

# Human skeletal muscle responses vary with age and gender during fatigue due to incremental isometric exercise

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**Kent Braun, J. A., A. V. Ng, J. W. Doyle, and T. F. Towse.** Human skeletal muscle responses vary with age and gender during fatigue due to incremental isometric exercise. *J Appl Physiol* 93: 1813–1823, 2002. First published August 2, 2002; 10.1152/jappphysiol.00091.2002.—The purpose of this study was to compare the magnitude and mechanisms of ankle dorsiflexor muscle fatigue in 20 young ( $33 \pm 6$  yr, mean  $\pm$  SD) and 21 older ( $75 \pm 6$  yr) healthy men and women of similar physical activity status. Noninvasive measures of central and peripheral (neuromuscular junction, sarcolemma) muscle activation, muscle contractile function, and intramuscular energy metabolism were made before, during, and after incremental isometric exercise. Older subjects fatigued less than young ( $P < 0.01$ ); there was no effect of gender on fatigue ( $P = 0.24$ ). For all subjects combined, fatigue was modestly related to preexercise strength ( $r = 0.49$ ,  $P < 0.01$ ). Neither central (central activation ratio) nor peripheral (compound muscle action potential) activation played a significant role in fatigue in any group. During exercise, intracellular concentrations of  $P_i$  and  $H_2PO_4^-$  increased more and pH fell more in young compared with older subjects ( $P < 0.01$ ) and in men compared with women ( $P < 0.01$ ). These varied metabolic responses to exercise suggest a greater reliance on nonoxidative sources of ATP in young compared with older subjects and in men compared with women. These results suggest that the mechanisms of fatigue vary with age and gender, regardless of whether differences in the magnitude of fatigue are observed.

physical activity; magnetic resonance spectroscopy; central fatigue; activation; excitation-contraction coupling; metabolism

MUSCLE FATIGUE CAN BE DEFINED as the fall in maximum force-generating capacity of the muscle. During exercise, the magnitude and mechanisms of human skeletal muscle fatigue vary widely and depend to a large extent on the individual, the type of muscle, and the exercise stimulus or task. In general, fatigue may arise during muscular contractions due to failure at one or more sites along the pathway of force production from the central nervous system to the contractile apparatus (16).

There is reason to believe that both age and gender can affect the fatigue process, although our understanding of these effects is hampered by a lack of consensus in the literature. Although it has been reported that older adults fatigue relatively more than young adults (12, 33) and that men fatigue more than women (18, 20, 36), some investigators have found no effect of age (31, 35, 44) or gender (14) on fatigue. Still others have found that older subjects fatigue relatively less than younger subjects (3, 14).

Along with the lack of clarity regarding the effects of age and gender on the magnitude of muscle fatigue, the mechanisms of these differences have not been established. Differences in fatigability across age or gender could occur as a result of differences in neural drive, fiber-type composition, contractile function, muscle membrane excitability, metabolic capacity, or muscle mass and blood flow. For example, it was recently suggested that central activation failure may play a relatively larger role in the fatigue of older compared with younger adults (2, 44). Other investigators have reported impairments in excitation-contraction coupling in the muscle of older adults (13), although the possible role of this impairment in fatigue has not been established. The results of some (37), but not all (9, 28), studies suggest that oxidative capacity may be impaired with aging, despite a general shift toward a more oxidative fiber-type profile in older compared with younger muscle (30, 34). An impaired oxidative capacity in the muscle of older adults might contribute to fatigue in this group. Finally, it is unclear how a gender-based difference in fatigue might interact with the aging process.

In addition to the effects of activation, contractile function, and metabolism on muscle performance, the degree of fatigue that develops during exercise may be affected by muscle size and, consequently, vascular constriction during contraction. The impact of larger muscle mass, greater strength, and higher target tensions during exercise in men compared with women has been addressed in several studies. In the adductor

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pollicis, a gender-based difference in endurance time during a submaximal contraction persisted despite matching subjects to similar strengths (18). More recently, Hunter and Enoka (21) showed a gender difference in endurance (time to failure to maintain target tension) of the elbow flexor muscles during a contraction sustained at 20% maximal voluntary contraction (MVC) force but similar fatigue (fall in MVC) in men and women at the end of this exercise. Notably, the gender difference in endurance was negated by accounting for preexercise differences in muscle strength. These and other (14) results suggest that the relationship between muscle strength and fatigue should be examined in studies of the effects of age or gender on fatigue.

The purpose of this study was to investigate the magnitude and mechanisms of fatigue (i.e., fall in MVC of the ankle dorsiflexor muscles) in healthy young and older men and women during a progressive, intermittent isometric dorsiflexion exercise protocol that proceeds from a steady-state oxidative phase to a more glycolytic, fatiguing phase (26). The dorsiflexor muscles are functionally important for locomotion, posture, balance (49), and the prevention of falls in older adults (7). Furthermore, habitual use of the dorsiflexor muscles may make men and women less susceptible to disuse deconditioning than use of muscles more typically involved in high-power activities (e.g., quadriceps femoris), which are not often used by older adults.

To examine the mechanisms of fatigue, we obtained simultaneous measures of central and peripheral muscle activation, muscle contractile properties, and intramuscular energy metabolism by using a unique combination of voluntary and electrically stimulated muscle contractions, electromyography (EMG), and phosphorus-31-magnetic resonance spectroscopy. The relationship between strength and fatigue was also examined. To control for the effects of varying levels of physical activity on these measures, we studied individuals with similar, relatively sedentary habitual activity levels. By simultaneously measuring many of the factors that have been suggested to explain age- and gender-based differences in fatigue, we hoped to resolve some of the current discrepancies in this area.

## METHODS

We used a cross-sectional design to make comparisons across age and gender. Measures of MVC force were made before, every 2 min during, and 0, 2, 5, and 10 min after the exercise protocol. Central activation was measured before and immediately after exercise. Measures of peripheral activation and contractile function were made before and 0, 2, 5, and 10 min after exercise. The metabolic measures were made before and continuously throughout exercise.

**Subjects.** Forty-one healthy, nonsmoking men and women aged 25–45 (10 men, 10 women) or 65–85 yr (11 men, 10 women) were recruited from the community. Individuals with chronic disease or those taking medications that might affect muscle function were excluded. All subjects were relatively sedentary in that they participated in two or less periods of continuous (>20 min) activity per week. To minimize the chances of including individuals with latent peripheral

vascular disease, any subject with resting supine ankle and/or brachial systolic blood pressure of <1.0 was eliminated from the study. All subjects provided written, informed consent, as was approved by the Committee on Human Research at the University of California, San Francisco. All studies were conducted in San Francisco.

To establish that our study groups were similarly active, physical activity was quantified by using a three-dimensional accelerometer (Tritrac R3D, Professional Products, Madison, WI). Each subject wore an accelerometer at the waist during waking hours for a period of 1 wk, as previously described (27). All subjects maintained a brief written log of activities that was examined and discussed on returning the monitor to the laboratory. The vector magnitude (arbitrary units) for all three dimensions was averaged over the 7 days and divided by 1,000 (for ease of expression) and used as the measure of physical activity.

**Experimental arrangement.** All measures of force, contractile properties, activation, and metabolism were acquired with the subject seated with one leg extended (knee fixed at ~170° extension) into the 30-cm-bore superconducting magnet, as described in detail elsewhere (24, 25, 28). The foot was secured to a platform (ankle angle 120°) under which was mounted a nonmagnetic force transducer, which in turn was coupled to a personal computer.

The stimulating electrode (pair of 10-mm nonmagnetic disks, Grass Instruments, West Warwick, RI; mounted on plastic) was placed over the peroneal nerve, ~1 cm distal to the fibular head. A copper ground plate was placed distally between the stimulating electrode and the EMG recording electrodes (see below). For each subject, supramaximal intensity [15% greater than that necessary to elicit a maximal compound muscle action potential (CMAP)] was determined and then used for all subsequent stimuli. Twitch (0.1-ms pulse) and tetanic (50-Hz, 500-ms train) forces were obtained at sampling rates of 2,500 and 500 Hz, respectively. CMAP was recorded at 2,500 Hz with nonmagnetic surface electrodes (10-mm disks) taped over the belly and distal tendon of the tibialis anterior muscle, as previously described and used (24, 25, 29, 39). Force and EMG data were acquired and transferred to spreadsheet for analysis.

Phosphorus magnetic resonance spectroscopy was used to acquire information regarding intramuscular energy metabolism, as performed previously (24). Data were collected in the 1.9-T superconducting magnet by using a 3 × 5-cm elliptical surface coil taped over the belly of the tibialis anterior muscle, just proximal to the EMG recording electrode. After collection, data were transferred to personal computer for analysis, described in *Force and contractile measurements*.

**Force and contractile measurements.** Before the fatigue protocol, the following measures were made, in order: CMAP and accompanying twitch, MVC force, central activation ratio (CAR), potentiated CMAP + twitch, and stimulated tetanus. Each measure was separated by 1 min of rest. The CMAP + twitch measure and the MVC measure were each repeated three times at 1-min intervals. Peak MVC force was determined from the best of the three 3- to 4-s trials. To ensure optimal performance by the subject, any MVC trial that resulted in a force of <90% of the other trials was repeated. Twitches were acquired before and 0, 2, 5, and 10 min after exercise, and tetani were acquired before and 0, 5, and 10 min after exercise. The postexercise and recovery twitch forces were scaled to the potentiated twitch, which was obtained immediately after the third baseline MVC.

Because contractile failure is often a source of fatigue (17) and because it has been suggested that excitation-contrac-

tion coupling may be impaired with age (13), we measured several indexes of contractile function by using stimulated twitch and tetanic contractions of the dorsiflexor muscles before, immediately after, and during recovery from exercise, as performed previously (27, 39). Contractile function may be quantified by the peak forces elicited during stimulated contractions as well as by the speeds of contraction and relaxation. Together, these provide indirect information related to changes in the periphery before (e.g., due to differences in fiber type) and during fatiguing exercise, in particular excitation-contraction coupling and calcium resequestration (5, 16, 17, 47).

To fully represent the contraction and relaxation characteristics of the muscle, both the maximum rates of force development ( $dF/dt$ ) and relaxation ( $-dF/dt$ ), and the more global measures of twitch contraction time and tetanic half-relaxation time, were determined. The  $dF/dt$  and  $-dF/dt$  were calculated for both the twitch and tetanic contractions. Because the rate of force development is faster with higher force production (38),  $dF$  was expressed as a percentage of the peak force achieved during each contraction. Thus these rates are expressed as percent peak force per millisecond. This approach allows comparisons of rates across individuals with differing torque-producing capacities. For the tetanus, the half time of force relaxation was calculated as the time (in ms) from the last CMAP in the train to the point at which force fell to 50%. For the twitch, the time to peak force (in ms) was calculated, with the use of the differential of the force trace, from the time of force onset to the time at which  $dF/dt = 0$ . These calculations were performed in an Excel spreadsheet (Microsoft, Redmond, WA), as previously reported (24, 27).

**Activation measurements.** Central activation, measured here as that portion of neuromuscular activation located proximal to the stimulating electrode, was quantified by using the CAR [CAR = MVC/(MVC + superimposed stimulated force); Ref. 25].

The stimulated force was elicited with a supramaximal train (50 Hz, 500 ms) that was superimposed on the voluntary contraction when force had reached maximal and plateaued. CAR was determined before and at the end of exercise.

Peripheral activation was assessed from CMAP, which reflects the excitability of the neuromuscular junction and muscle membrane (1). CMAP peak-to-peak amplitude (in mV) and duration of the negative peak (in ms) were determined.

**Metabolic measurements.** After acquisition of the baseline force and contractile and activation measures, the subject sat quietly while the magnet was shimmed and phosphorus data were acquired from the resting muscle. The repetition time for all acquisitions was 1.25 s. The data were averaged over 1 min for the rest spectrum (48 acquisitions) and every 30 s (24 acquisitions) during exercise. To ensure accurate quantification of overlapping peaks, all peaks in the spectra [bone broad component, phosphomonoesters,  $P_i$ , phosphodiester, phosphocreatine (PCr), 3 peaks of adenosine triphosphate] were fit by using NMR1 software (New Methods Research, White Plains, NY). The data were then imported into a spreadsheet, corrected for partial saturation, and used to calculate  $P_i/PCr$ ,  $P_i$  (in mM), diprotonated  $P_i$  ( $H_2PO_4^-$ , in mM), and pH, according to standard equations (46). Corrections for partial saturation of PCr and  $P_i$  were made by using values obtained experimentally and from the literature (4), respectively. Metabolic data were acquired before and continuously during exercise.

**Exercise and recovery protocol.** After acquisition of baseline measures of force, contractile properties, activation, and metabolism, each subject practiced several contractions at 10% MVC to become familiar with the target intensity and duty cycle of the exercise protocol. The subject then performed 16 min of isometric contractions (4-s contraction, 6-s relaxation). Exercise began at 10% of MVC and was incremented by 10% every 2 min. To determine the time course of fatigue, an MVC was performed at the beginning of each 2-min stage. Immediately postexercise, MVC with superimposed train (CAR), tetanic force, and CMAP with accompanying twitch force were measured. The primary fatigue variable was the fall of MVC at end of exercise, i.e., postexercise MVC/preexercise MVC. This protocol typically causes MVC to fall to ~70–75% of initial levels (26, 29).

**Statistical analyses.** Two-factor (age, gender) ANOVAs were used to examine differences between groups in preexercise force (MVC, tetanic force, twitch force), contractile properties (maximum rates of twitch and tetanic force development and relaxation, twitch contraction time, and tetanic half-relaxation time), peripheral activation (CMAP amplitude and duration), and metabolic variables at rest ( $P_i/PCr$ , pH). Due to the ceiling effect of the CAR measure, Mann-Whitney and Wilcoxon nonparametric procedures were used to detect differences across groups in pre- and postexercise CAR values. Two-factor (age, gender) repeated-measures (pre-, postexercise) ANOVAs were used to compare changes in force, contractile properties, and activation before vs. immediately after exercise. Changes in metabolites throughout exercise and the recoveries of MVC, tetanic force, twitch force, CMAP, and contractile properties were also compared across groups by using two-factor, repeated-measures ANOVA.

To investigate the role of muscle mass in fatigue, the association between preexercise MVC (a surrogate for mass, given complete activation and a consistent ankle angle) and fatigue was determined by using univariate linear regression analysis for all subjects combined. Likewise, to determine whether initial strength (mass) was related to the metabolic response to exercise, the relationship between preexercise MVC and end-exercise  $H_2PO_4^-$  was also determined by univariate linear regression analysis. To explore the relationship between the accumulation of metabolites typically associated with fatigue (11, 40, 48) and the development of fatigue (i.e., time course of the fall of MVC), linear regression analyses of the relationships between the change in MVC during exercise and  $P_i$ , pH, and  $H_2PO_4^-$  were performed for each subject group. For these three analyses, the MVCs obtained at the end of each 2-min stage were plotted against the metabolite value obtained during the final 30 s of each stage.

For all analyses, significance was established when  $P < 0.05$ . Descriptive data in Table 1 are presented as means  $\pm$  SD; all other data are presented as means  $\pm$  SE. There were no age-by-gender interactions for any of the measured variables, and these  $P$  values are not presented.

## RESULTS

**Subjects.** Descriptive data are provided in Table 1. To aid interpretation, data are grouped by age and gender throughout the paper. The men were taller and heavier than the women, with no age effect. Seven of the older women were on estrogen replacement therapy. There were no age or gender main effects ( $P > 0.05$ ) for physical activity level. Group sizes for the

Table 1. *Subject characteristics*

Measure	Young Women ( <i>n</i> = 10)	Older Women ( <i>n</i> = 10)	Young Men ( <i>n</i> = 10)	Older Men ( <i>n</i> = 11)
Age, yr	32.3 ± 4.8	75.0 ± 5.9	33.5 ± 6.5	74.4 ± 5.3
Height, cm	162.9 ± 12.0	158.4 ± 6.8	175.8 ± 7.9	174.2 ± 6.6
Weight, kg	62.0 ± 8.0	58.4 ± 9.9	79.0 ± 11.3	79.4 ± 11.8
Physical activity, AU	219.0 ± 56.5	172.5 ± 61.2	167.0 ± 23.1	152.2 ± 78.3

Values are means ± SD of descriptive data presented by age and gender groups; *n*, no. of subjects. Men were taller and heavier than women. AU, arbitrary units. There were no significant gender or age main effects or interactions for physical activity.

activity measurement were 10 young women, 8 older women, 9 young men, and 11 older men.

For each category of variables in the following sections, the data from measurements taken before the fatigue protocol are presented first, followed by comparisons of the exercise and recovery data.

**Force and fatigue.** Preexercise values for MVC, tetanic force, and twitch force are provided in Table 2. Overall, men were stronger than women, with no significant effect of age.

Figure 1 shows the changes in target force and MVC for each group during exercise. All groups performed the progressive exercise protocol similarly, up to ~60% MVC (Fig. 1A). Thereafter, it became increasingly difficult to achieve target force, particularly for the young. As shown in Fig. 1B, there was an effect of age on fatigue, with the older subjects showing less fatigue (postexercise MVC/preexercise MVC) at the end of exercise compared with the young subjects ( $P < 0.01$ ). There was no effect of gender on fatigue ( $P = 0.24$ ).

Fatigue was associated with preexercise strength ( $r = 0.49$ ,  $n = 41$ ,  $P < 0.01$ ), which suggests that ~25% of the variability in fatigue was related to muscle strength.

MVC and tetanic and twitch force data at end of exercise are presented in Table 3. As discussed above, there was a significant fall in MVC during exercise. At the end of exercise, tetanic force had also fallen in all groups ( $P < 0.01$ ), with no effect of age or gender on this change. At the end of exercise, twitch force had fallen relatively more in men compared with women ( $P = 0.04$ ), with no effect of age. During the recovery period, there were no differences across groups in the recovery of MVC, tetanic force, or twitch force.

**Contractile properties.** Before the fatigue protocol, older subjects showed the expected age-related slowing of contractile properties in response to twitch and tetanic stimuli (Table 2). Twitch contraction time was longer, and the maximum rates of twitch force development and relaxation were lower, in older compared

Table 2. *Preexercise muscle characteristics*

Measure	Young Women	Older Women	Young Men	Older Men
<b>Force</b>				
MVC, N†	218.4 ± 17.2	175.4 ± 8.5	309.4 ± 18.2	247.1 ± 17.0
Tetanic force, N†	153.4 ± 11.4	129.0 ± 8.1	200.1 ± 13.7	198.4 ± 9.3
Twitch force, N†	13.4 ± 2.5	17.5 ± 3.6	20.5 ± 5.2	22.5 ± 2.0
Potentiated twitch, N†	17.4 ± 3.2	21.6 ± 3.3	29.6 ± 6.3	32.7 ± 2.2
<b>Activation</b>				
CAR	1.00 ± 0.01	0.99 ± 0.01	1.00 ± 0.00	0.98 ± 0.01
CMAP amplitude, mV*	11.4 ± 0.9	8.7 ± 0.8	13.4 ± 1.8	8.4 ± 0.8
CMAP duration, ms	18.4 ± 2.0	16.0 ± 1.2	14.3 ± 0.6	16.6 ± 1.0
<b>Contractile properties</b>				
Twitch time, ms*	115.7 ± 5.0	145.5 ± 4.0	114.2 ± 3.4	134.1 ± 5.3
Twitch max rate force development, %peak force/ms*	1.85 ± 0.07	1.44 ± 0.05	1.75 ± 0.07	1.62 ± 0.07
Twitch max rate force relaxation, %peak force/ms*	-0.82 ± 0.04	-0.68 ± 0.03	-0.93 ± 0.09	-0.68 ± 0.04
Tetanic max rate force development, %peak force/ms*	0.61 ± 0.03	0.54 ± 0.03	0.70 ± 0.05	0.54 ± 0.03
Tetanic max rate force relaxation, %peak force/ms*	-1.06 ± 0.06	-0.77 ± 0.06	-0.91 ± 0.03	-0.79 ± 0.06
Tetanic half-time force relaxation, ms	123.3 ± 6.1	157.7 ± 9.7	137.6 ± 11.8	150.9 ± 16.6
<b>Metabolism</b>				
P <sub>i</sub> /PCr*	0.07 ± 0.01	0.06 ± 0.01	0.10 ± 0.01	0.06 ± 0.01
pH	7.06 ± 0.03	7.07 ± 0.02	7.10 ± 0.03	7.09 ± 0.03

Values are means ± SE for dorsiflexor muscle force, central activation ratio (CAR), peripheral activation (CMAP), and contractile properties given for each group. Men had higher forces [maximal (max) voluntary contraction (MVC), tetanic force, twitch force] compared with women, with no age effect. Central activation was similar in all groups. CMAP amplitude was higher and contractile speeds were faster in young compared with older groups, with no effect of gender. Twitch and CMAP data are from the unpotentiated measures. P<sub>i</sub>-to-phosphocreatine ratio (P<sub>i</sub>/PCr) was higher in young compared with older subjects, with no effect of gender. Intramuscular pH was similar in all groups. \*Significant effect of age,  $P < 0.05$ . †Significant effect of gender,  $P < 0.05$ .

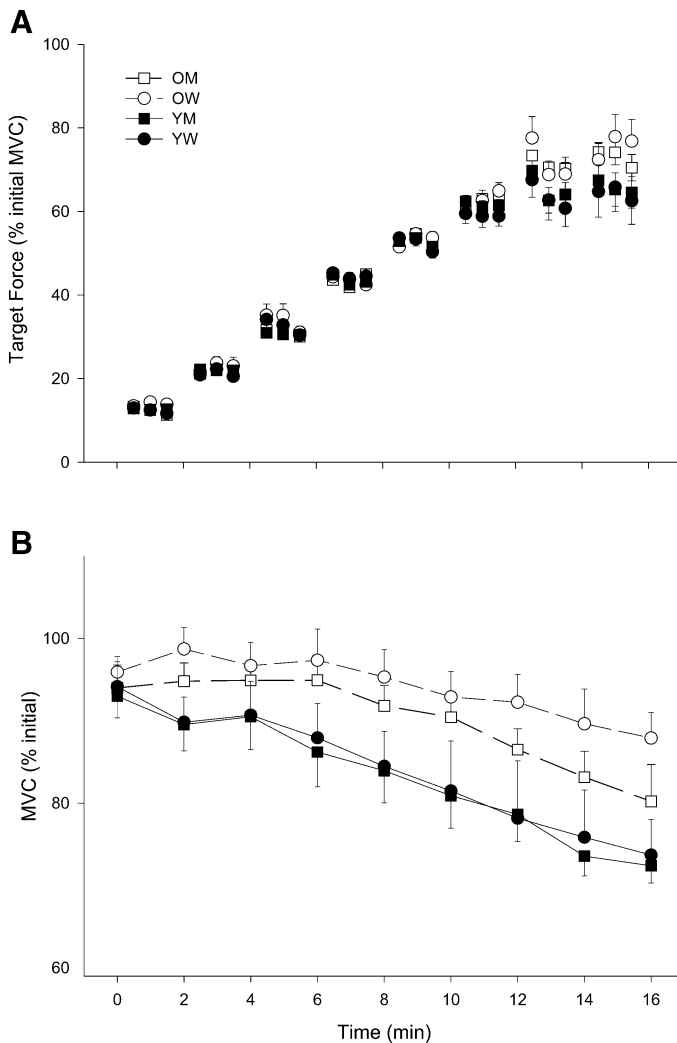


Fig. 1. Target force (A) and maximal voluntary contraction (MVC; B) during 16 min of intermittent isometric exercise in young and older men and women (means  $\pm$  SE). OM, older men; OW, older women; YM, young men; YW, young women. Note that all groups performed similarly through the first 10–12 min of exercise (A), beyond which time fatigue began to interfere with their ability to achieve target force. MVCs obtained at the end of every 2-min stage (B) indicated that young subjects fatigued more than older subjects ( $P < 0.01$ ), with no effect of gender.

with young subjects ( $P < 0.01$ , all). Likewise, the maximum rates of tetanic force development and relaxation were lower ( $P < 0.01$ , both), and the half-time of force relaxation tended to be longer ( $P = 0.07$ ) in older compared with young subjects. There was no effect of gender on these variables.

Before the exercise protocol, the potentiation of twitch force after baseline MVCs was greater in men ( $161 \pm 12\%$ ) than in women ( $133 \pm 7\%$ ,  $P = 0.02$ ), with no effect of age ( $P = 0.34$ ). The ratio of potentiated twitch to tetanic force was higher in older ( $0.17 \pm 0.01$ ) compared with young subjects ( $0.13 \pm 0.02$ ,  $P < 0.01$ ). There was no effect of gender on this variable.

Exercise had no effect on twitch contraction time or the maximum rates of twitch force development and relaxation in any group. However, there was an in-

crease in the maximum rate of tetanic force production after exercise ( $P < 0.01$ ), with a significant gender effect indicating that women had a greater increase in the speed of tetanic force production compared with men ( $P < 0.01$ ; Fig. 2). In contrast, there was a significant slowing of both the maximum rate and the half-time of tetanic force relaxation in response to exercise ( $P < 0.01$ , all; Fig. 2). The recovery of all twitch and tetanic contractile variables was similar across groups.

There was a significant gender effect ( $P < 0.01$ ) on the change in the twitch-to-tetanic force ratio from pre- to postexercise, such that this ratio increased by  $0.05 \pm 0.06$  in women, whereas in men it decreased by  $0.01 \pm 0.06$ . There was no effect of age on the change in the twitch-to-tetanic force ratio.

**Muscle activation.** As shown by the CAR data in Table 2, there was no difference between groups in the ability to maximally activate the dorsiflexor muscles before the exercise protocol. Likewise, CAR was unchanged in all groups at the end of the exercise protocol (Table 3).

The amplitude of the unpotentiated CMAP was significantly lower in older compared with young subjects ( $P < 0.01$ ; Table 2). Before the start of the exercise protocol, CMAP amplitude increased in all groups after potentiation by the three baseline MVCs ( $P < 0.01$ ). The duration of the unpotentiated CMAP was similar in all groups (Table 2), and there was a similar increase of CMAP duration in all groups after the MVCs ( $P < 0.01$ ). All postexercise CMAP values were compared with the potentiated CMAP.

At the end of exercise, there was no further change in CMAP amplitude from the potentiated level in any group. However, there was a significant shortening of CMAP duration ( $P < 0.01$ ) immediately after exercise, which was similar in all groups. There were no gender main effects for CMAP amplitude or duration, either before or after exercise. During the recovery period, CMAP amplitude increased in young relative to older adults ( $P = 0.04$ ).

**Muscle metabolism.** At rest,  $P_i/PCr$  was higher in young compared with older ( $P < 0.01$ ) subjects, with no effect of gender. Resting pH was similar in all groups (Table 2). There was no age effect on the change in  $P_i/PCr$  during exercise ( $P = 0.76$ ; Fig. 3), but there was a significant gender effect in that women had a smaller increase in  $P_i/PCr$  compared with men ( $P < 0.01$ ; Fig. 3). As shown in Fig. 3, the rate of change in  $P_i/PCr$  increased in the young and older men after  $\sim 8$  min of exercise, indicating the end of the steady-state, oxidative phase of this exercise protocol (8, 26). In contrast, women showed little change in the rate of increase of  $P_i/PCr$  during exercise, suggesting that oxidative metabolism was able to keep pace with energy needs in the women throughout exercise.

Elevations in the concentration of  $P_i$ ,  $H^+$ , and  $H_2PO_4^-$  have each been implicated as sources of fatigue during exercise (11, 40, 48). In the present study, there were both age and gender effects for the changes in these metabolites, as shown in Fig. 4. During exercise,  $P_i$  increased more in young compared with older sub-

Table 3. *End-exercise values for selected variables*

Measure	Young Women	Older Women	Young Men	Older Men
MVC (post/pre)*†	0.74 ± 0.04	0.88 ± 0.03	0.72 ± 0.02	0.80 ± 0.04
Tetanic force (post/pre)*	0.73 ± 0.06	0.79 ± 0.03 (8)	0.71 ± 0.10 (9)	0.77 ± 0.05
Twitch force (post/pre)‡	1.06 ± 0.17 (9)	1.22 ± 0.12 (9)	0.86 ± 0.18 (8)	0.67 ± 0.07 (10)
CAR	0.98 ± 0.01 (9)	0.99 ± 0.01 (9)	0.97 ± 0.02 (9)	0.94 ± 0.02
CMAP amplitude, mV	12.3 ± 1.4 (8)	10.9 ± 1.8 (9)	14.5 ± 2.9 (7)	9.4 ± 0.9 (10)
CMAP duration, ms*	16.4 ± 1.9 (10)	15.1 ± 1.4 (9)	13.2 ± 0.9 (7)	15.8 ± 1.0
Twitch time, ms	104.1 ± 4.8 (9)	146.0 ± 12.1 (9)	110.0 ± 5.3 (8)	124.2 ± 6.2 (10)
Twitch max rate force development, %peak force/ms	1.95 ± 0.10 (9)	1.58 ± 0.10 (9)	1.93 ± 0.08 (8)	1.72 ± 0.10 (10)
Twitch max rate force relaxation, %peak force/ms	-0.86 ± 0.07 (9)	-0.70 ± 0.09 (9)	-1.04 ± 0.10 (8)	-0.73 ± 0.04 (10)
Tetanic max rate force development, %peak force/ms*‡	0.79 ± 0.03 (9)	0.73 ± 0.03 (8)	0.76 ± 0.05 (9)	0.62 ± 0.04
Tetanic max rate force relaxation, %peak force/ms*	-0.87 ± 0.08 (9)	-0.68 ± 0.07 (8)	-0.81 ± 0.07 (9)	-0.64 ± 0.05
Tetanic half-time force relaxation, ms*	148.6 ± 14.8	204.7 ± 30.5 (8)	183.3 ± 29.9 (9)	174.6 ± 13.2

Values are means ± SE. Force data are presented as a percentage of the preexercise (pre) values vs. postexercise values (post). For measures in which there was missing data, the numbers in parentheses indicate subject numbers. \*Significant change from preexercise values (Table 2),  $P < 0.05$ . †Significant effect of age,  $P < 0.05$ . ‡Significant effect of gender,  $P < 0.05$ . See text for details.

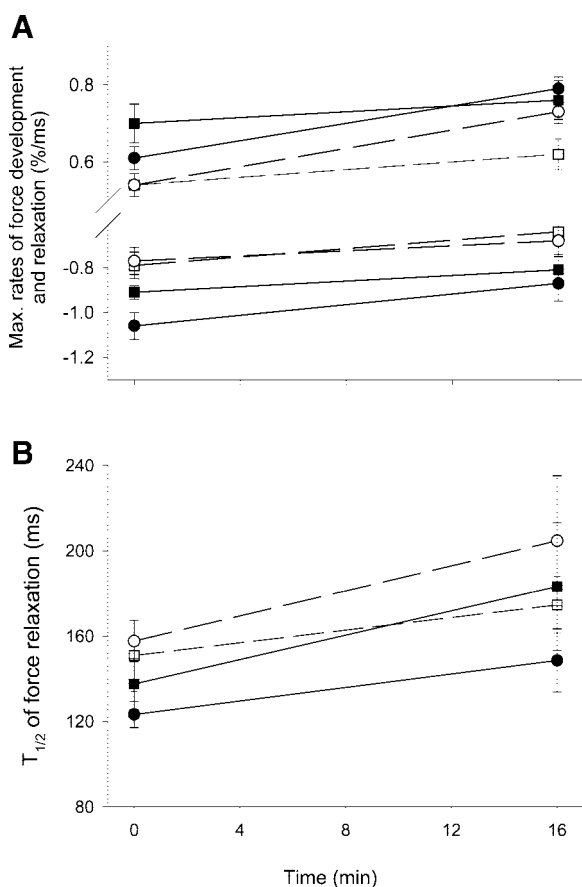


Fig. 2. Contractile properties (means ± SE) of the electrically evoked tetanus (50 Hz, 500 ms) before and at the end of 16 min of exercise. Before exercise, the maximum (max) rates of tetanic force development and relaxation (A) were significantly slower in older compared with young subjects ( $P < 0.01$ ), whereas the half-time ( $t_{1/2}$ ) of force relaxation (B) tended to be longer in the older group ( $P = 0.07$ ). At the end of exercise, the maximum rate of tetanic force development was increased (A, top), and women showed a greater increase than men ( $P < 0.01$ ). Both the maximum rate of force relaxation (A, bottom) and the  $t_{1/2}$  of force relaxation (B) slowed as a result of exercise, with no effect of age or gender. □, Older men; ○, older women; ■, young men; ●, young women.

jects and in men compared with women ( $P < 0.01$ , both). Intracellular pH decreased more in older compared with young subjects and in men compared with women ( $P < 0.01$ , both). Finally,  $H_2PO_4^-$  increased more in young compared with older subjects and in men compared with women ( $P < 0.01$ , both). The concentration of  $H_2PO_4^-$  during the final minute of exercise was linearly related to preexercise MVC or strength ( $r = 0.53$ ,  $P < 0.001$ ).

Although only age affected fatigue, there were both age and gender effects on the metabolic response to exercise. To investigate whether there might be a different role for metabolic inhibition of contraction in the fatigue across genders, we examined the relationship between  $H_2PO_4^-$ , a putative fatigue agent (48), and the development of fatigue during exercise for each group, as shown in Fig. 5. Although the range of this relationship was smaller in the women due to lower  $H_2PO_4^-$  production, the slope of their relationship between fatigue and  $H_2PO_4^-$  appeared steeper than that of the men. The relationships between fatigue and both  $P_i$  and pH were qualitatively similar to those for  $H_2PO_4^-$  (data not shown).

## DISCUSSION

The primary results of this study were that, during incremental isometric exercise, 1) older subjects exhibited less fatigue compared with young subjects, 2) there was no effect of gender on fatigue, and 3) the metabolic response to exercise varied with age and gender in a manner that suggests a greater reliance on nonoxidative sources of ATP in young compared with older subjects and in men compared with women. Of note is the fact that these results were obtained in groups with similar habitual physical activity levels, which minimizes the effect of activity on our measures.

**Contractile function.** There were three main findings related to contractile function. First, contraction and relaxation rates were slowed in the unfatigued muscles of the older compared with young subjects, as expected.

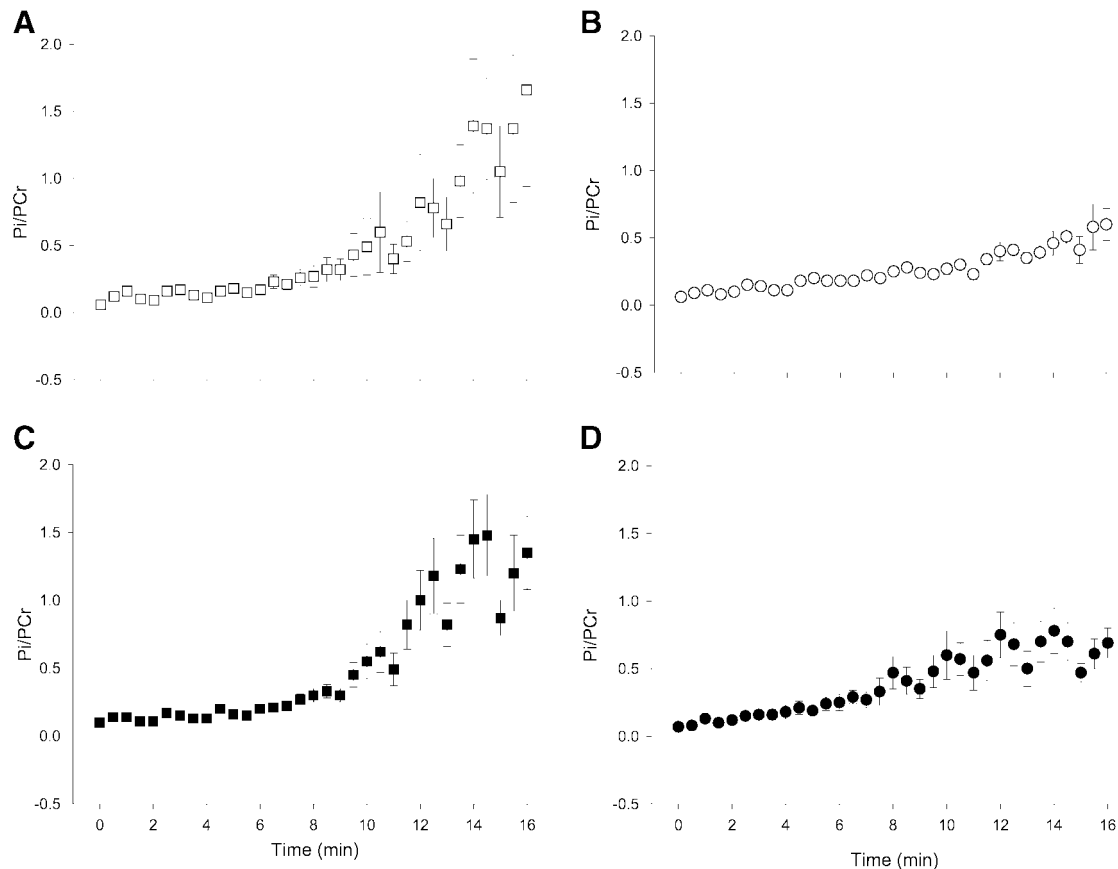


Fig. 3. Intracellular  $P_i$ -to-phosphocreatine ratio ( $P_i/PCr$ ) during exercise (means  $\pm$  SE). There was a similar, gradual increase in  $P_i/PCr$  during the first 6–8 min of exercise, which indicates that all groups had a similar capacity for oxidative metabolism during this steady-state portion of the protocol. Beyond  $\sim$ 8 min, there was a loss of the steady state, particularly in the young and older men. There was no effect of age on the change in  $P_i/PCr$  during exercise. At the end of exercise, there was a significant gender effect in that men had a higher  $P_i/PCr$  compared with women ( $P < 0.01$ ). A: older men. B: older women. C: young men. D: young women.

Second, there were no age-based differences in the degree of twitch potentiation before exercise or in the change in twitch-to-tetanus ratio, the increase in the rate of tetanic force development, and the slowing of force relaxation of the tetanus after exercise. Third, there was earlier potentiation of twitch force in men compared with women, with no effect of age. Overall, alterations in contractile function did not explain the age-related difference in fatigue that we observed.

Our finding of an age-related slowing of electrically evoked twitch and tetanic contractile properties in the unfatigued muscle is similar to the results from previous studies of the dorsiflexor (10, 39) and other (15) muscles. This slowing is consistent with the age-related shift toward a higher percentage of type I fiber content reported by others (22, 34).

Exercise caused a similar slowing of tetanic force relaxation in all groups, which is often a consequence of fatigue (5). Slowed force relaxation is likely due to the slowing of calcium resequestration by the sarcoplasmic reticulum in fatigued muscle (47). The fact that the older subjects showed no excessive slowing in either force development or relaxation during fatigue suggests that neither excitation-contraction coupling nor calcium ki-

netics were altered in this group compared with the young. The lack of an age-related effect on excitation-contraction coupling is further supported by the lack of an effect of age on the change in the twitch-to-tetanus ratio after exercise and by the similar recoveries of all force and contractile variables in all groups (17).

Before the exercise protocol, the potentiation of twitch force after three MVCs was greater in men compared with women, with no effect of age. This result suggests that there was a greater increase in actin-myosin  $Ca^{2+}$  sensitivity in response to three 3- to 4-s MVCs in the men and no impact of age on this system (41). At the end of exercise, tetanic force fell similarly in all groups, whereas twitch force fell more in men compared with women (Table 3). As a result, the twitch-to-tetanic force ratio increased in women but decreased in men during fatigue. Furthermore, although the maximum rate of tetanic force development increased in all groups in response to the exercise protocol, this increase was significantly higher in women compared with men (Table 3). Taken together, these observations suggest that the majority of force potentiation occurred very rapidly (i.e., after baseline MVCs) in men, whereas potentiation reached its max-

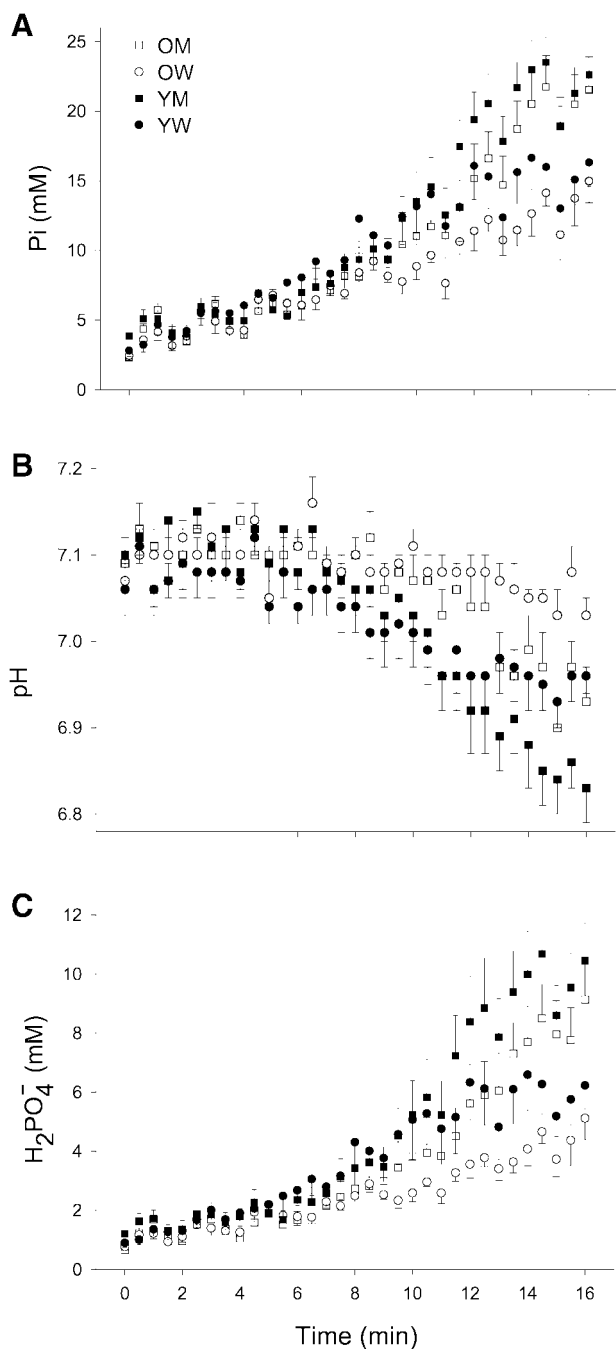


Fig. 4. Intracellular  $P_i$  (A), pH (B), and  $H_2PO_4^-$  (C) during exercise (means  $\pm$  SE). Beyond  $\sim 8$  min of exercise, the accumulation of  $P_i$ , pH, and  $H_2PO_4^-$  begins to occur at a more rapid rate, as oxidative metabolism is no longer able to keep pace with increasing energy demands, and anaerobic processes begin to contribute relatively more to the energy supply. Intracellular pH decreased, and  $P_i$  and  $H_2PO_4^-$  increased more in young compared with older subjects and in men compared with women ( $P < 0.01$ , all), suggesting a greater reliance on glycolytic metabolism in young subjects and men, respectively.

imum later, during the exercise protocol, in women. These results indicate a gender-based difference in the magnitude and timing of force potentiation that may reflect differences between men and women in actin-myosin  $Ca^{2+}$  sensitivity (41).

**Activation.** Neural activation may be separated broadly into central and peripheral components. In the present study, these are delineated by the location of the stimulating electrode, with all elements proximal to the electrode representing central activation and all elements distal to the electrode comprising peripheral activation. The main findings related to activation in this study were that neither central nor peripheral activation failure contributed to fatigue in any group in response to this incremental isometric protocol.

In contrast to some reports (2, 44), we observed no age-related impairment of central activation, either before (CAR, Table 2) or at the end (Table 3) of fatiguing exercise. Likewise, there was no difference between men and women in the ability to fully activate the dorsiflexor muscles. These results are consistent with our previous work in this muscle group (27), as well as with the work of others (20). It is likely that the moderate degree of fatigue observed with this protocol precluded the development of central fatigue, as central activation failure is often associated with more severely fatiguing exercise (e.g., Ref. 24).

Although there was no failure of central activation, per se, it is possible that lower motor unit discharge rates may have played a role in the greater fatigue resistance of the older subjects. It has been reported that discharge rates are reduced in older compared with young adults during both submaximal and MVCs (10, 23). During a progressive exercise protocol such as that used here, lower discharge rates in older adults could serve to 1) acutely limit the extent to which  $P_i/PCr$  increases and pH decreases during exercise as the ability to drive the muscle at higher frequencies is limited and 2) shift the muscle toward a more oxidative profile (i.e., the prolonged exposure of all fibers to lower discharge rates would result in adaptation toward a slower, more oxidative muscle). Precedence for the first possibility exists from a study of muscle fatigue in people with multiple sclerosis (MS). Fatigue in the MS and control groups was similar during the same incremental isometric exercise protocol reported here (29). However, the metabolic response to exercise (i.e.,  $P_i/PCr$ , pH) was markedly smaller in MS (29). The metabolic difference could not be explained by differences in motor unit recruitment in the MS group. Instead, this difference was likely because of an inability of MS patients to generate high discharge rates during exercise, as shown previously by Rice et al. (42).

The second possibility, related to a morphological adaptation to chronically reduced activation rates, is consistent with the age-related increase in type I fiber area reported in the tibialis anterior muscle, from 76% in young adults to 84% in older adults (22). The observation of slower contractile properties in the unfatigued muscle of the older adults in this study is compatible with such a fiber-type shift. This shift might arise both from the loss of type II fibers due to the denervation-reinnervation process that occurs with aging (6) as well as from the lower discharge rates experienced by the muscle of older adults. Regardless of the mechanism, the shift toward a slower muscle is consis-

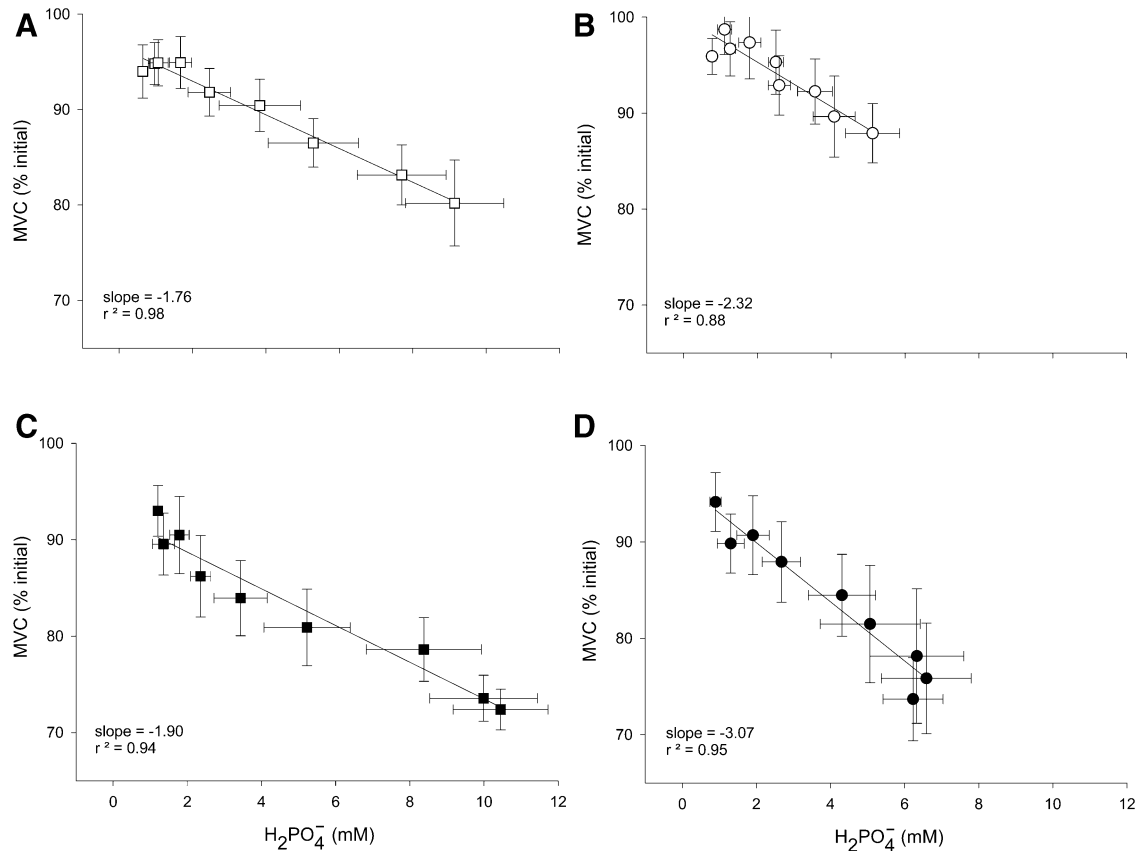


Fig. 5. Relationships between fatigue and  $\text{H}_2\text{PO}_4^-$  during exercise (means  $\pm$  SE) in older men (A), older women (B), young men (C), and young women (D). The fall of MVC during exercise is related to the increase in  $\text{H}_2\text{PO}_4^-$  in each group, regardless of the magnitude of fatigue or degree of metabolite accumulation. Although men had a nearly twofold greater increase in  $\text{H}_2\text{PO}_4^-$  during exercise, they developed no greater fatigue than women. As a result, the slope of the relationship between fatigue and  $\text{H}_2\text{PO}_4^-$  appears to be steeper for women. See text for details.

tent with the greater fatigue resistance observed in the older group in this study.

Although CMAP amplitude was smaller in older compared with young subjects before voluntary muscle activations (Table 2), the degree of potentiation of the CMAP in response to baseline MVC contractions was similar in all groups. This result suggests that, before fatigue, the enhancement of sarcolemmal  $\text{Na}^+\text{-K}^+$  pump activity in response to contraction (19) is unaffected by age or gender. At the end of exercise, there was no change from baseline in CMAP amplitude in any group (Table 3), which suggests that there was no decrease in peripheral excitability during fatigue. The duration of the CMAP was shorter in all groups after exercise, suggesting that conduction velocity across the neuromuscular junction or along the muscle membrane had increased during this submaximal protocol. An increase in conduction velocity may have occurred due to a "warm-up" effect in the muscle. Overall, peripheral activation failure did not appear to play a role in the development of fatigue in any group during this protocol. Furthermore, there was no evidence to suggest that differences in peripheral excitability across age had an impact on the age-related difference observed in fatigability in this study.

**Metabolism.** In contrast to the activation data, the metabolic data showed significant age- and gender-related differences in response to exercise. The exercise protocol used in this study begins with a low-intensity, metabolically steady-state portion and ends with relatively high-intensity contractions that produce greater changes in energy metabolites and pH (8, 26). During steady-state exercise,  $\text{P}_i/\text{PCr}$  reflects the ability of the muscle to respond oxidatively to the need for ATP (8, 26). In the present study, steady state was maintained similarly in all groups through the first half of the exercise protocol, which suggests a similar potential for oxidative metabolism in all groups. Beyond  $\sim 8$  min, which corresponded to an intensity of  $\geq 50\%$  MVC,  $\text{P}_i/\text{PCr}$  increased at a more rapid rate in men than in women (Fig. 3). This observation suggests that women continued to keep pace with the energy demand via oxidative phosphorylation throughout the exercise protocol, whereas men were less able to do so as the exercise progressed. There was no effect of age on the change in  $\text{P}_i/\text{PCr}$  during exercise, suggesting that the gender-based difference in metabolic pathway "preference" persists with aging. Interestingly, this difference is consistent with reports indicating a relatively

greater reliance on carbohydrate as a fuel in men compared with women (45).

In contrast to the  $P_i/PCr$  data, the changes in pH,  $P_i$ , and  $H_2PO_4^-$  showed both age and gender effects (Fig. 4). Each of these metabolites has, at various times, been implicated in the fatigue process (11, 24, 40, 48). At a pH of 6.75,  $P_i$  exists in equal proportions of its mono- and diprotonated species. As pH drops below 6.75, the diprotonated species predominates. Thus the concentration of diprotonated  $P_i$  ( $H_2PO_4^-$ ) reflects both the increase in  $P_i$  and the decrease in pH.

For all groups, there was a very strong relationship between the time course of fatigue and the accumulation of  $H_2PO_4^-$  (Fig. 5). Interestingly, however, the slope of this relationship appeared to be steeper in the women, suggesting a greater "sensitivity" of force production to the accumulation in  $H_2PO_4^-$  in women compared with men. This observation may, in part, explain the lack of a gender effect on fatigue despite the greater metabolic changes in men compared with women. The mechanism of this greater sensitivity in women is not clear but may be related to a generally lower reliance on glycolytic metabolism in female muscle. That is, if female muscle is typically less likely to encounter high concentrations of  $H^+$ ,  $P_i$ , and  $H_2PO_4^-$ , it may be more sensitive to these metabolites when they do accumulate.

The smaller change in  $H^+$  concentration in the older group suggests that older individuals may have a smaller capacity for glycolytic metabolism compared with young subjects. This possibility finds support in the literature from Larsson et al. (32), who reported lower lactate dehydrogenase activity in the vastus lateralis muscle of older compared with young men.

**Muscle strength.** As noted, it has been suggested that differences in muscle mass might account for some of the differences in fatigue observed across gender or age via the impact of intramuscular pressure on muscle perfusion during the contractions. Higher absolute forces will produce higher intramuscular pressure and, therefore, relatively less perfusion. This concept is supported by the recent report from Hunter and Enoka (21) in which gender differences in elbow flexor endurance were nullified after adjustment for strength. Similarly, differences in strength and absolute target tension were likely important factors in an earlier study of fatigue in which gender-based differences in the endurance response of the elbow flexors to immobilization were reported (43). In the present study, preexercise MVC was associated with ~24% of the fatigue that developed during exercise. This result provides some support for the possibility that the intramuscular pressure developed during each contraction may be relatively higher in the stronger subjects, thus leading to greater occlusion of blood flow to the working muscle during each contraction. A difference in blood flow would be particularly evident at the higher contraction intensities in our protocol; interestingly, it is at these intensities that the metabolic response to exercise diverges in young compared with older subjects and in men compared with women (Figs. 3 and 4). The signif-

icant relationship between strength (preexercise MVC) and end-exercise  $H_2PO_4^-$  concentration is also consistent with the possibility that oxygen delivery may have been relatively better in the weaker subjects, thereby allowing them to rely on oxidative pathways for longer periods during the exercise protocol.

It should be noted that the measure of fatigue selected by various investigators may be complicating our understanding of the effects of age and gender on muscle function. As mentioned previously, Hunter and Enoka (21) recently observed a difference in endurance time but no difference in fatigue (i.e., fall of MVC) in the elbow flexors after a contraction sustained at 20% MVC. A similar example is provided for aging by Bilodeau et al. (3), who reported similar fatigue in young and older subjects after a sustained 35% MVC elbow flexion contraction but a longer endurance time in the older subjects. The observations of similar fatigue but different endurance times across these study groups suggest that endurance and fatigue are, to some degree, physiologically distinct tasks. Thus, in addition to the need for accounting for differences in strength across study groups, there is a need for care when interpreting and comparing protocols with different criteria for fatigue.

In conclusion, the results of this study indicate that the dorsiflexor muscles of older adults have a greater resistance to fatigue during intermittent, submaximal isometric contractions compared with young adults of similar physical activity habits. There was no effect of gender on fatiguability, nor were there significant age- or gender-based differences in central or peripheral activation during exercise. Whereas the older group showed the expected slowing of muscle contractile properties before exercise, there was no evidence of an age-based difference in contractile function as a result of the fatiguing exercise. In contrast, the metabolic data suggest that both age and gender affect the response to intermittent isometric exercise. It appears that older compared with young subjects, and women compared with men, rely less on anaerobic pathways for the supply of ATP during muscular contractions.

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## REFERENCES

1. **Bellemare F and Garzaniti N.** Failure of neuromuscular propagation during human maximal voluntary contraction. *J Appl Physiol* 64: 1084–1093, 1988.
2. **Bilodeau M, Erb MD, Nichols JM, Joiner KL, and Weeks JB.** Fatigue of elbow flexor muscles in younger and older adults. *Muscle Nerve* 24: 98–106, 2001.
3. **Bilodeau M, Henderson TK, Nolte BE, Pursley PJ, and Sandfort GL.** Effect of aging on fatigue characteristics of elbow flexor muscles during sustained submaximal contraction. *J Appl Physiol* 91: 2654–2664, 2001.

4. **Brown TR, Stoyanova R, Greenberg T, Srinivasan T, and Murphy-Boesch J.** NOE enhancements and T1 relaxation times of phosphorylated metabolites in human calf muscle at 15 Tesla. *Magn Reson Med* 33: 417–421, 1995.
5. **Cady EB, Elshove H, Jones DA, and Moll A.** The metabolic causes of slow relaxation in fatigued human skeletal muscle. *J Physiol* 418: 327–337, 1989.
6. **Campbell MJ, McComas AJ, and Petito F.** Physiological changes in aging muscles. *J Neurol Neurosurg Psychiatry* 36: 174–182, 1973.
7. **Cavanagh PR, Mulfinger LM, and Owens DA.** How do the elderly negotiate stairs? *Muscle Nerve Suppl* 5: S52–S55, 1996.
8. **Chance B, Leigh JSJ, Clark BJ, Maris J, Kent J, Nioka S, and Smith D.** Control of oxidative metabolism and oxygen delivery in human skeletal muscle: a steady-state analysis of the work/energy cost transfer function. *PNAS* 82: 8384–8388, 1985.
9. **Chilibeck PD, Paterson DH, McCreary CR, Marsh GD, Cunningham DA, and Thompson RT.** The effects of age on kinetics of oxygen uptake and phosphocreatine in humans during exercise. *Exp Physiol* 83: 107–117, 1998.
10. **Connelly DM, Rice CL, Roos MR, and Vandervoort AA.** Motor unit firing rates and contractile properties in tibialis anterior of young and old men. *J Appl Physiol* 87: 843–852, 1999.
11. **Cooke R, Franks K, Luciani GB, and Pate E.** The inhibition of rabbit skeletal muscle contraction by hydrogen ions and phosphate. *J Physiol* 395: 77–97, 1988.
12. **Davies CTM and White MJ.** Contractile properties of elderly human triceps surae. *Gerontology* 29: 19–25, 1983.
13. **Delbono O, O'Rourke KS, and Ettinger WH.** Excitation-calcium release uncoupling in aged single human skeletal muscle fibers. *J Membr Biol* 148: 211–222, 1995.
14. **Ditor DS and Hicks AL.** The effect of age and gender on the relative fatigability of the human adductor pollicis muscle. *Can J Physiol Pharmacol* 78: 781–790, 2000.
15. **Doherty TJ and Brown WF.** Age-related changes in the twitch contractile properties of human thenar motor units. *J Appl Physiol* 82: 93–101, 1997.
16. **Edwards RH.** Human muscle function and fatigue. *Ciba Found Symp* 82: 1–18, 1981.
17. **Edwards RH, Hill DK, Jones DA, and Merton PA.** Fatigue of long duration in human skeletal muscle after exercise. *J Physiol* 272: 769–778, 1977.
18. **Fulco CS, Rock PB, Muza SR, Lammi E, Cymerman A, Butterfield G, Moore LG, Braun B, and Lewis SF.** Slower fatigue and faster recovery of the adductor pollicis muscle in women matched for strength with men. *Acta Physiol Scand* 167: 233–239, 1999.
19. **Hicks A and McComas AJ.** Increased sodium pump activity following repetitive stimulation of rat soleus muscles. *J Physiol* 414: 337–349, 1989.
20. **Hicks AL and McCartney N.** Gender differences in isometric contractile properties and fatigability in elderly human muscle. *Can J Appl Physiol* 21: 441–454, 1996.
21. **Hunter SK and Enoka RM.** Sex differences in the fatigability of arm muscles depends on absolute force during isometric contractions. *J Appl Physiol* 91: 2686–2694, 2001.
22. **Jakobsson F, Borg K, Edstrom L, and Grimby L.** Use of motor units in relation to muscle fiber type and size in man. *Muscle Nerve* 11: 1211–1218, 1988.
23. **Kamen G, Sison SV, Duke Du CC, and Patten C.** Motor unit discharge behavior in older adults during maximal-effort contractions. *J Appl Physiol* 79: 1908–1913, 1995.
24. **Kent-Braun JA.** Central and peripheral contributions to muscle fatigue in humans during sustained maximal effort. *Eur J Appl Physiol* 80: 57–63, 1999.
25. **Kent-Braun JA, and Le Blanc R.** Quantitation of central activation failure during maximal voluntary contractions in humans. *Muscle Nerve* 19: 861–869, 1996.
26. **Kent-Braun JA, Miller RG, and Weiner MW.** Phases of metabolism during progressive exercise to fatigue in human skeletal muscle. *J Appl Physiol* 75: 573–580, 1993.
27. **Kent-Braun JA and Ng AV.** Specific strength and voluntary muscle activation in young and elderly women and men. *J Appl Physiol* 87: 22–29, 1999.
28. **Kent-Braun JA and Ng AV.** Skeletal muscle oxidative capacity in young and older women and men. *J Appl Physiol* 89: 1072–1078, 2000.
29. **Kent-Braun JA, Sharma KR, Weiner MW, and Miller RG.** Effects of exercise on muscle activation and metabolism in multiple sclerosis. *Muscle Nerve* 17: 1162–1169, 1994.
30. **Larsson L, Grimby G, and Karlsson J.** Muscle strength and speed of movement in relation to age and muscle morphology. *J Appl Physiol* 46: 451–456, 1979.
31. **Larsson L and Karlsson J.** Isometric and dynamic endurance as a function of age and skeletal muscle characteristics. *Acta Physiol Scand* 104: 129–136, 1978.
32. **Larsson L, Sjodin B, and Karlsson J.** Histochemical and biochemical changes in human skeletal muscle with age in sedentary males, age 22–65 years. *Acta Physiol Scand* 103: 31–39, 1978.
33. **Lennermarken C, Bergman T, Larsson J, and Larsson LE.** Skeletal muscle function in man: force, relaxation rate, endurance and contraction time-dependence on sex and age. *Clin Physiol* 5: 243–255, 1985.
34. **Lexell J.** Human aging, muscle mass, and fiber type composition. *J Gerontol A Biol Sci Med Sci* 50: 11–16, 1995.
35. **Lindstrom B, Lexell J, Gerdle B, and Downham D.** Skeletal muscle fatigue and endurance in young and old men and women. *J Gerontol A Biol Sci Med Sci* 52: B59–B66, 1997.
36. **Maughan RJ, Harmon M, Leiper JB, Sale D, and Delman A.** Endurance capacity of untrained males and females in isometric and dynamic muscular contractions. *Eur J Appl Physiol* 55: 395–400, 1986.
37. **McCully KK, Fielding RA, Evans WJ, Leigh JSJ, and Posner JD.** Relationships between in vivo and in vitro measurements of metabolism in young and old human calf muscles. *J Appl Physiol* 75: 813–819, 1993.
38. **Miller RG.** Dynamic properties of partially denervated muscle. *Ann Neurol* 6: 51–55, 1979.
39. **Ng AV, and Kent-Braun J.** A Slowed muscle contractile properties are not associated with a decreased EMG/force relationship in older humans. *J Gerontol A Biol Sci Med Sci* 54: B452–B458, 1999.
40. **Nosek TM, Fender KY, and Godt RE.** It is diprotonated inorganic phosphate that depresses force in skinned skeletal muscle fibers. *Science* 236: 191–193, 1987.
41. **Palmer BM and Moore RL.** Myosin light chain phosphorylation and tension potentiation in mouse skeletal muscle. *Am J Physiol Cell Physiol* 257: C1012–C1019, 1989.
42. **Rice CL, Vollmer TL, and Bigland-Ritchie B.** Neuromuscular responses of patients with multiple sclerosis. *Muscle Nerve* 15: 1123–1132, 1992.
43. **Semmler JG, Kutzscher DV, and Enoka RM.** Gender differences in the fatigability of human skeletal muscle. *J Neurophysiol* 82: 3590–3593, 1999.
44. **Stackhouse SK, Stevens JE, Lee SC, Pearce KM, Snyder-Mackler L, and Binder-Macleod SA.** Maximum voluntary activation in nonfatigued and fatigued muscle of young and elderly individuals. *Phys Ther* 81: 1102–1109, 2001.
45. **Tarnopolsky LJ, MacDougall JD, Atkinson SA, Tarnopolsky MA, and Sutton JR.** Gender differences in substrate for endurance exercise. *J Appl Physiol* 68: 302–308, 1990.
46. **Taylor DJ, Styles P, Matthews PM, Arnold DA, Gadian DG, Bore P, and Radda GK.** Energetics of human muscle: exercise-induced ATP depletion. *Magn Reson Med* 3: 44–54, 1986.
47. **Williams JH and Klug GA.** Calcium exchange hypothesis of skeletal muscle fatigue: a brief review. *Muscle Nerve* 18: 421–434, 1995.
48. **Wilson JR, McCully KK, Mancini DM, Boden B, and Chance B.** Relationship of muscular fatigue to pH and diprotonated P<sub>i</sub> in humans: a <sup>31</sup>P-NMR study. *J Appl Physiol* 64: 2333–2339, 1988.
49. **Wolfson L, Judge J, Whipple R, and King M.** Strength is a major factor in balance, gait, and the occurrence of falls. *J Gerontol A Biol Sci Med Sci* 50: 64–67, 1995.