

Supraspinal Fatigue Is Similar in Men and Women for a Low-Force Fatiguing Contraction

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ABSTRACT

KELLER, M. L., J. PRUSE, T. YOON, B. SCHLINDER-DELAP, A. HARKINS, and S. K. HUNTER. Supraspinal Fatigue Is Similar in Men and Women for a Low-Force Fatiguing Contraction. *Med. Sci. Sports Exerc.*, Vol. 43, No. 10, pp. 1873–1883, 2011. **Purpose:** This study determined the contribution of supraspinal fatigue to the sex difference in neuromuscular fatigue for a low-intensity fatiguing contraction. Because women have greater motor responses to arousal than men, we also examined whether cortical and motor nerve stimulation, techniques used to quantify central fatigue, would alter the sex difference in muscle fatigue. **Methods:** In study 1, cortical stimulation was elicited during maximal voluntary contractions (MVC) before and after a submaximal isometric contraction at 20% MVC with the elbow flexor muscles in 29 young adults (20 ± 2.6 yr, 14 men). In study 2, 10 men and 10 women (19.1 ± 2.9 yr) performed a fatiguing contraction in the presence and absence of cortical and motor nerve stimulation. **Results:** Study 1: Men had a briefer time to task failure than women ($P = 0.009$). Voluntary activation was reduced after the fatiguing contraction ($P < 0.001$) similarly for men and women. Motor-evoked potential area and the EMG silent period increased similarly with fatigue for both sexes. Peak relaxation rates, however, were greater for men than women and were associated with time to task failure ($P < 0.05$). Force fluctuations, RPE, HR, and mean arterial pressure increased at a greater rate for men than for women during the fatiguing contraction ($P < 0.05$). Study 2: Time to task failure, force fluctuations, and all other physiological variables assessed were similar for the control session and stimulation session ($P > 0.05$) for both men and women. **Conclusions:** Supraspinal fatigue was similar for men and women after the low-force fatiguing contraction, and the sex difference in muscle fatigue was associated with peripheral mechanisms. Furthermore, supraspinal fatigue can be quantified in both men and women without influencing motor performance. **Key Words:** GENDER, MUSCLE FATIGUE, STRESS, TRANSCRANIAL MAGNETIC STIMULATION, CENTRAL FATIGUE, ELBOW FLEXORS

There are sex differences in muscle fatigue for both maximal and submaximal isometric tasks (11). For example, when men and women perform a submaximal isometric fatiguing contraction at the same relative intensity, women can sustain the contraction for a longer duration than men most of the time for many muscle groups including the elbow flexors, finger flexors, and knee extensors (see Hunter (11) for review). Similarly, women exhibit less of a reduction in maximal force than men during sustained and intermittent maximal contractions (12,24,31).

Neural and muscular mechanisms contribute to muscle fatigue experienced by men and women (12,31,39). The sex difference in muscle fatigue, however, and the contributing mechanisms are specific to the demands of the task and muscle groups involved (11). By stimulating the motor

nerve during maximal force contractions, reductions in voluntary activation (commonly known as central fatigue) can be assessed (7). Using motor nerve stimulation, central fatigue explained the sex difference in muscle fatigue during maximal fatiguing contractions of the dorsiflexor muscles (31) and the knee extensor muscles (24). For repeated maximal contractions of the upper limb, supraspinal fatigue did not contribute to the sex difference in muscle fatigue of the elbow flexor muscles (12). Supraspinal fatigue is a component of central fatigue and can be identified by stimulating at the motor cortex with transcranial magnetic stimulation (TMS) (7). Low-force fatiguing contractions, however, can also elicit substantial central fatigue originating from supraspinal and spinal sources that were collectively similar in men and women (39). This study therefore determined whether there were sex differences in supraspinal fatigue elicited from low-force fatiguing contractions. As found during maximal strength fatiguing contractions of the upper extremity (12), we hypothesized that supraspinal fatigue would contribute to muscle fatigue in men and women similarly after a low-intensity fatiguing contraction with the elbow flexor muscles.

The contribution of the neural mechanisms to the sex difference in performance of a low-intensity fatiguing contraction may depend on the state of arousal or mental

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Submitted for publication November 2010.

Accepted for publication February 2011.

0195-9131/11/4310-1873/0

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DOI: 10.1249/MSS.0b013e318216ebd4

attentiveness of men and women (38). Women demonstrated greater reductions in time to failure (greater fatigability) than men when exposed to a cognitive stressor (mental math) during a low-intensity fatiguing contraction with the elbow flexor muscles (38). Physical stressors are also used experimentally to effectively increase arousal in healthy adults, but the stress response can differ between men and women (23). Repeated exposure to electrical stimulation, for example, can evoke increased arousal and greater variability in motor output during isometric tasks particularly in women and individuals with high levels of trait anxiety (4,27).

Electrical stimulation is also an important technique used to quantify neural mechanisms of muscle fatigue (14). Stimulating the motor nerve or muscle can elicit an M wave (compound muscle action potential) and evoke a twitch or tetanic contraction that is subsequently used to calculate voluntary activation. TMS that is used to quantify supraspinal fatigue (7) is brief but is also typically repeated throughout experimental protocols. Thus, these stimulation techniques potentially promote an increase in stress-altering performance of a fatiguing contraction by different magnitudes in men and women. Electrical stimulation, for example, used to assess voluntary activation of the quadriceps, resulted in a reduction of quadriceps force and EMG in men (3). Therefore, a second purpose of this study was to compare time to failure and motor output variability for a low-intensity fatiguing contraction of men and women in the presence and absence of cortical and electrical stimulation. We hypothesized that cortical and electrical stimulations, which are used to assess neural mechanisms of fatigue, could be strong enough irritants (stressors) to alter the time to task failure and physiological adjustments during the fatiguing contraction in men and women. To understand the physiological adjustments during the fatiguing contractions with and without stimulation in both men and women, we monitored muscle activation patterns using EMG, cardiovascular adjustments (mean arterial pressure (MAP) and HR), and force fluctuations as a measure of motor output variability.

METHODS

Twenty-nine young adults (14 men (20.1 ± 1.9 yr) and 15 women (19.9 ± 3.2 yr)) volunteered to participate in a session that assessed the sex differences in supraspinal fatigue for a low-force fatiguing contraction with the elbow flexor muscles (study 1). A subset of these subjects, 20 young adults (10 men (19.8 ± 2.2 yr) and 10 women (20.3 ± 3.8 yr)) participated in an additional experiment to assess the influence of stimulation on fatigability (study 2). All subjects were healthy with no known cardiovascular or neurological disorders, and they were naive to the protocol. Each subject had low to moderate levels of trait anxiety (from 21 to 48) assessed with the State-Trait Anxiety Inventory (STAI) (32) and reported no history or current mental pathology, including anxiety or depressive disorder.

Before participation, each subject attended a familiarization session and provided written informed consent. All experiments were approved by the Marquette University Institutional Review Board.

The physical activity level of each subject was assessed by a questionnaire that estimated the relative kilocalorie expenditure per week (21). The day of the menstrual cycle on which the experimental protocols were performed was recorded for each female subject. The first day of menstruation was considered day 1 of the cycle. Hand dominance was estimated using the Edinburgh Handedness Inventory (28) with a score of 0.53 for men and 0.60 for women ($P = 0.52$), and a ratio of 1 indicated complete right-handedness.

All subjects participated in a familiarization session and then attended one experimental session for study 1 and an additional session for study 2 (counterbalanced among subjects). The experimental sessions were ≥ 7 d apart to perform a protocol that involved a fatiguing contraction with the elbow flexor muscles of the left arm. The familiarization session involved habituating the subject to the procedures including motor cortical and brachial plexus stimulation, performance of several trials of the maximal voluntary isometric contraction (MVC) task, and the submaximal voluntary contraction task.

For each study, the experimental procedures involved performance of MVCs with elbow flexor muscles followed by a fatiguing contraction at 20% of MVC until task failure and recovery measures that are described in greater detail in the experimental protocol. For study 1, subjects performed the experimental session with procedures that involved stimulation of the brachial plexus and motor cortex. For study 2, subjects attended two sessions: 1) a *stimulation session* as described above that involved using TMS to assess voluntary activation and corticomotor excitability and electrical stimulation of the brachial plexus (TMS followed by brachial plexus stimulation) and 2) a *control session* with no stimulation of the cortex or brachial plexus. The procedures were similar for the two sessions with the exception of the delivery of electrical and magnetic stimulation during the maximal contractions before and after the fatiguing task as well as during the submaximal fatiguing task.

Mechanical Recordings

Subjects were seated upright in an adjustable chair with their left arm slightly abducted. Their elbow rested comfortably on a padded support, and the elbow joint was flexed to 90° so that the forearm was horizontal to the ground. The shoulders were restrained by two nylon straps to minimize shoulder movement. The hand and forearm were placed in a modified rigid wrist-hand-thumb orthosis (Orthomerica, Newport Beach, CA) midway between pronation and supination, and the force was directed upward when the elbow flexor muscles were activated. The forces exerted by the wrist in the vertical and horizontal directions were measured with a force transducer (Force-Moment Sensor; JR-3,

Woodland, CA) that was mounted on a custom-designed adjustable support. The orthosis was fixed to the force transducer. The forces detected by the transducer were recorded online by using a Power 1401 A-D converter and Spike 2 software (Cambridge Electronics Design (CED), Cambridge, UK). The force exerted in the vertical direction was displayed on a 19-inch monitor located ~1.5 m in front of the subject, and the force signal was digitized at 500 samples per second. Force fluctuations, which typically increase during the fatiguing contraction (5,15), were quantified as a measure of motor output variability. The amplitude of the force fluctuations was quantified as the coefficient of variation of the force ($CV = SD/mean \times 100$) (15).

Electrical Recordings

As a global measure of muscle activation, EMG signals were recorded with bipolar surface electrodes (Ag–AgCl, 8-mm diameter; 16 mm between electrodes) that were placed over the biceps brachii, brachioradialis, and triceps brachii muscles. The bipolar electrode configuration was placed longitudinally over the muscle belly midway between the origin and insertion for each muscle, according to the European recommendations for surface EMG (10). Reference electrodes were placed on the lateral epicondyle of the elbow. The EMG signals were amplified (100 \times) and band-pass-filtered (13–1000 Hz) with Coulbourn modules (Coulbourn Instruments, Allentown, PA). The signal was displayed on an oscilloscope and recorded online via a Power 1401 A-D converter (CED). The EMG signals were digitized at 2000 samples per second.

Cardiovascular Measurements

To understand sex differences in cardiovascular adjustments (8,15), HR and MAP were monitored during the fatiguing contraction with an automated beat-by-beat, blood pressure monitor (Finapres 2300; Ohmeda, Madison, WI). The blood pressure cuff was placed around the middle finger of the relaxed right hand with the arm placed on a table adjacent to the subject at heart level. The blood pressure signal was recorded online to the computer at 500 samples per second.

Cognitive Assessment of Arousal (Study 2)

Cognitive levels of anxiety were assessed throughout the protocol using a visual analog scale (VAS) (19) and the state portion of the STAI questionnaire (32). The VAS for anxiety involved a 10-cm line anchored at the far left by “not at all anxious” and at the far right by “very anxious.” Subjects indicated their level of anxiety with a mark on the 10-cm line. They were instructed that anxiety was defined as the negative emotions regarding the immediate future (4). VAS for anxiety were recorded at six time points during the protocol: one immediately before being seated for the experimental session, one after performing the voluntary contractions (and

first bouts of stimulation during the stimulation session) and prior to the fatiguing contraction, one immediately after the fatiguing contraction, and then at 5, 10, and 20 min during recovery after the fatiguing contraction (Fig. 1). The STAI-state questionnaire involved 20 statements that required a response on a four-point Likert-type scale. Assessment of STAI was performed at baseline and at the start of the quiet rest (Fig. 1).

Stimulation

Subjects were stimulated at the brachial plexus with electrical stimulation and at the motor cortex with TMS for study 1 and the stimulation session of study 2.

Brachial plexus stimulation. The brachial plexus was electrically stimulated to produce a maximal compound muscle action potential (maximum M wave: M_{max}) of the biceps brachii, brachioradialis, and triceps brachii muscles. Stimulation intensity was increased until the M wave amplitude plateaued for all three muscles. The stimulation intensity ranged between 120 and 300 mA. A cathode was placed in the supraclavicular fossa and an anode on the acromion. A constant-current stimulator (model DS7AH; Digitimer, Welwyn Garden City, Hertfordshire, UK) was used to deliver a single stimulus (100 μ s in duration) to the brachial plexus.

Motor cortex stimulation. TMS was delivered via a round coil (13.5-cm outside diameter) over the vertex (Magstim 200; Magstim, Whitland, UK) to elicit motor-evoked potentials (MEP) in biceps brachii, brachioradialis, and triceps brachii muscles. The vertex of the motor cortex was identified, and the scalp was marked to ensure repeatability of coil placement throughout the protocol. The right cerebral hemisphere was stimulated by the direction of the current flow in the coil to preferentially activate the left limb. A single pulse was delivered over the motor cortex at

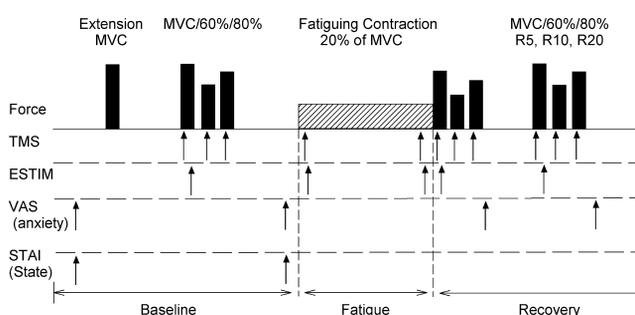


FIGURE 1—Experimental protocol. The *top panel* shows the order of force tasks performed by each subject with the elbow flexor muscles. MVC with the elbow extensors were performed followed by MVC of the elbow flexor and brief contractions at 60% and 80% of MVC, which were also performed during recovery of the fatiguing contraction (R5, R10, and R20 denotes recovery at 5, 10, and 20 min, respectively). In the *second and third rows*, the *arrows* denote the time points that TMS and electrical stimulation of the brachial plexus (ESTIM) were delivered, respectively, during the stimulation session only. The STAI questionnaire was assessed twice throughout the protocol. Please note that the schematic is not to scale for time or force.

an intensity (80%–95% of maximum stimulator output) that produced a large MEP in the agonist biceps muscle (minimum amplitude of 50% of M_{\max} during a brief MVC of the elbow flexor muscles but only a small MEP in the antagonist triceps muscle amplitude <20% of M_{\max}) (37). TMS was delivered during voluntary contractions only.

Experimental Protocol

At the start of the session for study 1 and stimulation session for study 2, optimal levels of stimulation intensities to the motor cortex and brachial plexus were determined, and these levels remained constant throughout the rest of the protocol. All procedures thereafter were as follows and indicated in Figure 1:

1. *MVC*. Two MVC of the *elbow extensors* were performed so that peak EMG values could be obtained to normalize the triceps EMG activity during the fatiguing contractions. No stimulation was delivered during the elbow extensor contractions for either session. Four sets of brief contractions (2–3 s) with the elbow flexor muscles were performed and separated by 2 min of rest to minimize fatigue. Each set involved performance of a MVC followed by contractions at 60% and 80% MVC. Within each set, the start of each contraction was separated by 3–4 s. If peak forces from two of the four MVC trials were not within 5% of each other, additional trials were performed until this was accomplished. During the stimulation session, TMS was delivered during each contraction, and brachial plexus stimulation was delivered during the MVC only. During the control session, all maximal and submaximal contractions were performed without the motor cortical or brachial plexus stimulation.
2. *Fatiguing Contraction*. A fatiguing contraction was performed with the elbow flexor muscles in each session at a target value of 20% MVC force (calculated from the peak MVC force). Each subject was required to match the vertical target force that was displayed on the monitor and encouraged to sustain the force for as long as possible. The fatiguing contraction was terminated when the force had declined by 10% of the target value for two of four consecutive seconds. Task failure was detected automatically using a custom-designed program (Spike 2; CED) that monitored the force signal, and this time was recorded as the time to task failure. During the stimulation session, TMS and brachial plexus stimulation were delivered at the start and end of the fatiguing contraction (Fig. 1). As an index of perceived effort, subjects verbally indicated their RPE using the modified Borg 10-point scale at the start of the fatiguing contraction, every minute thereafter and at task failure (2). The scale was anchored so that 0 represented the resting state and 10 corresponded to the strongest contraction that the arm muscles could perform. The RPE was recorded at the

beginning of the contraction and every minute thereafter until task failure.

3. *Recovery Measures*. Torque measurements, voluntary activation, and perceived levels of anxiety were assessed immediately on task failure, and then at 5, 10, and 20 min after termination of the fatiguing contraction (Fig. 1).

Data Analysis

The MVC force was quantified as the average value during a 0.5-s interval that was centered about the peak of the MVC. The torque for the MVC and submaximal contractions was calculated as the product of force and the distance between the elbow joint and the point at which the wrist was attached to the force transducer. The maximal EMG for each muscle was determined as the root mean squared (RMS) value during a 0.5-s interval about the same interval of the MVC torque measurement. The maximal EMG value for the biceps brachii, brachioradialis, and triceps brachii was then used to normalize the RMS EMG values recorded during the fatiguing contraction for each respective muscle. The RMS EMG of the elbow flexor muscles and triceps brachii muscles and the fluctuations in force (CV of force) were quantified during the fatiguing contraction at the following time intervals: the first and last 30 s of task duration and 15 s either side of 25%, 50%, and 75% of time to failure.

HR and MAP were recorded during the fatiguing contraction and analyzed by comparing ~15-s averages at 25% intervals. For each interval, the blood pressure signal was analyzed for the mean peaks (systolic blood pressure (SBP)), mean troughs (diastolic blood pressure (DBP)), and number of pulses per second (multiplied by 60 to determine HR). MAP was calculated for each epoch with the following equation: $MAP = DBP + 1/3(SBP - DBP)$.

The amplitude of the superimposed twitch (SIT) elicited by TMS is reported as a percentage of the voluntary torque measured immediately before TMS (7). The SIT amplitude was also used to calculate voluntary activation. Voluntary activation was quantified by expressing the amplitude of the SIT (elicited by TMS) as a fraction of the estimated amplitude of the response evoked by the same stimulus at rest (estimated resting twitch, eRT). Because motor cortical and spinal cord excitability increase with activity, a control resting twitch was not able to be achieved at rest; therefore, the amplitude of the resting twitch was estimated rather than measured directly (36). During the sets of brief maximal and submaximal contractions (MVC followed by 60% and 80% MVC contractions), TMS was delivered, and the resting twitch was estimated by extrapolation of the linear relation between the amplitude of the SIT and voluntary force. One regression analysis was performed for each set of brief contractions. The y intercept was taken as the estimated amplitude of the resting twitch evoked by TMS. The amplitude of the estimated resting twitch can be accurately determined

from three data points in fresh or fatigued muscle when the contractions are >50% MVC (36). Voluntary activation (%) was calculated as a percentage measured by cortical stimulation $[(1 - \text{SIT/eRT}) \times 100]$ (36). Data points were excluded (5.5%) for subjects at different time points when the regression of the estimated twitch was $r < 0.9$.

Contractile properties of the elbow flexor muscle fibers were also assessed. The amplitude of the estimated resting twitch was used as an index of the force-generating capacity of the elbow flexor muscles, and the fall of the force after cortical stimulus was used to determine the peak relaxation rate of the whole muscle (35). Peak relaxation rates were determined during each MVC by calculating the steepest falling of the force during the EMG silence immediately after TMS (35). This was determined as the highest negative derivative of the force for an interval of 10 ms between two cursors placed either side of the decline in force during the silent period. The steepest rate of force decline was normalized to the total force (MVC plus SIT) before the silent period (35).

The amplitude and area of MEP and M wave were measured between two cursors placed at the start and end of the waveform for the biceps, brachioradialis, and triceps muscles. As the MEP amplitude and area showed similar changes, only MEP area is reported. M waves were elicited after each MEP, but because there were no changes in M wave, the MEP is represented as a percent change from their baseline values. When TMS is delivered during a voluntary contraction, the MEP is followed by a period of near-silence in the EMG (17), lasting >200 ms with a high-intensity stimulus. The silent period was measured as the interval from the stimulus to the resumption of continuous EMG. Voluntary torque was quantified by calculation of the mean torque during a 500-ms period immediately before TMS at the start and end of each sustained fatiguing contraction, during control and recovery MVC, and during the submaximal contractions at 60% and 80% MVC.

Statistical Analysis

Data are reported as means \pm SD within the text and displayed as means \pm SEM in the figures. For study 1, two-way ANOVA with repeated measures over time and sex as a between-subject factor (men vs women) were used to compare the various dependent variables. Statistical design were as follows: 1) fatigue (before vs after the fatiguing contraction) \times sex for comparison of MVC, SIT, voluntary activation, estimated resting twitch, MEP area, silent period duration, and peak relaxation rate of muscle fibers; and 2) time (0%, 25%, 50%, 75%, and 100% of time to failure) \times sex for RMS EMG, MAP, HR, RPE, and force fluctuations during the fatiguing contraction. A separate repeated-measures ANOVA was used to compare baseline measures with those immediately after the fatiguing contraction (time effect at task failure), and an additional repeated-measures ANOVA was used to compare recovery measures (time

effect during recovery). Independent *t*-tests were used to compare men and women for the time to task failure, various physical characteristics, STAI (trait) levels, and physical activity levels. Stepwise linear regression was performed to determine the contribution of dependent variables to the total variation in the time to task failure of men and women (SPSS version 17, Chicago, IL).

For study 2, ANOVA with repeated measures for task and over time with sex (men and women) as a between-subject factor were used to compare the various dependent variables. Repeated-measures factors included session (control and stimulation sessions), stimulation (baseline, after initial stimulation, after fatiguing task, and recovery), time (0%, 25%, 50%, 75%, and 100% of time to failure), and fatigue (before and after the fatiguing contraction). Specifically, the statistical designs were as follows for the dependent variables: 1) session \times sex for time to task failure; 2) session \times fatigue \times sex for comparison of MVC; 3) session \times time \times sex for levels of anxiety (VAS) throughout the session; and 4) session \times time \times sex for RMS EMG, MAP, HR, RPE, and force fluctuations during the fatiguing contraction. Rates of change for several variables were calculated for each subject as the absolute difference from the start to the end of the contraction divided by the time to task failure. The strength of an association is reported as the squared Pearson product-moment correlation coefficient (r^2). A significance level of $P < 0.05$ was used to identify statistical significance.

RESULTS

Study 1: Sex Differences and Supraspinal Fatigue

Men and women were similar in age, physical activity levels, and STAI scores ($P > 0.05$) but were different in height and body mass ($P < 0.05$; Table 1). Men were twice the strength of women ($P < 0.05$) before and after the fatiguing contraction, and their reductions in strength at task failure were similar (Table 1). Time to task failure, however, was longer for women than for men ($P = 0.009$; Table 1). MVC torque was negatively associated with time to task failure ($r = -0.45$, $r^2 = 0.20$, $P = 0.01$), indicating that the stronger subjects had a briefer time to task failure. When men and women were analyzed separately, the associations were not significant (men: $r = -0.28$, $P = 0.34$; women: $r = -0.19$, $P = 0.49$). Day of menstrual cycle was not associated with

TABLE 1. Subject characteristics, strength, and time to failure for men and women in study 1.

Variable	Men	Women	<i>P</i> (Sex Effect)
Age (yr)	20.1 \pm 1.9	19.9 \pm 3.2	0.89
Height (cm)	179.7 \pm 4.0	167.2 \pm 6.7	<0.001
Body mass (kg)	78.7 \pm 9.2	67.6 \pm 8.6	0.002
STAI (trait)	31.4 \pm 7.5	33.9 \pm 6.8	0.35
PAQ	55.5 \pm 39.5	46.0 \pm 34.8	0.50
MVC (N-m)	81.9 \pm 16.0	40.3 \pm 6.2	<0.001
Reduction in MVC (%)	41.3 \pm 10.0	43.1 \pm 10.3	0.63
Time to failure (min)	8.3 \pm 2.7	12.9 \pm 6.3	0.009

The last column indicates the *P* values for the comparison of men and women. PAQ, physical activity questionnaire.

time to failure for women ($r = 0.35$, $r^2 = 0.12$, $P = 0.2$), suggesting that hormonal fluctuations did not influence their time to failure.

Force fluctuations. Force fluctuations (CV, %) increased throughout the fatiguing contraction (time effect, $P < 0.001$) for both men and women (time \times sex interaction, $P = 0.15$; Fig. 2A) with no main effect of sex ($P = 0.50$). The rate of increase was more rapid for the men than for the women ($0.56\% \cdot \text{min}^{-1} \pm 0.22\% \cdot \text{min}^{-1}$ and $0.38\% \cdot \text{min}^{-1} \pm 0.21\% \cdot \text{min}^{-1}$, respectively, $P = 0.03$).

EMG activity. Biceps brachii EMG activity (% MVC) increased throughout the fatiguing contraction (time effect, $P < 0.001$) similarly for men and women (time \times sex interaction, $P = 0.41$; Fig. 2B) with no main effect of sex ($P = 0.95$). The rate of increase in EMG activity did not differ for men and women ($1.7\% \cdot \text{min}^{-1} \pm 1.0\% \cdot \text{min}^{-1}$ and $1.2\% \cdot \text{min}^{-1} \pm 1.1\% \cdot \text{min}^{-1}$, respectively, $P = 0.18$). Brachioradialis EMG activity (% MVC) increased throughout

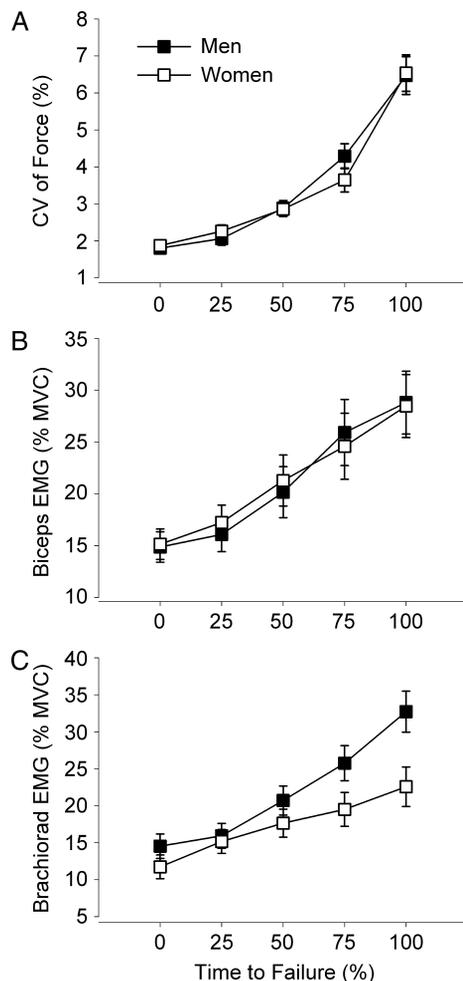


FIGURE 2—Force fluctuations and EMG activity during the fatiguing contraction. A, CV (%) of force showing an increase in force fluctuations for men (closed squares) and women (open squares). B and C, RMS EMG (% MVC) of the biceps brachii (B) and brachioradialis (C) for men (closed squares) and women (open squares) during the fatiguing contraction. Each data point represents means \pm SE at 25% increments of the time to task failure for a 30-s interval for A–C.

the fatiguing contraction (time effect, $P < 0.001$); however, this increase was different for men and women (time \times sex interaction, $P = 0.001$; Fig. 2C). Men had a greater increase in EMG than the women for the brachioradialis during the fatiguing contraction ($2.2\% \cdot \text{min}^{-1} \pm 1.2\% \cdot \text{min}^{-1}$ and $0.8\% \cdot \text{min}^{-1} \pm 0.4\% \cdot \text{min}^{-1}$, respectively, $P = 0.001$). Triceps EMG activity increased throughout the fatiguing contraction for both men and women (time effect, $P = 0.04$) with no interaction of time \times sex ($P = 0.61$) and no main effect of sex ($P = 0.47$).

RPE. RPE increased for men and women throughout the fatiguing contraction (time effect, $P < 0.001$) with no interaction of time \times sex ($P = 0.12$) and no main effect of sex ($P = 0.53$). The rate of rise for RPE was greater for men than for women (0.9 ± 0.1 and 0.6 ± 0.1 RPE per minute, respectively, $P < 0.001$).

Voluntary activation. The increments in torque generated by stimulation to the motor cortex during the MVC (SIT) were expressed relative to the torque just before the stimulation. SIT increased from baseline to immediately after task failure for both men and women (2.5 ± 2.5 to 7.4 ± 5.0 N·m for men vs 3.2 ± 2.2 to 9.3 ± 6.6 N·m for women, time effect, $P < 0.001$) with no time \times sex interaction ($P = 0.55$). Voluntary activation, which was calculated from the SIT, was similar at baseline (during control MVC) for men and women ($93.2\% \pm 4.8\%$ vs $92.1\% \pm 3.9\%$, respectively, sex effect, $P = 0.51$). The reduction in voluntary activation after the fatiguing contraction (time effect at task failure, $P < 0.001$) was similar for men and women (time \times sex interaction, $P = 0.45$; Fig. 3A). During recovery, voluntary activation increased similarly for both men and women (time effect during recovery, $P = 0.001$), indicating that they were almost fully recovered ($92.0\% \pm 7.1\%$ for men and $88.9\% \pm 6.5\%$ for women) after 5 min of recovery (time \times sex interaction, $P = 0.34$).

MEP. Biceps brachii, brachioradialis, and triceps brachii MEP were evoked during the MVC at baseline, immediately on task failure, and during recovery. The M wave area (measured from brachial plexus stimulation during the MVC) did not change between baseline and after the fatiguing contraction (time effect, $P = 0.48$). MEP are therefore presented relative to their baseline values. Biceps brachii MEP area increased similarly for both men and women during the MVC from baseline to task failure (time effect at task failure, $P = 0.003$; Fig. 3B) and returned to baseline for men and women from task failure within 5 min of recovery (time effect after 5 min of recovery, $P = 0.001$). Brachioradialis MEP area also increased from baseline to task failure when measured during the MVC for both men and women (time effect, $P = 0.001$) with no time \times sex interaction ($P = 0.67$). Triceps MEP area did not change from baseline measures to task failure measured during the MVC (time effect, $P = 0.65$) for men or women (time \times sex interaction, $P = 0.18$).

Biceps brachii MEP were also elicited at the start and end of the fatiguing contraction. MEP area of the bicep brachii

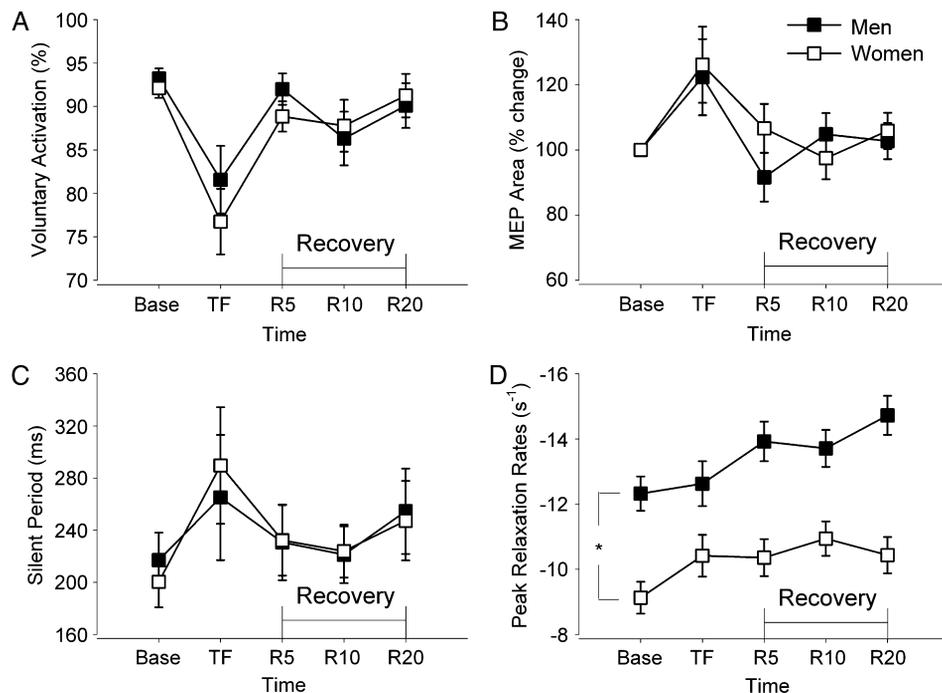


FIGURE 3—Voluntary activation (A), MEP area (B), silent period (C), and peak relaxation rates (D) for the biceps brachii muscle. Values are represented as the mean \pm SE for men (closed squares) and women (open squares). Base, baseline measures before the fatiguing contraction; TF, measures recorded immediately on task failure; R5, R10, and R20, 5, 10, and 20 min of recovery, respectively. *Sex difference in peak relaxation rates, $P < 0.001$.

increased between the start of the 20% contraction and task failure (time effect, $P = 0.001$) with no interaction of time \times sex ($P = 0.21$) and no effect of sex ($P = 0.21$). Neither the M wave area nor amplitude changed from the start of the 20% contraction to task failure ($P > 0.05$).

Silent period. The silent period evoked during the MVC increased from baseline to task failure (time effect at task failure, $P = 0.001$) similarly for both men and women (time \times sex interaction, $P = 0.36$; Fig. 3C). The silent period recovered to baseline values within 5 min after the fatiguing contraction (time effect during recovery, $P = 0.02$) similarly in men and women (time \times sex interaction, $P = 0.99$).

Estimated resting twitch. The amplitude of the estimated resting twitch decreased (time effect at task failure, $P < 0.001$) after the fatiguing contraction from baseline values for men (23.4 ± 5.7 to 19.9 ± 5.9 N·m) and women (13.6 ± 2.7 to 11.2 ± 4.1 N·m). The estimated resting twitch amplitude was greater for men than for women before and after the fatiguing contraction (sex effect, $P < 0.001$), and there was no interaction of time \times sex ($P = 0.43$). The percent decline in the amplitude of estimated resting twitch after the fatiguing contraction was similar for men and women ($14.1\% \pm 16.6\%$ vs $16.4\% \pm 27.8\%$, respectively, $P = 0.79$). Baseline estimated resting twitch values correlated with maximal torque ($r = 0.72$, $r^2 = 0.52$, $P < 0.001$), indicating that the stronger subject had a larger resting twitch amplitude.

Peak relaxation rate of muscle fibers. Peak relaxation rates (measured during the TMS-induced silent period)

were greater for men than for women during the MVC at baseline (-12.3 ± 1.5 vs -9.1 ± 2.2 s^{-1} , respectively, $P < 0.001$; Fig. 3D). Peak relaxation rates were not significantly different after the fatiguing contraction compared with before fatigue for both men and women, but there was a trend for peak relaxation rates to increase after fatigue (time effect, $P = 0.07$). There was no time \times sex interaction ($P = 0.24$), indicating that men and women had similar changes in peak relaxation rates after the fatiguing contraction. During recovery, peak relaxation rates continued to increase for men and women (time effect, $P = 0.02$) but more so for the men than for the women (time \times sex interaction, $P = 0.01$).

Initial peak relaxation rates were associated with time to task failure ($r = 0.37$, $r^2 = 0.13$, $P = 0.05$) and initial MVC ($r = -0.65$, $r^2 = 0.42$, $P < 0.001$). Thus, individuals with a briefer time to task failure and stronger muscles had faster peak relaxation rates.

Cardiovascular measurements during the fatiguing contraction. MAP increased during the fatiguing contraction (time effect, $P < 0.001$; Fig. 4A). Men had a greater rate of increase in MAP during the fatiguing contraction ($P = 0.01$). The rate of increase for men was 5.1 ± 2.7 mm Hg·min⁻¹ and for women was 1.9 ± 1.1 mm Hg·min⁻¹ throughout the fatiguing contraction ($P < 0.001$). The increase in MAP was positively associated with MVC torque ($r = 0.60$, $r^2 = 0.36$, $P = 0.001$), indicating that stronger subjects had a greater increase in MAP by the end of the fatiguing contraction.

HR increased during the fatiguing contraction (time effect, $P < 0.001$; Fig. 4B). There was no interaction of time \times sex ($P = 0.2$), but overall, men had a greater HR than women throughout the fatiguing contraction (sex effect, $P = 0.01$). The rate of increase during the fatiguing contraction for men was 2.4 ± 2.5 beats \cdot min $^{-1}\cdot$ min $^{-1}$ and that for women was 1.1 ± 0.8 beats \cdot min $^{-1}\cdot$ min $^{-1}$ ($P = 0.07$).

Stepwise regression analysis. Stepwise linear regression analysis indicated that the primary and only significant predictor for time to task failure of men and women was the baseline maximal voluntary torque ($r = 0.453$, $P = 0.015$), which explained 21% of the variance ($r^2 = 0.21$). Thus, stronger individuals exhibited a briefer time to task failure.

Study 2: Sex Differences in the Presence and Absence of Stimulation

There was no difference in time to task failure or MVC torque (before and after the fatiguing contraction) in the presence and absence of stimulation ($P > 0.05$; Table 2) for both men and women. There was no difference in the increase in force fluctuations between the control and stimulation sessions (session effect, $P = 0.71$) for both men and women (session \times sex interaction, $P = 0.21$). EMG activity also increased similarly for the biceps brachii and brachioradialis during the fatiguing contraction in the control and stimulation sessions ($P > 0.05$) for both men and women ($P > 0.05$). Furthermore, there was no effect of the stimulation on RPE, HR, and MAP ($P > 0.05$) during the fatiguing contraction for both men and women ($P > 0.05$). Thus, any sex differences in time to failure, MVC force, force fluctuations, EMG activity, HR, MAP, and RPE were not altered during the stimulation session compared with control.

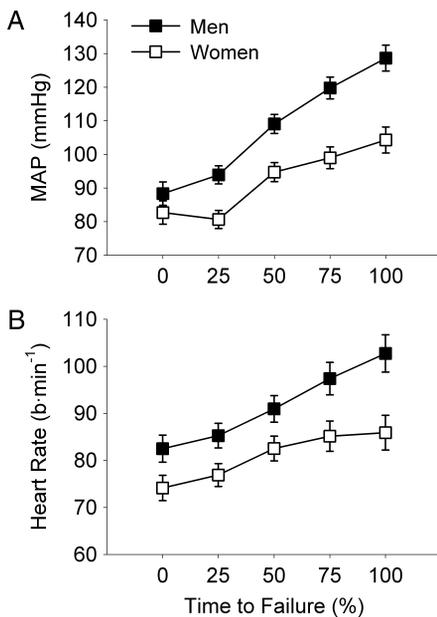


FIGURE 4—MAP (A) and HR (B) during the fatiguing contractions. Values are presented as mean \pm SE at 25% increments of the time to task failure for men (closed squares) and women (open squares). Averages of 15-s intervals were used for the MAP and HR.

TABLE 2. MVC data and time to task failure for men and women for the control and stimulation sessions in study 2.

Variable	Control	Stimulation	<i>P</i> (Session Effect)
MVC (N·m)	M: 83 \pm 15 W: 45 \pm 6	M: 82 \pm 18 W: 43 \pm 9	0.13
Reduction in MVC (%)	43.7 \pm 7.0	44.4 \pm 10	0.44
Time to failure (min)	10.5 \pm 4.5	10.2 \pm 4.5	0.62

The last column indicates the *P* values for the comparison of the control and stimulation session.

VAS scores for anxiety and the state STAI anxiety scores were, however, slightly elevated throughout the stimulation session compared with the control sessions ($P < 0.05$), but there was no change or increase after the initial exposure to the stimulation before the fatiguing contraction ($P > 0.05$).

DISCUSSION

The novel findings from these studies were that 1) supraspinal fatigue contributed to neuromuscular fatigue after a low-force isometric fatiguing contraction and this was similar for men and women, 2) the greater fatigue resistance in women was related to muscular mechanisms that included slower contractile properties and lower absolute strength sustained during the fatiguing contraction, and 3) cortical and brachial plexus stimulation did not influence the fatigability or the increase in fluctuations in motor output of the elbow flexor muscles in young men and women, despite some indicators that the men and women were slightly more anxious with the stimulation procedures. Thus, the stimulation used to induce increases in arousal but applied to investigate supraspinal and spinal contributions to muscle fatigue influenced neither fatigability of the muscle and variability in motor output nor the sex difference in muscle fatigue.

Supraspinal Fatigue and Sex Differences in Fatigability

Women were less fatigable than men for the low-force isometric contraction (11). Furthermore, men and women had similar declines in MVC force, indicating that both groups had reached similar physiological states at task failure. This was also demonstrated by the similar RPE at task failure for the men and women. The reduction in MVC force was accompanied by an increase in force evoked by cortical stimulation during the MVC, demonstrating that some of the loss in maximal force at task failure was due to suboptimal output from the motor cortex (7). There was, however, no sex difference in voluntary activation measured during the control MVC before the fatiguing contraction or immediately after the fatiguing contraction during recovery. Thus, despite the sex difference in performance, both men and women had similar deficits in neural drive to the motor cortex at task failure and after the fatiguing contraction. These results are consistent with other studies for the elbow flexor muscles that demonstrate men and women exhibit similar magnitudes of supraspinal fatigue during and after repeated maximal

contractions (12) and central fatigue upstream of the motor neuron after a low-force fatiguing contraction (39). These findings for the elbow flexor muscles, however, are in contrast to those for leg muscles because reductions in voluntary activation quantified with motor nerve stimulation contributed to a sex difference in knee extensor (24) and dorsiflexor muscles (31) after repeated maximal contractions. The differential contribution of central fatigue to the sex difference in muscle fatigue across different muscles is not fully understood but may involve sex-specific actions of groups III and IV afferents onto the motor neuron pool of different muscle groups (11). Inhibitory feedback from group III and IV afferents can play a role in spinal or supraspinal fatigue via inhibition of alpha motor neurons (34) and differs between extensor and flexor muscles (24) and probably differs between men and women (11,24,31). Taken together, the sex difference in central fatigue appears to be muscle dependent and the sources (supraspinal vs spinal) contributing to these sex differences may differ.

There was also no sex difference in the EMG responses elicited from cortical stimulation before or after the fatiguing task. MEP elicited during the sustained 20% fatiguing contraction, and the MVC before and after the fatiguing contraction increased similarly in men and women due to an increase in corticomotor excitability (34). Thus, men and women demonstrated similar increases in corticomotor excitability immediately after the low-force fatiguing contraction and during recovery. Factors that contribute to changes in the *M* wave may contribute to changes in the MEP during maximal fatiguing tasks (33), but there was no change in the *M* wave from baseline to task failure and throughout recovery for either men or women. Thus, there was no impairment in transmission of the action potential across the neuromuscular junction for both sexes, and the *M* wave did not contribute to changes in the MEP for the elbow flexor muscles.

The silent period evoked during the MVC increased similarly for men and women with fatigue. The silent period represents the inhibition within the motor cortex or the period of silence in the EMG after the MEP; this typically lasts >200 ms with a high-intensity stimulus (33). Inhibition of descending drive and reduced excitability of the neurons may contribute to the initial part of the silent period. However, the silent period continues beyond the recovery of motoneuronal excitability at ~100 ms (17), so that the latter part of the silent period and its end should reflect the intracortical inhibition during maximal voluntary contractions (7), although more recent findings indicate that the long-interval inhibition is also due to inhibition in the spinal cord (25). The similar duration of the silent period in men and women after the low-force fatiguing contraction is consistent with prior studies using maximal isometric fatiguing contractions (12) showing no sex differences in inhibitory processes within the cortex and spinal cord with fatigue.

Peripheral contributions to sex differences after a low-intensity fatiguing contraction. The longer time

to task failure of the women than the men was related to a sex difference in contractile speed of the muscle and differences in absolute strength exerted during the fatiguing task. The primary predictor of the time to failure of the low-force task, however, for the men and women was the absolute strength, which confirms findings from our previous studies (13,15). Peak relaxation rates also correlated with time to failure, indicating that subjects with slower muscle fibers were more fatigue resistant. Peak relaxation rates were faster in men than in women before and after the fatiguing contraction, suggesting that men had a greater proportion of type II fibers (18) and differences in calcium uptake into the sarcoplasmic reticulum, which is associated with fiber types (16). These results contribute to a growing body of literature that show women can have slower contractile properties than men and these contractile properties influence their fatigability (12,24). Peak rates of relaxation, however, did not change significantly after the fatiguing contraction for either men or women. The slowing of the muscle that can occur during maximal isometric fatiguing protocols (12,24) usually reflects changes in the excitation–contraction coupling (6). However, contractile properties do not always slow after low-force fatiguing contractions (22) and may be influenced by increases in muscle temperature (35). Although the contractile speed did not alter with fatigue, there was a reduction in the estimated twitch amplitude. These findings paralleled the change in MVC at task failure because men and women had similar relative reductions for the estimated twitch amplitude and MVC after the low-force fatiguing contraction.

During the fatiguing contraction, the men exhibited a greater rate of increase than the women did for several variables that are modulated by mechanisms within the muscle and, in particular, absolute strength. Mean arterial pressure, for example, increased at a greater rate for the men than for the women, and this has been shown for several studies during low-force sustained contractions with the elbow flexor muscles (14,15,39). Presumably, men who are stronger than women had greater intramuscular pressures, more occluded blood flow, a greater buildup of metabolites, greater activation of metaboreceptors (group III and IV afferents), and larger rates of increase in MAP (pressor reflex) (30). The pressor response was correlated with the absolute strength, which has been observed previously (14). MAP is also regulated by central command, which is the parallel activation of neural circuits in the brain stem and spinal cord that control motor, ventilatory, and cardiovascular functions (9). Accordingly, HR and RPE, which are regulated by central command, increased at greater rates for men than for women during the fatiguing contraction, indicating that men required a greater rate of increase in central command to sustain the fatiguing task (8). Fluctuations in motor output (force fluctuations) also increased for men at a greater rate than women ending at similar values for both sexes. The increase in fluctuations of motor output during a fatiguing contraction is due to both neural and muscular mechanisms (5). Muscle fatigue can result in a decrease in the motor unit discharge rate that

can increase the discharge rate variability and, consequently, increase force fluctuations (26). Collectively, these physiological adjustments that are modulated by both central command and muscular processes during the fatiguing contraction reflect an increased rate in the development of muscle fatigue during submaximal tasks in men compared with women.

Men and women also seemed to adopt different activation strategies among the elbow flexor muscles during the fatiguing contraction. In contrast to the biceps EMG, the brachioradialis EMG increased at a much greater rate in men than in women, with the men showing higher activation than the women at task failure. Because the amplitude of the EMG is related to the net motor activity that represents the recruitment and the discharge rates of active motor units (29), these results indicate that the rates of increase in recruitment and discharge of motor units of men and women differed among the elbow flexor muscles. The reason for the differences is not clear but may represent physiological sex differences that influence the rate of fatigue in the brachioradialis relative to the biceps brachii. Although there are differences in fiber types between the two muscles (20), it is unknown whether there is a sex difference in the fiber-type composition within the brachioradialis. Alternatively, the biceps brachii of the men may have been more inhibited than that of the women via afferent feedback from brachioradialis (1), although any sex or strength differences during sustained contractions have not been identified. Ultimately, the strategy adopted by the men and women differed in that men required greater activation of the brachioradialis than women did to sustain the required force.

Stimulation of the nervous system does not influence the sex difference in muscle fatigue. An important finding in this study was that the magnitude of muscle fatigue (reduction in MVC force) at task failure, the time to task failure and the increase in fluctuations of motor output did not change for either men or women when stimulation was applied at the motor cortex and motor nerve to quantify supraspinal fatigue compared with control conditions (no stimulation). Time to task failure was reduced with exposure to acute cognitive stress (38), and steadiness was reduced with exposure to noxious electrical stimulation (4,27) more so for women than for men. However, none of our measures of neuromuscular performance were different in men or women when exposed to the motor cortical and

brachial plexus stimulation. Furthermore, average EMG activity of the elbow flexor muscles and RPE were also similar during the two sessions, demonstrating similar increases in neural activation (motor unit recruitment and discharge rates) (29) and perceived levels of activation. Thus, the current study indicates that the single-pulsed stimuli delivered at high intensities over the motor cortex and motor nerve do not influence time to task failure or other indicators of motor performance during a fatiguing contraction for men and women.

Accordingly, the physiological measures of stress and arousal that included HR and MAP were similar during the control and stimulation sessions. These are indicators of sympathetic activity that can be elevated with arousal and increased stress (27,38) and more so in women than in men. Perceived anxiety measures (VAS and STAI state) of the subjects, however, were greater during the stimulation session than during the control session for both men and women. The levels of increased perceived arousal, however, were minimal (4), and there was no sex difference. Despite the increased levels of anxiety throughout the stimulation session, this did not produce a greater physiological stress response (HR and blood pressure) or effect muscle fatigue in either men or women.

In conclusion, supraspinal fatigue contributed to neuromuscular fatigue for a low-force fatiguing contraction but did not explain the sex differences in time to task failure. Rather, this study indicates that the mechanisms contributing to the sex difference in muscle fatigue were attributable to muscular mechanisms that involved a sex difference in absolute muscle strength exerted during the task and initial peak relaxation rates. The stimulation techniques used to quantify supraspinal fatigue did not alter the sex difference in fatigue and the physiological adjustments during a low-force fatiguing contraction. Thus, supraspinal fatigue can be quantified in both men and women without influencing motor performance.

This research was supported by awards to S.K.H. (a Marquette University Regular Research grant and 3 T42 OH008672 from the National Institute for Occupational Safety and Health).

There are no conflicts of interest to report. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of National Institute for Occupational Safety and Health.

The results of this study do not constitute endorsement by the American College of Sports Medicine.

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