, voluntary activation was not different between the men and women for the fifth (final) control trial (95.7 ± 3.0 vs. 93.3 ± 3.6%; P > 0.05).

Fatigue. MVC torque declined for men and women during the six contractions sustained for 22 s (P < 0.05). By the end of the last sustained MVC, the men exhibited a greater absolute decline in torque (45.0 ± 6.5 N·m) compared with the women (20.9 ± 6.2 N·m; P < 0.05; Fig. 3A). The relative reduction in torque from mean of the initial control MVCs to the end of the sixth sustained MVC was significantly greater for the men.

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Fig. 3. MVC torque for the men (n = 9) and women (n = 8) before, during, and after the fatiguing task. A: MVC torque is expressed in N·m (means ± SE) and is shown for the control trials (mean of 5 brief MVCs), at the start and end of each sustained 22-s MVC, and during brief MVCs for the 10-min recovery. B: MVC torque is normalized to the mean MVC torque during control contractions for each subject and is shown in the same format as in A. The men had greater absolute and relative reductions in torque than the women during the intermittent fatiguing contractions. C: control MVC torque is plotted against the relative decline in MVC torque by the end of the 6th contraction for each subject. A quadratic relation is shown (r² = 0.75, y = 1.8x − 0.0114x² − 1.8). Those individuals who were stronger experienced greater fatigue.
Brief MVCs performed in the recovery period increased with time for both men and women ($P < 0.05$). However, at 10 min recovery, men were significantly less recovered (76.4 ± 9.0% of initial MVC values) compared with the women (88.4 ± 7.8%; $P < 0.05$; Fig. 3B).

There was an association between the initial MVC (mean of 5 control trials) and the relative decline in MVC at the end of the sixth sustained MVC. The fatigue was related to the initial absolute maximal torque (quadratic relation: $r = 0.87$, $r^2 = 0.75$, $P < 0.05$) (Fig. 3C) such that stronger individuals exhibited greater fatigue.

For the women, there was no association between the day of menstrual cycle on which the experiment was performed and the absolute or relative decline in MVC torque during the fatiguing contraction ($P > 0.05$).

**Voluntary activation and fatigue.** The increments in torque (superimposed twitch) generated by motor cortex stimulation during each 22-s maximal effort (Fig. 1C) were expressed relative to the torque before the stimulation. Superimposed twitches increased during the sustained MVCs for men and women from 1.9 ± 1.6% at the start of the contraction to 9.1 ± 5.7% at the termination of the fatiguing task ($P < 0.05$). Superimposed twitches were similar for men and women throughout the fatiguing task (5.5 ± 4.1 vs. 7.3 ± 4.7%; $P > 0.05$), as well as at the end of the sustained contraction (7.8 ± 5.9 vs. 10.5 ± 5.5%; $P > 0.05$; Fig. 4A). During recovery, superimposed twitches decreased to similar levels during the 10 min to 1.9 ± 1.0% for the men and to 2.0 ± 1.3% for the women (Fig. 4A).

Voluntary activation was calculated using the estimated resting twitch with TMS. It decreased similarly for the men and women from the start of the sustained maximal contractions (91.4 ± 7.4 vs. 90.4 ± 6.8%; $n = 13$, 6 women) to the end of the sixth sustained contraction (77.2 ± 13.3 vs. 73.1 ± 19.6%; $n = 10$, 5 women; Fig. 4B). The men and women increased to similar levels of voluntary activation during the 10 min of recovery to 84.6 ± 8.4% for the men ($n = 5$) and 91.6 ± 4.6% for the women ($n = 6$) ($P = 0.11$, Fig. 4B).

**MEPs and Silent Period**

**Control trials.** For the biceps brachii, the largest MEP area (82 ± 18% $M_{max}$ in men and 78 ± 14% $M_{max}$ in women) occurred during the 60% MVC, and the smallest occurred during the MVC (53 ± 13% $M_{max}$ in men and 57 ± 14% $M_{max}$ in women). The MEP area was similar for the men and women during each contraction strength of the control trials. There was also no sex difference for the area of the small MEP in triceps brachii (10.7 ± 7.0%).

In biceps, the duration of the silent period following cortical stimulation during a MVC was similar for men (149 ± 97 ms) and women (144 ± 77 ms, $P > 0.05$) across the five control trials (Fig. 5B).

**Fatigue and recovery.** The area (%$M_{max}$) of the MEP in biceps increased similarly during the fatiguing maximal contractions for both men and women (Fig. 5A). MEP area increased from 63 ± 3% at the start of the first contraction to 96 ± 7% ($P < 0.05$) at the end of the sixth sustained MVC. It also decreased similarly for men and women to 45 ± 3% after 10 min of recovery.

The silent period in biceps EMG increased in duration from the start to the end of the fatiguing task and during each of the 22-s sustained contractions ($P < 0.05$; Fig. 5B). The increase in the silent period duration was similar for the men and women ($P > 0.05$).

**Twitch Contractile Properties**

**Estimated resting twitch amplitude.** The amplitude of the estimated resting twitch was greater for men (17.9 ± 7.8 N·m) than women (11.7 ± 3.7 N·m; $P < 0.05$) during the control trials. It declined during the fatiguing task for both men and women ($P < 0.05$; Figs. 2B and 6A). However, by the end of the sixth sustained MVC, the relative reduction in amplitude was greater for the men (59 ± 12%) than the women (27 ± 19%; $P < 0.05$). After 10 min of recovery, the men were 42 ± 12% of control twitch amplitude, and the women were at 77 ± 13% ($P < 0.05$) of control values.

**Peak rate of relaxation after cortical stimulation.** The magnitude of the normalized peak relaxation rate (measured during...
the TMS-induced silent period) was greater for the men (13.5 ± 2.2 s) than women (9.3 ± 1.8 s; P < 0.05) in the control trials. That is, the muscle of the men relaxed more quickly than that of the women. During the fatiguing task, the peak relaxation rate declined for both sexes (P < 0.05) but more so for the men than the women (P < 0.05; Fig. 6B). The change in peak relaxation rate for the men was 53% and for the women 22% from initial values at the start of the fatiguing task (P < 0.05). Both the men and women recovered to initial control values at 10 min of recovery.

**DISCUSSION**

This study used motor cortical stimulation to compare the magnitude of supraspinal fatigue during sustained isometric MVCs performed with the elbow flexor muscles of young men and women. The main findings were that 1) men were stronger than women for the elbow flexor muscles but exhibited greater muscle fatigue; 2) twitch torques (%MVC) evoked by stimulation of the motor cortex during MVCs increased and thus voluntary activation decreased with fatigue, but twitch torques were similar for men and women during the final control MVC, the fatiguing contractions and recovery; 3) MEP size and the silent period duration increased with fatigue but were similar for men and women; and 4) the reductions in the amplitude of the estimated resting twitch and in the peak relaxation rate of muscle during fatigue were greater for the men than the women. Thus men experienced greater muscle fatigue than women during the fatiguing task. Supraspinal fatigue increased similarly during the sustained maximal contractions for both men and women, but peripheral fatigue was greater for the men.

**Women Were Less Fatigable than Men but Voluntary Activation Was Similar**

The men were stronger than the women but the reduction in maximal torque during the fatiguing task was greater for the men. These findings are consistent with other studies that have observed greater fatigue resistance for women compared with men for submaximal and maximal contractions in young adults (2, 3, 5, 12, 15, 26, 28, 38). Furthermore, there was an
association such that the stronger subjects experienced greater fatigue (Fig. 3C). Similar relations are observed for sustained isometric contractions (6, 12, 13, 15) but not for intermittent isometric tasks in which the contraction duration is relatively brief (~5 s) compared with the rest intervals (7, 14, 26). Consequently, the greater fatigue experienced by the men compared with the women appears related to their greater strength but only for tasks that involve longer duration sustained contractions.

The sex difference in the reduction of MVC torque of the elbow flexor muscles was not related to a sex difference in voluntary activation measured with motor cortex stimulation. This was contrary to our original hypothesis. The size of the superimposed twitch increased in both men and women during the fatiguing task. These results indicate that voluntary descending drive was not sufficient to optimally activate the motoneuron pool, and that the reductions in maximal torque during the fatiguing task were in part due to central fatigue at a site at or above the level of the motor cortical output. However, there was no sex difference in the degree of supraspinal fatigue. Both estimates of voluntary activation (the increments in torque from the cortical stimulation and the voluntary activation calculated using the superimposed twitch torque relative to the estimated twitch torque) were similar for men and women. The level of supraspinal fatigue quantified by the increments in torque relative to the ongoing torque (9.1%) was similar to that observed for maximal sustained and intermittent contractions (range of 5.2–9.8%) (9, 31). Voluntary activation calculated using the estimated resting twitch was also similar at the end of the fatiguing task (76.7%) to another fatiguing protocol (79.6%), which required the force to decline to 60% of the initial MVC (35). The firing of group III and IV muscle afferents, which are sensitive to ischemia and the metabolites of fatigue, may act at a supraspinal level to impair voluntary activation (4, 9), and it has been suggested that the higher intramuscular pressure in stronger muscles may lead to greater discharge of group III and IV muscle afferents in men than women. However, our results do not support a difference in the supraspinal influence of fatigue-sensitive afferents in men and women.

**MEP Area and Silent Period Were Similar for Men and Women**

Changes in the EMG responses to cortical stimulation with fatigue were similar for the men and women. The area of MEPs elicited during the sustained contractions increased with fatigue as reported in previous studies (30–32). This increase was similar for men and women. The size of the MEP will depend on the balance of all the excitatory and inhibitory influences to the corticospinal neurons, the response of the motoneuron pool to the descending volleys, and the muscle fiber action potentials. We normalized the MEP to Mmax elicited at rest with stimulation of the brachial plexus, and hence we did not account for any activity-dependent changes in the muscle fiber action potential (32). However, this was not likely to be different between men and women. Alterations in the amplitude of the M wave with fatigue did not account for the sex difference in muscle fatigue of the dorsiflexor muscles (26). Furthermore, responses to stimulation of descending tracts at the cervicomedullary level do not increase with fatigue for the elbow flexor muscles (8, 30). Thus the growth in the MEP size likely represented an increase in cortical excitability (30, 32). The MEP recovered relatively quickly compared with the voluntary activation, which remained depressed for both men and women up until 10 min of recovery. The dissociation in recovery between the MEP and voluntary activation has been observed previously (31), and it indicates that for both men and women the increased increments in torque due to the cortical stimulation do not entirely depend on the recruitment of neurons that are represented by the increased MEP.

The duration of the silent period increased with fatigue similarly for the men and women. Whereas the initial part of the silent period (the first 50–100 ms) is likely influenced by spinal mechanisms, including recurrent inhibition and afterhyperpolarization, the latter part represents intracortical inhibition (16). Thus the increase in the duration of the silent period with fatigue may reflect increased intracortical inhibition. Because the silent period lengthened similarly for the men and women, this change is unlikely to contribute to the sex difference in muscle fatigue that we observed. Our findings of similar changes in the EMG responses to TMS, as well as similar supraspinal fatigue in men and women, suggest that the cortical effects of muscle fatigue are not different between the sexes.

**Peripheral Fatigue Was Greater for the Men than the Women**

The mechanisms for the sex differences in muscle fatigue must be located at levels distal to the output of the motor cortex, potentially at sites in the spinal cord or the muscle. Accordingly, we found evidence that the elbow flexor muscles of women were less fatigable. The amplitude of the estimated resting twitch decreased with fatigue and this reduction was greater for the men than the women. Thus the men experienced greater peripheral fatigue of the muscle compared with the women by the end of the fatigue task. Furthermore, twitch amplitude was not fully recovered for either sex after 10 min but was more depressed for the men than the women. The changes in the amplitude of the estimated resting twitch were similar to those observed in the MVC for the men and women. The parallel changes in the estimated resting twitch and MVC suggests that the sex difference in muscle fatigue may be largely explained by processes within the muscle. The peak relaxation rates of the muscle were consistent with a different distribution of fiber types in the elbow flexors of men and women with more fast twitch fibers in the men. The men had faster relaxation rates prior to fatigue and slowed more during the fatigue task. A recent study by Russ et al. (27) showed higher rates of glycolytic metabolism in men than women during isometric MVCs (27). This is also consistent with differences in the fiber-type composition and area of muscle in men and women although some studies show this sex difference is equivocal (17, 22–24, 29, 37).

Although our study does not provide direct evidence on motoneuron behavior, the firing of group III and IV muscle afferents does not appear to reduce motoneuron excitability for the elbow flexor muscles (4), so that sites at the spinal level may have a limited contribution to the sex difference in muscle fatigue for these muscles. However, for other muscles, central mechanisms may be more important in explaining the sex
difference in muscle fatigue. For the ankle dorsiflexor muscle, men had greater decrements in voluntary activation measured with stimulation at the motor nerve during maximal contractions (26), indicating that the sex differences for this muscle were central in origin. Indeed, there may be differences between muscle groups in the actions of group III and IV afferents on the motoneuron pool. Although group III and IV afferents do not inhibit motoneuron activity of the elbow flexor muscles (4), stimulation of the descending tracts shows that the motoneuron pool of the elbow extensors muscles is depressed by maintained firing of group III and IV muscle afferents after a fatiguing contraction (19). Consequently, it is conceivable that the site for the sex difference in muscle fatigue varies not only with the task performed but also with the muscle being assessed.

In conclusion, men had greater reductions in MVC torque than women during repeated sustained maximal fatiguing contractions. Supraspinal fatigue was similar for men and women. This was shown by the similar increases in the superimposed twitch torques and similar reductions in voluntary activation. Changes in the EMG responses to cortical stimulation were also similar for men and women. In contrast, peripheral fatigue, which was assessed by the size of the estimated resting twitch, was greater for men than women, and comparison of muscle relaxation rates suggested that this may be due to a different distribution of muscle fiber types. Thus the greater muscle relaxation rates suggested that this may be due to a difference in muscle fiber types. Thus the greater fatigue exhibited by men compared with women during a maximal fatiguing contraction of the elbow flexor muscles is not explained by a sex difference in supraspinal fatigue but is largely due to sex differences in limitations within the elbow flexor muscles.

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REFERENCES

