5-1-2018

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Accepted version. *Medicine & Science in Sports & Exercise*. Vol. 50, No. 5 (May 2018): 1070-1083). DOI.

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ABSTRACT

Purpose: The purpose of this study was to determine whether supraspinal mechanisms contribute to the sex difference in fatigability during and recovery from a dynamic and isometric fatiguing task with the knee extensors.

Methods: Transcranial magnetic stimulation and electrical stimulation were used to determine voluntary activation and contractile properties of the knee extensors in 14 men and 17 women (20.8 +/- 1.9 yr) after a 1) 60-s sustained, maximal voluntary isometric contraction (MVIC), and 2) dynamic fatiguing task involving 120 maximal voluntary concentric contractions with a 20% MVIC load.

Results: There were no differences between men and women in the reduction of maximal torque during the sustained MVIC (54.4% +/- 18.9% vs 55.9% +/- 11.2%, *P* = 0.49) or in the decrease in power during the dynamic fatiguing task (14.7% +/- 20.1% vs 14.2% +/- 18.5%, *P* = 0.92). However, MVIC torque recovered more quickly for women than men after the sustained MVIC and the dynamic task (*P* < 0.05). The transcranial magnetic stimulation-elicited superimposed twitch was larger for men than for women during the sustained MVIC and in recovery (immediately post, R0.1: 4.7% +/- 3.3% vs 2.4% +/- 1.9% MVIC; *P* = 0.02), with no sex difference after the dynamic task (*P* = 0.35). The reduction in resting twitch amplitude was larger for men than for women immediately after the dynamic task (37% +/- 22% vs 23% +/- 18%; *P* = 0.016) with no sex difference after the sustained MVIC (64% +/- 16% vs 67% +/- 11%; *P* = 0.46).

Conclusions: Supraspinal fatigue contributed to fatigability of the knee extensors more for men than for women after a maximal isometric task, whereas contractile mechanisms explained the sex difference in torque recovery after the fast-velocity dynamic task. The mechanisms for the sex difference in fatigability are task dependent.

Fatigability of limb muscles in men and women is characterized by an acute activity-induced reduction in the expected force or power during or in recovery from a fatiguing task, and the responsible mechanisms involve both neural and muscular processes (1,2). Understanding the magnitude and involved mechanisms of fatigability is important because, fatigability 1) often defines the physiological limits of tasks in men and women during exercise, work-related tasks, and rehabilitation, and 2) is the basis of neuromuscular overload and adaptation that is necessary for improvement in training and rehabilitation of skeletal muscle. However, there are sex differences in fatigability of limb muscles (3). Women are usually less fatigable than men during repeated or sustained isometric contractions, and recovery of force is more rapid for women for several upper limb muscles including the elbow flexor and handgrip muscles, and some lower limb muscles (4,5). Much of what is known about sex differences in fatigability during a fatiguing task and recovery is based on isometric tasks of upper limb muscles, with minimal knowledge about the lower limb muscles, dynamic tasks, and the involved mechanisms (3).

The sex difference in fatigability is specific to the details of the fatiguing task; thus, the magnitude of the sex difference in fatigability and the contributing mechanisms (site and rate) can differ with the demands of the task (5,6). For example, the sex difference in fatigability can be quite large for the elbow flexor muscles during isometric contractions (7-9) and slow velocity contractions (10), with a minimal sex difference in fatigability during dynamic contractions at fast velocities for the elbow flexor muscles (3,4,11). The greater fatigue resistance of women compared with men for isometric and slow, dynamic contraction tasks and recovery from these tasks is typically associated with contractile mechanisms of the skeletal muscle (10,12,13), likely reflecting sex differences in skeletal muscle metabolism and muscle fiber composition (5). There is, however, minimal evidence for a sex difference in the reduction of neural drive to the muscle (i.e., a reduction in voluntary drive, often termed "central fatigue") of the upper limb muscles (10,12-14).

The sex difference in fatigability of lower limb muscles and the involved mechanisms, however, may differ from that of the upper limb. For example, women were less fatigable than men for repeated dynamic shortening contractions performed as quickly as possible with the plantar flexor muscles and a load

equivalent to 30% maximal voluntary isometric contraction (MVIC) (15). The average velocity of contraction during shortening, however, was ~120[degrees][middle dot]s^{-1} (15), which is less than half the velocity achieved by the elbow flexor and knee extensor muscles with a 20% MVIC load (11). The sex difference was attributed to a more fatigue-resistant muscle of the women than the men (15). For the knee extensor muscles that demonstrate a sex difference in fatigability for isometric and slow dynamic contraction tasks (16-18), the reduction in power during repeated fast-velocity dynamic contractions with a low load (20% MVIC) was similar for men and women (11). However, the reduction in MVIC torque immediately after the dynamic task was greater for men than for the women despite no sex differences in the reduction of angular velocity (11). The mechanisms contributing to this sex difference in the reduction of MVIC torque for the knee extensor muscles are not known.

For several lower limb muscles, including the knee extensor and ankle dorsiflexor muscles, the greater fatigability of MVIC of the men compared with women was explained by central mechanisms, because there was a larger reduction in voluntary activation in the men than in the women (19,20). Accumulation of metabolites in the active skeletal muscle and the subsequent excitation of metabolically sensitive small afferent sensory nerve fibers (groups III and IV) can inhibit voluntary drive (21), possibly more so in men than in women in the lower limb muscles. In these studies, voluntary activation was assessed by stimulating the motor nerve during brief MVIC tasks so that the exercise-induced decline in voluntary activation (central fatigue) could have been due to altered drive from spinal and supraspinal sources (19,20). However, the contribution of supraspinal mechanisms to the reduction in voluntary activation and the sex difference in fatigability of the lower limb is not known. It is also not clear if larger reductions in maximal torque after fast dynamic contractions observed in men compared with women (11) is due to sex differences in voluntary drive from suprapsinal sources or contractile processes within the skeletal muscle, or both.

Supraspinal fatigue is the reduction in voluntary activation attributed to the failure to generate output from the motor cortex (1) and can be quantified by the increase in the force output in response to transcranial magnetic stimulation (TMS) over the motor cortex while performing maximal effort contractions (22). Any increase in the force output evoked by TMS indicates that at the moment of stimulation, the output of the motor cortex is not maximal (some output remains untapped) and not adequate to activate all the motor units to produce maximal muscle force (23). The response of the EMG signal to TMS including the motor-evoked potential (MEP) and silent period can also provide insight into the neural adjustments during fatiguing contractions of limb muscles (23,24). The purpose of this study was to determine whether supraspinal fatigue contributed to a sex difference in fatigability during and in recovery of the knee extensor muscles for a 1) sustained MVIC for 60 s and 2) dynamic fatiguing task performed with a submaximal load at a fast velocity. We *hypothesized* that for both the sustained MVIC and the fast-velocity dynamic task, men would exhibit slower recovery of MVIC torque after the fatiguing task, as observed previously (11), and this would be due to both contractile mechanisms and greater supraspinal fatigue in the men compared with the women.

METHODS

Fourteen young men (20.6 +/- 1.9 yr, 18-26 yr) and 17 young women (20.8 +/- 1.4 yr, 19-25 yr) volunteered to participate in one familiarization session and two experimental sessions. Each experimental session involved a fatiguing contraction (isometric or dynamic task) with the knee extensor muscles of the dominant leg. Leg dominance was determined by preferred kicking foot (25,26); all participants, except one woman, reported right leg dominance. Participants were healthy with no known neurological disease or contraindications to exercise; in addition, participants were carefully screened for contraindications to TMS. Participants were excluded if they had a diagnosis of epilepsy, a pacemaker, cranial metal implant (except dental implant), or a history of skull fracture; suffered a concussion within the previous 6 months; or were pregnant-no participants were excluded because of these criteria. Before involvement, each participant provided written informed consent and the protocol was approved by the Marquette University Institutional Review Board (HR-1645) for ethical approval in accordance with the Declaration of Helsinki for human experimentation.

Experimental Design

The familiarization session involved practice of contractions that were central to each protocol, including brief MVIC and maximal voluntary (fast-velocity) concentric (shortening) contractions (MVCC) with the knee extensor muscles. Each participant was also habituated to electrical stimulation of the knee extensor muscles and TMS over the motor cortex. During the familiarization session, physical activity was assessed with a questionnaire that estimated the relative kilocalorie expenditure of energy per week based on a 12-month recall of occupational and leisure physical activity (27), and leg dominance was determined with a questionnaire (26).

The two experimental sessions involved performance of a fatiguing task that was either a sustained MVIC for 60 s or 120 MVCC (1 every 3 s) performed over 6 min with a load equivalent to 20% MVIC torque. Each participant performed all contractions with the knee extensor muscles of the dominant leg on a Biodex System 4 dynamometer (Biodex Medical, Shirley, NY). For each session, participants were seated with 90[degrees] of hip and knee flexion. Padded straps mounted on the seat were securely tightened across each shoulder and the waist to limit ancillary movement. The dominant leg was positioned such that the axis of rotation of the knee joint was aligned with the axis of rotation of the dynamometer at 90[degrees] of knee flexion (Fig. 1). The positioning in the chair was replicated between sessions.

Experimental Protocol

Baseline measures common to both experimental sessions

At the beginning of each session, maximal torque for knee extensors was determined with three brief MVIC tasks (~3 s) performed sans stimulation. Additional MVIC tasks were performed if the participant did not achieve two MVIC torque values within 5%. Participants received strong verbal encouragement throughout all testing procedures in each experimental session and were instructed to "kick as hard as possible." After the baseline MVIC, electrical stimulation of the femoral nerve was used to elicit a maximal compound muscle action potential (M_{max} as described in the "electrical stimulation" section). Participants then performed four additional MVIC tasks during which TMS and electrical stimulation were superimposed to estimate voluntary activation of the knee extensor muscles (see the "data analysis" section). Electrically evoked twitch contractions were elicited immediately after each MVIC (<1.5 s) at rest and used as the control twitch to calculate voluntary activation and contractile properties of the muscle group.

Isometric fatiguing task session

The isometric fatiguing protocol involved a 60-s sustained maximal isometric contraction. Single-pulse TMS was performed at 15-s intervals throughout the sustained MVIC (i.e., at the start of the contraction and 15, 30, 45, and 60 s; Fig. 2B). During recovery, one MVIC was initiated within 6 s of termination of the sustained MVIC (R0.1) and then 2.5, 5, and 10 min after the end of the fatiguing contraction (R2.5, R5, and R10, respectively). Participants were *strongly* encouraged verbally throughout the sustained MVIC.

Dynamic fatiguing task session

After the baseline MVIC tasks, participants performed 10 MVCC tasks with a load equivalent to 20% MVIC to minimize the learning effect of dynamic contractions (11). MVCC tasks were performed through an 85[degrees] range of motion, starting at 90[degrees] of knee flexion to 5[degrees] of knee extension. After 2 min of rest, the dynamic fatiguing protocol was initiated. The fatiguing protocol involved 120 MVCC tasks of the knee extensor muscles through an 85[degrees] range of motion with one MVCC every 3 s (6 min total). Individuals actively performed the concentric phase for knee extension and the dynamometer passively returned the limb to the initial position at 90[degrees] of knee flexion. During recovery, one MVIC was initiated within 6 s of termination of the fatiguing task (R0.1) and then at 2.5, 5, and 10 min of recovery. For this session, a set of five MVCC tasks (1 every 3 s) was performed after each MVIC during each recovery time point. During all MVCC tasks, participants were instructed to "kick as hard and as fast as possible" and each MVCC was initiated via strong verbal command from the investigators, "KICK." The authors provided the verbal cue each 3 s on the basis of a visual cue from a custom-designed data collection program, and participants were encouraged to maintain maximal effort throughout the dynamic fatiguing task.

Mechanical and Electrical Recordings

EMG electrodes (Ag-AgCl, 8-mm diameter; 20-mm interelectrode distance) were placed on three agonist muscles (rectus femoris, vastus lateralis, and vastus medialis) in a bipolar arrangement according to recommendations (28), with three reference electrodes (one for each muscle) placed over the patella. The EMG signals were amplified (100x), filtered (13-1000 Hz; Coulbourn Instruments, Allentown, PA), and digitized (2000 Hz). Mechanical recordings from the Biodex dynamometer corresponding to torque, velocity, and position were digitized at 500 Hz each. All analog signals (EMG and Biodex dynamometer) were digitized using a 1401 A-D converter and Spike2 software (Cambridge Electronics Design, Cambridge, UK).

TMS

TMS was delivered via a concave double-cone coil (Magstim 200; Magstim, Whitland, UK; 11.0-cm outside diameter) over the motor cortex area for the dominant knee extensor muscles to elicit MEP recorded from the agonist muscles. The vertex of the motor cortex was identified, and the scalp was marked 1.0 cm lateral to the vertex (over the motor area corresponding to the dominant knee extensors) to ensure repeatability of coil placement during the experimental protocol (29). The optimal *position* of the TMS was determined each day during brief contractions of the knee extensor muscles at 20% MVIC. TMS was elicited during the contractions, and fine adjustments in the TMS coil position (~0.5 cm) were made to determine which site evoked the largest superimposed twitch (SIT) torque and MEP of the rectus femoris muscle. Optimal stimulator intensity was also determined with brief contractions (2-3 s) of knee extensor muscles (50% MVIC), which is the intensity that is known to elicit maximal MEP (30,31). The intensity of the stimulation (% maximal of stimulator intensity) was increased by 5% increments until maximal twitch torque of the quadriceps and maximal MEP of the rectus femoris muscle were elicited. The brief contractions at 50% MVIC were separated by 30-s rest periods to avoid fatigue when establishing the intensity of TMS.

Electrical Stimulation

Single-pulse (200-[mu]s duration, 400 V) electrical stimulation was used for femoral nerve (80-300 mA) and percutaneous muscle stimulation (100-500 mA; DS7AH; Digitimer, Ltd., Welwyn Garden City, UK). A single stimulation of the femoral nerve was used to elicit the M_{max} of three agonist muscles (rectus femoris, vastus lateralis, and vastus medialis), and a single pulse of percutaneous stimulation of the muscle belly was used to elicit twitch torque to estimate voluntary activation and contractile properties of the knee extensor muscles. Although doublet-stimulations elicit a larger torque response (32) that further increases the signal-to-noise ratio when assessing voluntary activation, we chose single stimulations that were considerably less painful for the participants and the signal-to-noise ratio of the resting twitches were high both before (48.4 +/- 17.4 N[middle dot]m; 28.4% +/- 6.3% MVIC) and after the fatiguing contractions (16.8 +/- 10.1 N[middle dot]m; 16.3% +/- 7.6% MVIC).

Peripheral nerve (femoral) stimulation

Nerve stimulation was performed to elicit the M_{max} of the three agonist muscles (rectus femoris, vastus lateralis, and vastus medialis) and used to normalize the MEP elicited via TMS. After baseline MVIC tasks, the femoral nerve was stimulated using supramaximal intensities, with the cathode electrode (Ambu Neuroline electrodes, Ballerup, Denmark; 1.5-cm diameter) placed over the femoral nerve within the femoral triangle and the anode placed over the greater trochanter of the femur. The intensity of the nerve stimulation was determined by increasing the current until the M_{max} amplitude of all three knee extensor muscles plateaued; the stimulation intensity was then increased further by 20% to ensure maximal excitation of the femoral nerve. The twitch amplitude elicited from the femoral nerve stimulation was 29.4% +/- 7.0% MVIC (20.9%-43.7% MVIC) for young men and 27.7% +/- 5.7% MVIC (20.8%-47.0%) for young women. These responses were compared with the twitch amplitudes elicited from the percutaneous stimulation.

Percutaneous muscle stimulation

The knee extensor muscles were stimulated percutaneously with custom-made pad electrodes (6 x~15 cm). The cathode was placed near (within 10 cm) the area of the femoral triangle, and the anode was placed proximal to the patella without hindering knee flexion/extension of the participant. The stimulator intensity was determined by increasing the current until the resting twitch amplitude plateaued; the stimulation intensity was then increased further by 20% to ensure a maximal activation (supramaximal intensity) of the

knee extensor muscles. Percutaneous muscle stimulation elicited a potentiated resting twitch amplitude which was not different from the twitch elicited via femoral nerve stimulation (33.6 +/- 10.5 N[middle dot]m vs 46.9 +/- 17.1 N[middle dot]m, respectively; $P = 0.12$) as has been observed previously (33). The twitch amplitude from percutaneous and femoral nerve stimulation was linearly correlated ($r = 0.828$, $r2 = 0.686$, $P < 0.001$). After the M_{max} was established with the femoral nerve stimulation, percutaneous muscle stimulation was used throughout the experimental protocol because this procedure is more tolerable for the participants than the nerve stimulation (33).

Data Analysis

The torque during each MVIC was quantified as the average value over a 0.1-s interval before the onset of the TMS pulse. The maximum angular velocity, power, and torque during dynamic contractions were quantified as the maximum value during the concentric phase of the contraction. The torque during MVCC tasks was calculated as the average torque during the concentric phase of the contraction. The work was calculated for each MVCC as the product of torque and angular displacement (range of motion), and the *relative* work was calculated relative to baseline MVIC torque values. The peak angular acceleration was calculated during the concentric phase of each MVCC as the maximal value of the first derivative of the angular velocity curve. The work-to-rest ratio (duty cycle) was calculated as: (active contraction time)/(active contraction time + relaxation time) (34). The variables from the dynamic fatiguing task are presented as the average from five consecutive contractions during the task, at baseline (contractions 1-5) or the end of the fatiguing task (contractions 116-120).

Voluntary activation was assessed with both TMS and electrical stimulation. Voluntary activation with TMS was estimated with the SIT expressed as a percentage of the total torque, that is, [SIT/(MVIC + SIT) x 100%] (1,35). For electrically evoked contractions, voluntary activation was calculated as the ratio of the SIT to the control twitch with the following equation: voluntary activation = (1 - SIT/resting twitch) x 100% (1,22).

Contractile properties of the knee extensor muscles were quantified from the resting twitch elicited with percutaneous electrical stimulation of the knee extensor muscles. Variables included the peak amplitude of the resting twitch, contraction time, and half-relaxation time. Contraction time was the time interval in milliseconds from the start of force development of the twitch to its peak amplitude. Half-relaxation time was determined as the time interval in milliseconds elapsed from the peak twitch amplitude until the torque reached 50% of the peak twitch amplitude.

Electrophysiological properties of the knee extensors were also assessed with peak-to-peak amplitude of the MEP for the agonist muscles (rectus femoris, vastus lateralis, and vastus medialis) elicited via TMS during MVIC tasks. The duration of the EMG silent period was determined as the interval from the time of the TMS to the return of continuous EMG after the MEP (36). The relative change in variables from before to after the fatiguing task was calculated as [1 - (end value/initial value)] x 100%. Variables included MVIC torque, MVCC velocity, power, work-to-rest ratio, range of motion, peak applied torque, average applied torque, work, relative work and maximal angular acceleration, voluntary activation, twitch amplitude, contraction time, half-relaxation time, EMG silent period, and MEP (% M_{max}).

Statistical Analysis

Data are reported as mean +/- SD in the text and displayed as mean +/- SEM in the figures. Leg dominance, a nonparametric statistic, was compared between men and women using the Mann-Whitney *U* test, with sex as a between-subject factor. Univariate ANOVA with sex as a between-subject factor was used to compare physical characteristics, physical activity levels, and baseline measures of muscle properties and voluntary activation. To verify changes across time (fatigue or recovery) during each session (isometric or dynamic session), separate repeated-measures ANOVA with sex as between-subject factor and repeated measures were used to compare dependent variables of MVIC torque, MVCC velocity, power, duty cycle, range of motion, peak applied torque, average applied torque, work, relative work and maximal angular acceleration, electrically evoked twitch amplitude, half-relaxation time, contraction time, EMG silent period, MEP amplitude, and voluntary activation (electrical stimulation and TMS as the SIT). To determine the time effect of fatigue, comparison of variables was between baseline measurements to the end of the fatiguing task or

immediately after the fatiguing task (R0.1), whereas recovery was the time effect from immediately after the fatiguing contraction (R0.1) until the end of the 10-min recovery period (R10). Thus, two repeated-measures ANOVA were performed for each fatiguing session: one including baseline through the end of the fatiguing task (F60 or R0.1; fatigue) and the other including the end of fatigue through recovery (F60 or R0.1 through R10; recovery). For each ANOVA, the sphericity of data was verified (Mauchly's test) and technical corrections were performed whenever necessary. *Post hoc* analysis (LSD pairwise comparison) with Bonferroni corrections for *P* values was used as denoted. After checking for normality of data (Shapiro-Wilk test), regression analysis was used to determine association between variables. Significance was determined at $P < 0.05$, and all the analyses were performed in IBM statistical package for social sciences (SPSS) version 24.

RESULTS

Baseline Measurements

Men and women did not differ in body mass index (sex effect, $P = 0.06$) or self-reported physical activity (sex effect, $P = 0.21$); however, men were taller and had greater body mass than women (sex effect, $P < 0.001$; Table 1). There were no sex-related differences in leg dominance (sex effect, $P = 0.794$). Men generated greater MVIC torque of the knee extensor muscles than the women (41% sex difference; sex effect, $P < 0.001$) across both sessions (sex effect, $P < 0.001$), had higher peak angular velocities (420[degrees][middle dot]s^{-1} +/- 150[degrees][middle dot]s^{-1} vs 290[degrees][middle dot]s^{-1} +/- 60[degrees][middle dot]s^{-1}; 31% sex difference; sex effect, $P < 0.001$), demonstrated higher peak knee extensor power (454 +/- 105 W vs 301 +/- 74 W; 34% sex difference; sex effect, $P < 0.001$), and had higher maximal angular acceleration (17.1[degrees][middle dot]ms^{-2} +/- 2.8[degrees][middle dot]ms^{-2} vs 13.6[degrees][middle dot]ms^{-2} +/- 1.9[degrees][middle dot]ms^{-2}, respectively; 20% sex difference; sex effect, $P < 0.001$) during the MVCC with the 20% MVIC load.

Men had a larger electrically evoked resting twitch amplitude (sex effect, $P < 0.001$) and shorter half-relaxation times compared with women (sex effect, $P < 0.001$). Men and women, however, demonstrated similar SIT amplitude (% MVIC) that was elicited with TMS (sex effect, $P = 0.646$; see Table 1).

At baseline, all variables were similar across the two experimental sessions for both men and women. There was no difference between sessions and no interaction with sex for baseline measures of MVIC torque (session effect, $P = 0.66$), SIT amplitude elicited with TMS (session effect, $P = 0.76$), and electrically evoked twitch amplitude (session effect, $P = 0.74$), contraction time (session effect, $P = 0.70$), and half-relaxation time (session effect, $P = 0.97$). Thus, the mean values from the two experimental sessions are reported in Table 1.

Sustained Isometric Fatiguing Task Session

MVIC torque

Men and women demonstrated similar reductions in MVIC torque during the 60-s isometric fatigue task (F60: 55.9% +/- 11.2% and 54.4% +/- 18.9%; time effect, $P < 0.001$; time x sex, $P = 0.494$, Fig. 3A). During recovery (up to 10 min post), MVIC torque increased similarly for both men and women (time effect, $P < 0.001$; time x sex, $P = 0.676$); however, men showed greater reductions in torque compared with women (mean of R0.1-R10, 26.1% vs 16.9%, respectively; sex effect, $P = 0.007$; Fig. 3A).

Voluntary activation

Voluntary activation was quantified with TMS for all subjects by calculating the SIT amplitude relative to the sum of MVIC and the SIT (% MVIC + SIT). The SIT (%) increased during the sustained isometric fatiguing contraction for both men and women (1.1% +/- 1.3% to 4.4% +/- 5.3% at F60; time effect, $P = 0.003$; time x sex, $P = 0.83$; Fig. 3B). However, men demonstrated larger SIT amplitudes *throughout* the fatiguing contraction compared with women (mean of F0-F60, 4.3% +/- 0.8% vs 1.8% +/- 0.8%, respectively; sex effect, $P = 0.041$). During recovery, SIT amplitude (%) declined for both men and women (time effect, $P < 0.001$; time x sex, $P = 0.851$), but men had a greater SIT amplitude (lower voluntary activation) than did women during recovery (sex effect, $P = 0.038$; Fig. 3B).

Voluntary activation, estimated with electrically evoked contractions, was reduced immediately after the fatiguing task (R0.1) for both men and women (77.1% +/- 16.7% vs 79.8% +/- 20.1%; time effect, $P = 0.033$; time x sex, $P = 0.532$). Voluntary activation increased during the recovery from the fatiguing task for both men and women (time effect, $P = 0.035$; time x sex, $P = 0.918$); however, men had lower voluntary activation compared with women throughout recovery (average R0.1-R10, 80.0% +/- 2.1% vs 88.4% +/- 1.5%; sex effect, $P = 0.004$).

Contractile properties

The electrically evoked resting twitch contraction amplitude was reduced immediately after the isometric fatiguing contraction, with no difference in the decline between men and women (R0.1; time effect, $P < 0.001$; time x sex, $P = 0.461$; Fig. 3C). The resting twitch increased during the recovery time, and this recovery was similar between men and women (time effect, $P < 0.001$; time x sex, $P = 0.619$).

Men and women demonstrated a prolonged half-relaxation time after the isometric fatiguing task, which was similar for men and women (time effect, $P < 0.001$; time x sex, $P = 0.797$), followed by a similar decrease in the half-relaxation time for the men and women during the 10 min of recovery (time effect, $P < 0.001$; time x sex, $P = 0.639$). The contraction time of the resting twitch increased after the fatiguing task (time effect, $P = 0.031$; time x sex, $P = 0.221$) and decreased during the 10 min after the fatiguing task (time effect, $P = 0.026$; time x sex, $P = 0.563$), similarly for men and women. See Table 2.

MEP and silent period

The MEP amplitude (% M_{max}) increased from the baseline measures to immediately after the fatiguing isometric task (R0.1) similarly for men and women, for the rectus femoris (47.3% +/- 9.3% M_{max} vs 63.6% +/- 17.9% M_{max}; time effect, $P < 0.001$; time x sex, $P = 0.788$), vastus lateralis (38.6% +/- 10.9% M_{max} vs 58.3% +/- 18.5% M_{max}; time effect, $P < 0.001$; time x sex, $P = 0.192$), and vastus medialis (37.6% +/- 12.1% M_{max} vs 58.3% +/- 18.5% M_{max}; time effect, $P < 0.001$; time x sex, $P = 0.150$). The MEP amplitude (% M_{max}) decreased during the 10-min recovery period, similarly for men and women, for the rectus femoris (R10, 47.4% +/- 15.3% M_{max}; time effect, $P = 0.002$; time x sex, $P = 0.934$), vastus lateralis (R10, 37.0% +/- 13.4 % M_{max}; time effect, $P = 0.001$; time x sex, $P = 0.499$), and vastus medialis (R10, 34.4% +/- 16.5% M_{max}; time effect, $P < 0.001$; time x sex, $P = 0.472$).

The EMG silent period in response to the TMS increased from baseline to immediately after the fatiguing contraction (R 0.1), similarly for men and women, for the rectus femoris (124 +/- 43 ms vs 298 +/- 104 ms; time effect, $P < 0.001$; time x sex, $P = 0.764$), vastus lateralis (127 +/- 67 ms vs 292 +/- 105 ms; time effect, $P < 0.001$; time x sex, $P = 0.405$), and vastus medialis (110 +/- 32 ms vs 280 +/- 121 ms; time effect, $P < 0.001$; time x sex, $P = 0.508$). The EMG silent period in response to the TMS decreased during the 10-min recovery period, similarly for men and women, for the rectus femoris (R10, 163 +/- 90 ms; time effect, $P = 0.002$; time x sex, $P = 0.779$), vastus lateralis (R10, 154 +/- 85 ms; time effect, $P < 0.001$; time x sex, $P = 0.734$), and vastus medialis (R10, 158 +/- 91 ms; time effect, $P < 0.001$; time x sex, $P = 0.358$).

Associations

Stronger individuals (larger MVIC at baseline) demonstrated larger decrements in MVIC after the 60-s sustained isometric contraction ($r = 0.514$, $r^2 = 0.264$, $P = 0.003$). In addition, individuals who demonstrated greater reductions in MVIC torque measured immediately after the sustained isometric fatiguing task had greater reductions in the twitch amplitude evoked with electrical stimulation at rest. This was best fit as a quadratic relation (R0.1; $r = 0.436$, $r2 = 0.190$, $P = 0.009$; Fig. 3D).

Dynamic Fatiguing Task Session

MVIC torque

MVIC torque was reduced from baseline when assessed immediately after the dynamic fatiguing task at R0.1 (time effect, $P< 0.001$; Fig. 4A); however, men had greater decrements in MVIC torque than did women (35.0% +/- 13.4% vs 23.1% +/- 8.4% reduction; time x sex, $P < 0.001$; Fig. 4A and Table 2). MVIC torque recovered during the 10-min period after the fatiguing contraction for both men and women (time effect, $P <$

0.001); however, men had lower relative torque compared with women throughout the 10 min of recovery (sex effect, *P* = 0.007; time x sex, *P* = 0.676).

MVCC angular velocity, power, and acceleration during the fatiguing task

There was no difference between men and women in the reduction of MVCC angular velocity from the start to the end of the dynamic fatiguing task (16.7% +/- 19.1% vs 11.7% +/- 12.2% reduction, respectively; time effect, *P* < 0.001; time x sex, *P* = 0.498). In addition, the increase in MVCC velocity during recovery was similar for men and women (time effect, *P* < 0.001; time x sex, *P* = 0.141).

Men and women demonstrated similar reductions in peak MVCC power from the start to the end of the dynamic fatiguing task (14.7% +/- 20.1% vs 14.2% +/- 18.5% reduction; time effect, *P* < 0.001; time x sex, *P* = 0.925), and recovery was similar for both sexes (time effect, *P* < 0.001; time x sex, *P* = 0.529). Men and women had similar reductions in maximal angular acceleration during the MVCC from the start to the end of the dynamic fatiguing task (10.5% +/- 13.9% vs 6.3% +/- 11.0%, respectively; time effect, *P* < 0.001; time x sex, *P* = 0.274). Men and women also had a similar increase in angular acceleration during recovery (6.9% +/- 10.0% vs 7.0% +/- 9.3%, respectively; time effect, *P* < 0.001; time x sex, *P* = 0.809).

Work-to-rest ratio (duty cycle) during the fatiguing task

The ratio of concentric contraction time to the rest within each 3-s cycle (work-to-rest ratio) was similar between men and women during the first five dynamic contractions (13.9% +/- 2.4% vs 13.7% +/- 3.4%, respectively; sex effect, *P* = 0.783). As angular velocity declined, the work-to-rest ratio increased during the fatiguing task (time effect, *P* < 0.001), although, this was similar for men and women (19.2% +/- 21.6% vs 21.2% +/- 27.6% increase, respectively; time x sex, *P* = 0.883). In addition, the reduction in work-to-rest ratio during recovery after the fatiguing task (time effect, *P* < 0.001) was similar for men and women (time x sex, *P* = 0.907).

Range of motion during the fatiguing task

The range of motion over which men and women performed the concentric knee extension did not differ (82.3[degrees] +/- 8.0[degrees] vs 84.1[degrees] +/- 11.6[degrees]; respectively, sex effect, *P* = 0.643) and did not change during the dynamic fatiguing task (time effect, *P* = 0.134; time x sex, *P* = 0.703). The range of motion also did not change during recovery after the fatiguing task (time effect, *P* = 0.308; time x sex, *P* = 0.238).

Applied torque during the fatiguing task

Because men were stronger than women, the peak applied torque (91.4 +/- 17.7 N[middle dot]m vs 63.3 +/- 10.1 N[middle dot]m, respectively; sex effect, *P* < 0.001) and the average applied torque (64.3 +/- 13.4 N[middle dot]m vs 43.2 +/- 7.7 N[middle dot]m, respectively; sex effect, *P* < 0.001) during the concentric phase of the dynamic knee extension were greater for men compared with women at the start of the fatiguing task. During the fatiguing task, men and women had similar reductions of peak applied torque (7.3% +/- 11.8% vs 7.3% +/- 9.3% reduction, respectively; time effect, *P* = 0.001; time x sex, *P* = 0.754) and average applied torque (3.4% +/- 13.3% vs 8.6% +/- 10.6% reduction, respectively; time effect, *P* = 0.014; time x sex, *P* = 0.391). During recovery, both men and women had increases in the peak applied torque (time effect, *P* < 0.001; time x sex, *P* = 0.354) and average applied torque (time effect, *P* = 0.013; time x sex, *P* = 0.834).

MVCC work during the fatiguing task

Concentric muscular work was calculated during each dynamic contraction as the product of the average torque during the concentric phase of knee extension x angular displacement (range of motion), and the relative work was calculated similarly, expressing the average torque relative to MVIC torque (% MVIC). MVCC work was greater for men, because men are stronger than women, at baseline (4725 +/- 1083 N[middle dot]m[middle dot][degrees] vs 3242 +/- 602 N[middle dot]m[middle dot][degrees], respectively; sex effect, *P* < 0.001); however, MVCC *relative* work was similar for men and women (2327 +/- 324 AU vs 2425 +/- 425 AU, respectively; sex effect, *P* = 0.517). The reduction in MVCC work at the end of the dynamic fatiguing task was similar for men and women for both absolute work (6.4% +/- 18.6% vs 10.1% +/- 13.5% reduction, respectively; time effect, *P* = 0.015; time x sex, *P* = 0.902) and *relative* work (8.1% +/- 19.9% vs 11.3% +/-

13.5% reduction, respectively; time effect, $P = 0.003$; time x sex, $P = 0.522$). The increase in MVCC work during recovery was similar for men and women for both absolute work (time effect, $P < 0.001$; time x sex, $P = 0.217$) and *relative* work (time effect, $P = 0.013$; time x sex, $P = 0.255$).

Voluntary activation

The SIT torque (% MVIC + SIT) elicited with TMS did not increase for men and women from baseline (2.67% +/- 1.70% vs 2.63% +/- 1.41%, respectively) to after the dynamic fatiguing task (R0.1, 2.69% +/- 2.35% vs 2.75% +/- 1.53%, respectively; time effect, $P = 0.136$; time x sex, $P = 0.306$) and did not change during recovery after the task (R10, 2.66% +/- 2.49% vs 2.78% +/- 2.23%, respectively; time effect, $P = 0.280$; time x sex, $P = 0.606$; Fig. 4B).

Voluntary activation, assessed with electrical stimulation of the muscle, declined for men and women from baseline (92.9% +/- 5.8% vs 94.3% +/- 6.5%, respectively) to immediately after the dynamic fatiguing task (R0.1, 88.3% +/- 9.2% vs 86.4% +/- 6.3%; time effect, $P < 0.001$; time x sex, $P > 0.538$). Men and women had no change in voluntary activation after 10 min of recovery (R10, 88.0% +/- 7.9% vs 89.5% +/- 6.6%; time effect, $P = 0.614$; time x sex, $P = 0.405$).

Contractile properties

Resting twitch amplitude elicited with electrical stimulation declined for both men and women between baseline and immediately after the dynamic fatiguing task (time effect, $P < 0.001$). Men however, had greater reductions in the twitch amplitude compared with women (R0.1; time x sex, $P = 0.016$, Fig. 4C). During the 10 min of recovery, the resting twitch amplitude increased (recovered) more rapidly for women than for men (time effect, $P < 0.001$; time x sex, $P = 0.035$), although by 10 min, the twitch amplitude was still reduced relative to baseline for both sexes.

The half-relaxation time of the electrically evoked twitch contraction increased between baseline and immediately after the dynamic fatiguing task (time effect, $P < 0.001$; Table 2), similarly for men and women (time x sex, $P = 0.612$), and there were no sex-related differences during recovery (time effect, $P < 0.001$; time x sex, $P = 0.249$). Men and women demonstrated a similar prolonged contraction time of the electrically evoked twitch contraction after the dynamic fatiguing task (time effect, $P = 0.006$; time x sex, $P = 0.707$), and the contraction time did not change during recovery for men or women (time effect, $P = 0.115$; time x sex, $P = 0.989$).

MEP and silent period

The MEP amplitude (% M_{max}) increased from baseline to immediately after the fatiguing contraction (R0.1) for the rectus femoris (48.0% +/- 12.3% vs 60.2% +/- 19.4%; time effect, $P = 0.004$; time x sex, $P = 0.731$) and vastus medialis (39.0% +/- 27.4% vs 41.5% +/- 17.2%; time effect, $P = 0.011$; time x sex, $P = 0.188$), but not the vastus lateralis (37.0% +/- 13.7% vs 41.5% +/- 19.9%; time effect, $P = 0.558$; time x sex, $P = 0.159$), and the men and women demonstrated similar changes in MEP amplitude for each muscle. The MEP amplitude declined during the 10-min recovery period, similarly for men and women, for the rectus femoris (R10, 51.7% +/- 11.5%; time effect, $P = 0.029$; time x sex, $P = 0.174$) and vastus medialis (R10, 32.2% +/- 15.7%; time effect, $P = 0.045$; time x sex, $P = 0.354$), but not the vastus lateralis (R10, 33.3% +/- 13.8%; time effect, $P = 0.051$; time x sex, $P = 0.338$).

The EMG silent period in response to TMS increased from baseline to immediately after the fatiguing contraction (R0.1) for the rectus femoris (152 +/- 62 ms vs 209 +/- 91 ms; time effect, $P = 0.005$; time x sex, $P = 0.867$), vastus lateralis (144 +/- 63 ms vs 190 +/- 102 ms; time effect, $P = 0.003$; time x sex, $P = 0.713$), and vastus medialis (156 +/- 65 ms vs 194 +/- 87 ms; time effect, $P = 0.002$; time x sex, $P = 0.426$), and the increased silent period was similar for men and women for each muscle. The EMG silent period in response to TMS decreased during the 10-min recovery period, similarly for men and women, for the rectus femoris (R10, 158 +/- 71 ms; time effect, $P = 0.018$; time x sex, $P = 0.732$), vastus lateralis (R10, 144 +/- 68 ms; time effect, $P= 0.033$; time x sex, $P = 0.769$), and vastus medialis (R10, 135 +/- 55 ms; time effect, $P = 0.001$; time x sex, $P = 0.395$).

Associations

During the dynamic session, half-relaxation time at baseline was associated with decrements in MVCC velocity and MVCC power, such that individuals with a shorter half-relaxation time had larger decrements during the fatiguing task in MVCC velocity (r = 0.509, r^2 = 0.259, P = 0.005) and MVCC power (r = 0.462, r^2 = 0.213, P = 0.010). However, the changes in half-relaxation time after the fatiguing task were not associated with reductions in MVCC velocity (P = 0.171) or MVCC power (P = 0.118) during the fatiguing task. In addition, the reduction in resting twitch amplitude (after the dynamic fatigue task) was linearly correlated with the reduction in MVIC torque (r= 0.651, $r2$ = 0.424, P < 0.001), MVCC velocity (r = 0.455, $r2$ = 0.207, P = 0.012), and MVCC power (r = 0.417, $r2$ = 0.174, P = 0.024), such that individuals with larger reductions in MVIC torque, MVCC velocity, and MVCC power had larger reductions in twitch amplitude (Fig. 4D).

DISCUSSION

This study established that the contribution of supraspinal and contractile mechanisms of fatigability during recovery of torque after isometric and dynamic fatiguing tasks with the knee extensor muscles differed between the fatiguing tasks and also between men and women. Specific to the sex differences, the novel findings were as follows: 1) men demonstrated greater fatigue-induced reductions of MVIC torque than did women during recovery *after* the sustained isometric and dynamic fatiguing task, despite no sex-related differences in fatigability *during* the fatiguing tasks; 2) during the sustained isometric task and the 10 min of recovery, men exhibited greater supraspinal fatigue (increases in SIT torque) than women, with no sex differences in the contractile mechanisms indicted by the similar change for the sexes in the twitch amplitude; and 3) during recovery from the dynamic fatiguing task, men had greater reductions in twitch amplitude than did the women, with no sex difference in supraspinal fatigue. Thus, the slower recovery of MVIC torque of knee extensors in the men compared with the women after the *sustained isometric task*was due to supraspinal mechanisms and, in contrast, was explained by contractile mechanisms after the *dynamic fatiguing task*. Thus, the sex difference in recovery from fatiguing tasks with the knee extensor muscles and the involved mechanisms differed for a sustained maximal isometric and dynamic contraction protocol.

Sex Differences in Strength, Power, and Contractile Properties

As expected, men were stronger (41% difference in MVIC torque) and more powerful than women (34% difference in MVCC power), and these sex differences in strength and power are similar to previous findings for the knee extensor muscles (11). Measures of voluntary activation evoked with electrical stimulation at the muscle and magnetic stimulation of the motor cortex indicate that there were no sex differences in the ability to activate the knee extensor muscles or drive to the motor cortex at baseline, as seen before for the elbow flexor muscles (10,12,13). Thus, men and women exerted similar effort at baseline during maximal contractions, indicating that the sex difference in strength and power of the knee extensor muscles were due to contractile mechanisms (37) and not due to a sex difference in neural drive. Accordingly, the women exhibited a slower relaxing muscle (half-relaxation time, 12% difference) and a lower evoked twitch amplitude (43% difference). These contractile properties probably reflect a greater proportional area of fibers that possess type I myosin heavy-chain isoforms and the associated slower Ca^{2+} kinetics in the sarcomere in the whole muscle of the women than the men (3,5). There is also evidence of sex-related differences in tendon viscoelastic properties, such that women have lower stiffness and hysteresis compared with men (38), and so it is possible that these sex-based differences could also contribute to slower contractions in the women compared with the men.

Sex Differences in Recovery of Force from a Maximal Sustained Isometric Task

Men demonstrated a slower recovery of MVIC torque after the isometric fatiguing contraction despite no sex difference in the decline in maximal isometric torque *during* the 60-s contraction. Because the isometric contraction was maximal, muscle perfusion was likely minimal with the high intramuscular pressures during the task for both men and women (39,40). Thus, it is not surprising that the sex difference in fatigability in our study was not apparent until brief MVIC tasks were performed intermittently during the 10 min of recovery when the quadriceps were perfused. Similarly, Russ and Kent Braun (19) showed no sex difference in fatigability of intermittent MVIC when blood was occluded via pneumatic cuff from the ankle dorsiflexor

muscles, but the sex difference in fatigability (reduction in maximal force) was apparent for an intermittent contraction task *without* occlusion.

The more rapid recovery of MVIC torque for the women than for the men was paralleled by larger reductions in the voluntary activation when assessed with electrical stimulation of the muscles and TMS. Martin and Rattey (20) also reported greater central fatigue (reduction in voluntary activation) in the men than in the women when assessed with electrically evoked contractions of the muscle, with no sex difference in contractile mechanisms. Our findings extend these findings to show that the sex difference in fatigability during recovery was in part due to supraspinal fatigue because the increase in the amplitude of the SIT torque elicited with TMS was concomitant with a larger reduction in the recovery MVIC. These findings suggest that despite maximal effort, the men had a larger reserve of untapped motor cortical output at the time of stimulation and a greater failure to generate output from the motor cortex compared with the women. Thus, some of the greater central fatigue exhibited by the men compared with the women was supraspinal.

The increase in the central fatigue indicated by a decrease in voluntary activation (increase in the SIT) assessed by stimulation at the motor cortex and muscle could also be in part due to less responsive motoneurons (21,23). Thus, although the increased SIT torque indicated that the drive from the motor cortex was suboptimal, it is possible that the men and women had similar reductions in motor cortical output, but the men had less effective descending drive due to a decrease in excitability of the motoneuron. However, the EMG responses to TMS during the MVIC tasks suggested that the change in the excitability of the corticospinal pathways did not differ between the sexes. We found that there were no sex-related differences in the increase in MEP amplitude (normalized to the M wave) during the fatiguing contraction and no difference in the decline of the MEP during recovery for any of the quadriceps muscles. 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 (41). Recently, it was shown, however, that for the knee extensor muscles, there was minimal change in the EMG response to thoracic corticospinal tract stimulation during a sustained isometric fatiguing contraction, indicating that cortical mechanisms rather than altered net responsiveness of the motoneurons pool were responsible for the increase in the MEP in both men and women (24). Further studies using cervicomedullary or thoracic spine stimulation during fatiguing contractions (24,42) would determine whether there are fatigue-related differences in excitability of the corticospinal tract between men and women.

We also showed that there was no sex-related difference in the increase in the duration of the EMG silent period of the quadricep muscles during the maximal effort contractions. The initial part of the silent period (the first 50-100 ms) is likely influenced by spinal mechanisms, including recurrent inhibition and after hyperpolarization, whereas the latter phase represents intracortical inhibition (43). Thus, the increase in the duration of the silent period during the fatiguing contraction probably reflects increased intracortical inhibition (24,44). Because the silent period in the quadricep muscles lengthened similarly for the men and women, and as observed for the elbow flexor muscles (12,13), this change did not contribute to the sex difference in fatigability during recovery of the knee extensor muscles that we observed.

The fatigue in the muscle was large immediately after the fatiguing task for both sexes, because the electrically evoked twitch amplitude was reduced to ~36% and 33% of baseline for men and women, respectively. Although muscular mechanisms did not explain the sex difference in the recovery of MVIC torque, the magnitude of fatigue within the muscle was substantial and contributed to fatigability of the knee extensors. Indices of contractile mechanisms of fatigability included a reduced twitch amplitude and longer half-relaxation time of the electrically evoked resting twitch. Collectively, these results can reflect a reduction in the number of active cross-bridges, a slowing of the active cross-bridge, and a slowing of calcium kinetics as the metabolic milieu changes including an increased H^+ and inorganic phosphate (2,45). Accordingly, the change in twitch amplitude was associated (albeit weakly) with the reduction in the MVIC torque immediately after the sustained MVIC, explaining ~19% of the variance in the reduction in MVIC (Fig. 3D). Thus, although the contractile mechanisms did not explain the sex difference in fatigability during the recovery up to 10 min after exercise, muscular mechanisms may have contributed to the increases in the SIT immediately after the task (at R0.1) for both sexes via feedback from group III and IV afferents (21), although initial evidence

indicates that their influence on excitability of the motoneuron pool during fatiguing contractions with the knee extensors may be minimal (24).

Sex Differences in Recovery of Torque from a Dynamic Task

During recovery of the fast-velocity dynamic fatiguing task, men demonstrated greater reductions in knee extensor MVIC torque than did women despite a similar relative decline in peak concentric velocity and power during the task. In addition, the relative changes in the work-to-rest ratio, the average applied torque, and the work during the dynamic task did not differ for the men and women. These results confirm our previous findings of a slower recovery of MVIC torque in the knee extensor muscles of men compared with women up to 10 min after the velocity-dependent dynamic fatiguing contraction (11). The new findings also include that although both central and contractile mechanisms contributed to fatigability (reductions in MVIC torque and MVCC power) for both sexes, the slower recovery of MVIC torque for the men compared with the women was primarily due to contractile mechanisms because the potentiated twitch amplitude (muscle stimulation) decreased more for the men (Table 2). The central mechanisms that contributed to fatigability (SIT torque, MEP amplitude, and EMG silent period), however, were similar in men and women.

The reduction in the MVIC torque for the men and women immediately after the dynamic fatiguing task (35.0% and 23.1%, respectively) was similar to that of the electrically evoked twitch (36.6% and 22.9% reduction, respectively). Furthermore, correlation analysis indicated that ~42% of the reduction in MVIC torque was explained by the variance in the reduction of the electrically evoked twitch amplitude (Fig. 4D). The fatigability of maximal voluntary torque and twitch amplitude is thought to be due to impairments in excitation-contraction coupling and/or the cross-bridge involving a reduced number of cross-bridges that transition from the low- to high-force state, less force per cross-bridge, or a reduction in intracellular Ca^{2+} sensitivity (2,46). These intracellular mechanisms are associated with increased intracellular hydrogen ions and inorganic phosphate that increase during fatiguing contractions (46).

In contrast, we showed that there was no sex difference in the decline of shortening velocity during repeated concentric contractions (dynamic fatiguing task). The decline of velocity during fatiguing dynamic contractions may be due to changes in maximal shortening velocity and fatigue-related shifts in the force-velocity relationship. The maximal shortening velocity of the fiber is associated with limits of cross-bridge cycle speed and determined by the dissociation of adenosine triphosphate from the cross-bridge (2), and thus did not seem to differ between men and women. The maximal force that can be produced by skeletal muscle decreases as the shortening velocity increases in a predictable relationship, as specified in the Hill equation (47). The force-velocity relationship is altered with fatigue, such that at the same shortening velocity, less force can be produced in fatigued compared with "fresh" muscle (48). This change ("shift") in the force-velocity relationship suggests a slowing of cross-bridge detachment (48) that may have contributed to the observed decline in MVCC velocity; however, the magnitude of the reduction in MVCC velocity and power during the fatiguing task did not differ between the sexes in our study. In addition, any fatigue-related changes in tendon viscoelastic properties and musculotendinous compliance in the knee extensor muscles (49) may also reduce transmission of force from the muscle to tendon, in both men and women.

In contrast to the sustained isometric contraction, central mechanisms of fatigability did not differ between the sexes during recovery of maximal torque from the dynamic fatiguing task. There was no sex difference during recovery from the dynamic contraction when voluntary activation was assessed with cortical and electrically evoked muscle stimulation. Nor were there any sex differences in indices of corticospinal excitability during recovery of the dynamic fatiguing task including the MEP and silent period at baseline and the increase in these variables with fatigue. Collectively, these data indicate that although both neural and contractile mechanisms contributed to fatigability of the dynamic fatiguing task with the knee extensor muscles, the greater reductions in the MVIC for the men compared with the women were primarily due to contractile mechanisms. Although there was no change in voluntary activation elicited via TMS, there was a small yet significant reduction in voluntary activation elicited via electrical stimulation, possibly suggesting reductions in activation and force due to spinal mechanisms.

CONCLUSIONS

Different mechanisms contributed to the greater fatigability of maximal isometric torque and slower recovery of maximal torque in men than in women after isometric and dynamic tasks with the knee extensor muscles. Recovery of maximal torque after a sustained isometric contraction was slower in men than in women because of greater supraspinal fatigue. In contrast, contractile mechanisms were the primary mechanism for slower recovery of maximal torque in men compared with women after the dynamic fatiguing contraction. Thus, these results show that the mechanisms for the sex difference in recovery of a fatiguing task are dependent on the task details. These findings may have important implications for optimal loads and contraction types for training and rehabilitation of young men and women.

This work was supported by a National Institute of Aging award (R21AG045766) to S. K. H. We acknowledge the valuable assistance of Mr. Vincent Spears during the study.

No conflicts of interest, financial or otherwise, are declared by the authors. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation, and statement that results of the present study do not constitute endorsement by the American College of Sports Medicine.

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Key Words: MUSCLE FATIGUE; KNEE EXTENSORS; GENDER; SUPRASPINAL FATIGUE; VOLUNTARY ACTIVATION

Image Gallery

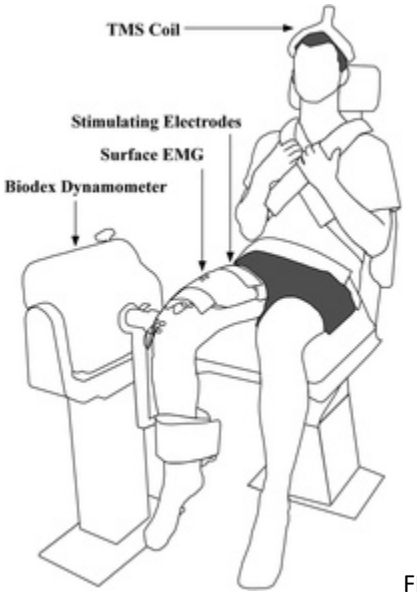

FIGURE 1—Experimental setup and participant positioning during each of the experimental sessions that assessed fatigability and recovery of the sustained MVIC and dynamic fatiguing task with the knee extensor muscles.

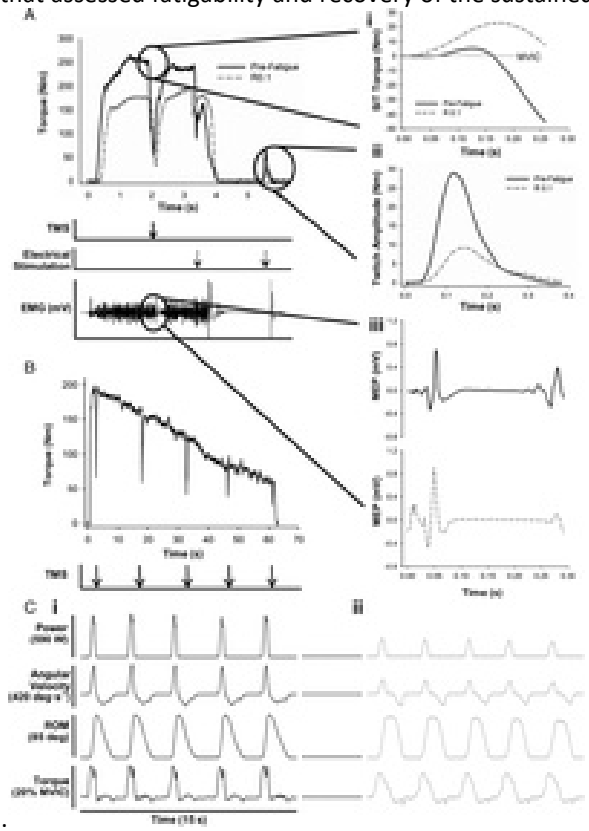

FIGURE 2—Representative data for MVIC torque, SIT torque, resting twitch amplitude,MEP and MVCC power, velocity, range of motion (ROM), and applied torque.A, Torque signal of a participant performing anMVIC, and submaximal contractions at 60% and 80%MVIC with stimulation shown with arrows. The darker line represents baseline data, and the lighter dashed line is data immediately after the sustainedMVIC fatiguing task (R0.1). The insets show the SIT torque during an MVIC elicited with TMS (inset i), an electrically evoked resting twitch (inset ii), and MEP elicited via TMS duringMVIC (inset iii). B, Torque during a 60-s sustained MVICtask. C, Angular power, velocity, ROM, and applied torque during sets of five MVCC that were performed at the beginning (panel i; contractions 1–5, dark solid lines) and at the end (panel ii; contractions 116–120, lighter lines) of the dynamic fatiguing task.

Variables	Units	Men (n = 14)	Women (n = 17)
Age	yr	20 (1.0)	21 (1.4)
Height	m	1.79 (0.05)	1.64 (0.07)*
Body mass	kg	76.3 (10.4)	58.8 (8.3)*
BMI	$kg \cdot m^{-2}$	23.8 (3.1)	21.8 (2.5)
PAQ	$MET \cdot h \cdot wk^{-1}$	59.0 (55.2)	38.5 (32.5)
MVIC	N·m	228 (54)	134 (27)*
Voluntary activation (ES)	%	92.9 (5.6)	94.9 (5.1)
Contraction time (ES)	ms	82.6 (7.8)	83.8 (7.2)
Half-relaxation time (ES)	ms	56.5 (14.4)	63.4 (11.3)*
Resting twitch amplitude (ES)	N·m	64.6 (13.4)	36.5 (7.3)*
SIT torque (TMS)	% MVIC	3.2 (2.2)	3.7 (2.1)
RF MEP	% M_{max}	48.7 (9.3)	46.4 (9.0)
VL MEP	% M_{max}	41.1 (16.7)	37.2 (7.9)
VM MEP	% M_{max}	42.7 (29.4)	34.9 (9.8)

Values are displayed as mean (SD).
*Denotes sex differences, $P < 0.05$.
BMI, body mass index; ES, electrical stimulation; PAQ, Physical Activity Questionnaire; RF, rectus femoris; TMS, transcranial magentic stimulation; VL, vastus lateralis; VM, vastus medialis.

TABLE 1. Baseline characteristics of the male and female participants averaged across two experimental sessions.

Variables	Units	Men (n = 14)	Women (n = 17)
Age	yr	20 (1.0)	21 (1.4)
Height	m	1.79 (0.05)	1.64 (0.07)*
Body mass	kg	76.3 (10.4)	58.8 (8.3)*
BMI	kglm-^{2}	23.8 (3.1)	21.8 (2.5)
PAQ	METIhIwk-^{1}	59.0 (55.2)	38.5 (32.5)
MVIC	NIm	228 (54)	134 (27)*
Voluntary activation (ES)	%	92.9 (5.6)	94.9 (5.1)
Contraction time (ES)	ms	82.6 (7.8)	83.8 (7.2)
Half-relaxation time (ES)	ms	56.5 (14.4)	63.4 (11.3)*
Resting twitch amplitude (ES)	NIm	64.6 (13.4)	36.5 (7.3)*
SIT torque (TMS)	% MVIC	3.2 (2.2)	3.7 (2.1)
RF MEP	% *M*max	48.7 (9.3)	46.4 (9.0)
VL MEP	% *M*max	41.1 (16.7)	37.2 (7.9)
VM MEP	% *M*max	42.7 (29.4)	34.9 (9.8)

Values are displayed as mean (SD).
*Denotes sex differences, P G 0.05.
BMI, body mass index; ES, electrical stimulation; PAQ, Physical Activity Questionnaire; RF, rectus femoris; TMS, transcranial magentic stimulation; VL, vastus lateralis; VM, vastus medialis

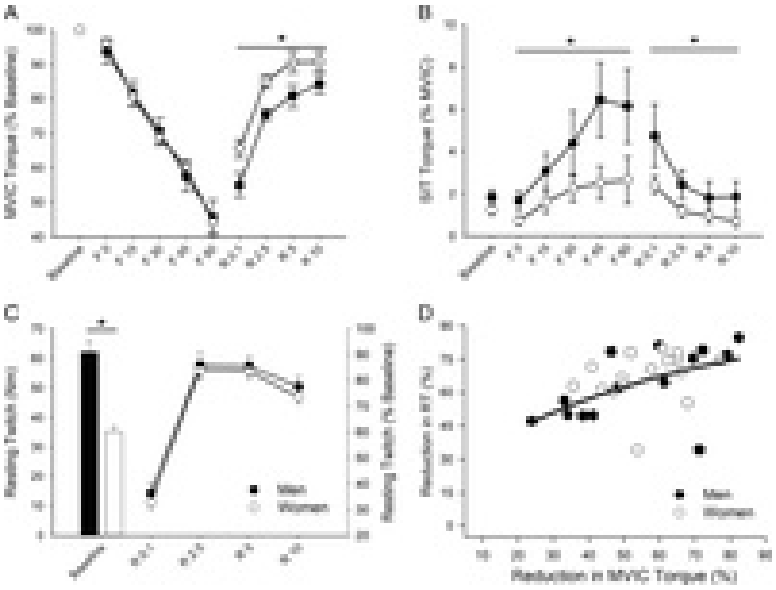

FIGURE 3—Voluntary and evoked torque during and in recovery from the 60-s sustained MVIC. Shown are the means and SEM at every 15 s during the sustained contraction and then during recovery MVIC tasks. A, MVIC torque during the isometric fatiguing task. Men and women had similar reductions in MVIC, but the men remained more depressed during recovery than the women. B, SIT torque evoked with TMS during the sustained isometric fatiguing task and in recovery during brief MVIC tasks. Men had larger SIT amplitudes during the 60-s MVIC (F0–F60) and during recovery (R0.1–R10). C, Resting twitch amplitude evoked from electrical stimulation at baseline (NIm; left y-axis) and relative to baseline (%) during recovery (right y-axis). Men and women had similar reductions in the resting twitch amplitude after the sustained MVIC and during recovery (P 9 0.05). D, The reduction in MVIC immediately after the isometric fatiguing contraction (R0.1) was associated with the reduction in resting twitch amplitude (RT) (A: r = 0.436, r2 = 0.190, P = 0.009). *Sex difference at P G 0.05.

TABLE 2. Percentage change in neuromuscular properties after the isometric and dynamic fatiguing tasks.

		Isometric Session				Dynamic Session	
	Men		Women		Men		Women
Contraction time (ES)	0.9 (12.7)		4.4 (10.1)		1.6 (12.0)		5.6 (10.0)
Half-relaxation time (ES)	27.5 (64.6)		25.2 (52.5)		27.2 (22.9)		30.4 (33.6)
Resting twitch amplitude (ES) MVIC torque	j63.5 (15.9) j54.4 (18.9)		j67.1 (11.0) j55.9 (11.2)		j36.6 (21.8) j35.0 (13.4)		j22.9 (18.2)* j23.1 (8.4)*

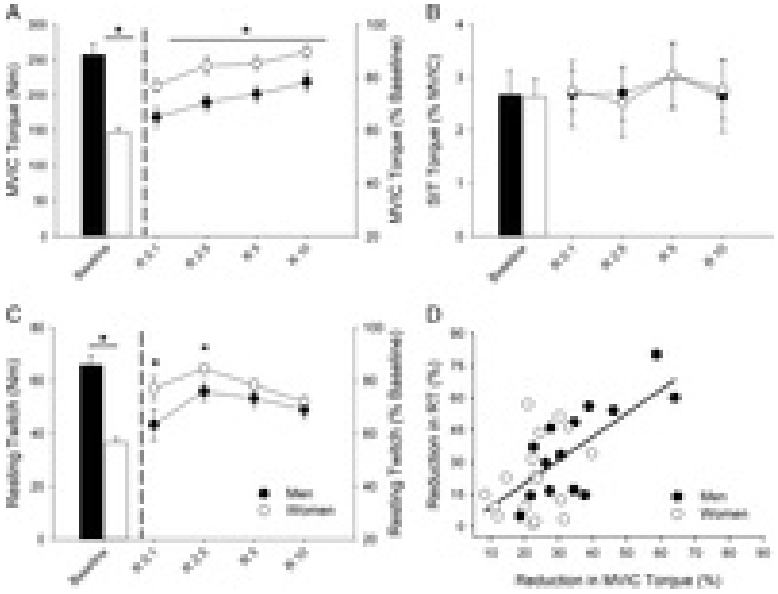

FIGURE 4—Voluntary and electrically evoked torque at baseline and recovery from the dynamic fatiguing contraction. Shown are the means and SEM. Men are in the black (filled) bars and circles and women in the white and open bars and circles. A, Torque from brief MVIC at baseline (NIm; left y-axis) and during recovery relative to baseline (%). Men were stronger than women at baseline (P G 0.05), and men had greater reductions in MVIC throughout recovery (R 0.1–R 10). B, The SIT (% MVIC) did not increase after the dynamic fatiguing contraction and was similar between men and women at baseline and during recovery (P 9 0.05). C, The resting twitch amplitude at baseline (NIm; left y-axis) was larger in the men than in the women (P G 0.05). The men had greater relative reductions in twitch amplitude (%; right y-axis) after the dynamic fatiguing task than did the women (R 0.1), and men had a lower resting twitch amplitude at the start of recovery relative than did women (R0.1–R10; time–sex effect, P G 0.05). D, The reduction in MVIC immediately after the dynamic fatiguing contraction (R0.1) was associated with the reduction in resting twitch amplitude (RT; r = 0.651, r_2 = 0.424, P G 0.001). *Sex difference at P G 0.05.