Age-related resistance to skeletal muscle fatigue is preserved during ischemia

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Chung LH, Callahan DM, Kent-Braun JA. Age-related resistance to skeletal muscle fatigue is preserved during ischemia. J Appl Physiol 103: 1628–1635, 2007. First published August 9, 2007; doi:10.1152/japplphysiol.00320.2007. —During voluntary contractions, the skeletal muscle of healthy older adults often fatigues less than that of young adults, a result that has been explained by relatively greater reliance on muscle oxidative metabolism in the elderly. Our aim was to investigate whether this age-related fatigue resistance was eliminated when oxidative metabolism was minimized via ischemia induced by cuff (220 mmHg). We hypothesized that (1) elderly men \( (n = 12) \) would fatigue less than young men \( (n = 12) \) during free-flow (FF) contractions; (2) both groups would fatigue similarly during ischemia; and (3) reperfusion would reestablish the fatigue resistance of the old. Subjects performed 6 min of intermittent, maximal voluntary isometric contractions of the ankle dorsiflexors under FF and ischemia-reperfusion (IR) conditions. Ischemia was maintained for the first 3 min of contractions, followed by rapid cuff deflation and reperfusion for 3 additional minutes of contractions. Central activation, peripheral activation, and muscle contractile properties were measured at 3 and 6 min of contractions. Older men fatigued less than young men during FF \( (P \leq 0.02) \), ischemia \( (P < 0.001) \), and reperfusion \( (P < 0.001) \). During FF, activation and contractile properties changed similarly across age groups. At the end of ischemia, central \( (P = 0.02) \) and peripheral \( (P \leq 0.03) \) activation declined more in the young, with no effect of age on the changes in contractile properties. Thus age-related fatigue resistance was evident during FF and IR, indicating that differences in blood flow and oxidative metabolism do not explain the fatigue resistance of old age.

Central activation; peripheral activation; contractile properties; muscle strength; reperfusion; isometric

MUSCLE FORCE IS PRODUCED AS a result of a coordinated series of events between the motor cortex of the brain and the actomyosin complex of the sarcomere. The energy required to support muscle contractions is derived directly from ATP, which is generated in the muscle by oxidative and nonoxidative (anaerobic glycolysis and phosphocreatine breakdown) processes. While muscular mass and strength decline with advancing age \( (18, 27, 35) \), it appears that the muscle’s ability to resist fatigue and maintain force production during repeated contractions may be preserved \( (33, 37, 52) \) or enhanced \( (9, 15, 28, 32, 50) \) in older human skeletal muscle.

Fatigue resistance in older adults has been observed during submaximal \( (23, 28) \) and maximal \( (9, 15, 21, 23) \) isometric and dynamic contractions in the ankle dorsiflexor, knee extensor, elbow flexor, and thenar muscles. Notably, observations of greater fatigue in the elderly during dynamic contractions in some \( (3, 47) \), but not all \( (29, 32, 34) \), studies suggest that the age-related fatigue resistance may depend, in part, on the type of contraction used. In addition to the type of contraction, it has been suggested that some of the fatigue resistance of the elderly may be secondary to differences in muscle strength and mass. When present, the age-related resistance to muscle fatigue does not appear to be associated with differences in peripheral activation \( (9, 28, 32) \), defined as excitability of the neuromuscular junction and muscle membrane, or changes in contractile properties during muscular activity \( (15, 21, 28, 32) \). Although some investigators have reported age-related impairments in central activation \( (i.e., \text{initiation and propagation of motor action potentials from the brain to the spinal cord}) (7, 52) \), for the most part, healthy older adults appear to have the ability to fully activate the muscle in a manner similar to that of young adults, both before \( (29) \) and during fatiguing contractions \( (15, 23, 28, 32) \). Rather, differences within the muscle \( (specifically, \text{intramuscular energetics}) \) appear to be a primary mechanism for the fatigue resistance observed in the aged \( (28, 31) \). Under a variety of conditions, we have observed that the reliance on oxidative metabolism is higher and the accumulation of the fatigue-inducing metabolites \( [e.g., \text{inorganic phosphate, diprotonated inorganic phosphate, and proton (H}^+]) \) (cf. Ref. 17) is lower in old compared with young skeletal muscle \( (28, 31) \). As yet, the impact of blood flow on this energetic “advantage” of the elderly has not been determined during fatiguing contractions.

Thus the primary aim of this study was to test the hypotheses that (1) older adults would fatigue less than young adults during free-flow (FF) contractions; (2) young and older adults would fatigue similarly during ischemia; and (3) older adults would once again fatigue less than young adults during reperfusion. This pattern of results would be consistent with the notion that differences in muscle energetics, in particular oxidative metabolism, are an important mechanism of the age-related resistance to muscle fatigue. To test these hypotheses, all subjects performed two fatiguing, isometric contraction protocols [FF and ischemia-reperfusion (IR)] of the ankle dorsiflexor muscles. In both contraction protocols, the potential mechanisms associated with fatigue were further examined by measuring central activation, peripheral activation, and contractile properties during electrically stimulated contractions. Because age-related differences in muscle strength have often been suggested to play a role in the fatigue resistance of the elderly \( (1, 28, 32) \), we also tested our hypotheses in subgroups of strength-matched subjects.

METHODS

Subjects came to the laboratory for a total of three visits, consisting of one habituation visit and two testing sessions. The two testing sessions were separated by 7 days. The order of the fatigue conditions (FF and IR) was randomized and blocked by age group.

Subjects. Healthy, untrained young \( (n = 12) \) and older \( (n = 12) \) men, between the ages of 21–35 yr and 65–80 yr, were recruited from the university and local communities. All individuals gave signed,

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informed consent, as approved by the Institutional Review Board of the School of Public Health and Health Sciences at the University of Massachusetts, Amherst. The study was conducted according to the Declaration of Helsinki, and the Health Insurance Portability and Accountability Act procedures were followed. Subjects were excluded if they had any history of myocardial pathologies (e.g., coronary artery disease), hypertension, diabetes, neurological disorders, peripheral vascular disease, or any other major health problem; or if they were taking any medications that might alter muscle function or blood flow (e.g., antihypertensives, statins, etc.). The ankle brachial index (ABI; ankle-to-brachial systolic blood pressure ratio) was measured with the subject supine to ensure that no volunteer had latent peripheral vascular disease. All older individuals had physician’s clearance before their participation in the study. To avoid the potential impact of habitual physical activity level on our measures of muscle function, participants with similar levels of physical activity were recruited.

**Experimental setup.** Subjects were positioned with the dominant leg placed in a custom-built apparatus with a foot plate fixed at an angle of 125° relative to the horizontal plane (i.e., 35° plantarflexion). A force transducer mounted underneath the foot plate (Interface, Scottsdale, AZ) measured force production in response to isometric ankle dorsiflexion. Surface electromyography recording electrodes (10-mm-diameter gold-plated disks) were placed over the belly of the tibialis anterior muscle and its distal tendon. A pair of stimulating electrodes (10-mm-diameter gold-plated disks) were placed over the peroneal nerve near the fibular head. A copper ground plate was placed between the recording and stimulating electrodes. Electrical stimulation of the peroneal nerve was delivered by a constant current stimulator (model D107A, Digitimer, Hertfordshire, UK), using a 500-μs pulse width. The maximal stimulus intensity was determined for each subject by application of a single pulse at progressively greater intensity until the maximum compound muscle action potential (CMAP) amplitude was found. A supramaximal pulse (15% above maximal intensity) was used for all subsequent stimuli.

**Habituation session.** Subjects completed a medical history and physical activity readiness questionnaire. Their height, mass, and resting blood pressure measures were determined. Mean arterial pressure (MAP) and body mass index (BMI) were calculated for each subject. Because physical function typically changes with age, we further characterized our subjects by measuring foot-tap speed [rapid taps for 10 s on each foot, while in a seated upright position (44)], as well as the time for ascent and descent of eight stairs. The ascent and descent of stairs were timed separately and performed twice; the shortest time for each was recorded.

Each subject was familiarized with the contraction protocol, electrical stimulation measures, and cuff inflation. Subjects practiced three maximal voluntary contractions (MVCs) (3- to 4-s duration), each separated by 2 min of rest. Additional MVCs were performed if the forces recorded were not within 10% of one another. Next, subjects experienced the electrical stimulation measures of central activation, twitch, and tetanus (see below). The first minute of the contraction protocol was then performed with and without cuff inflation so that the subjects were accustomed to the nature of the contractions. The cuff was positioned around the thigh for all visits.

To quantify daily physical activity level, subjects wore a uniaxial accelerometer (model SYS7164-2, Manufacturing Technology, Fort Walton Beach, FL) during waking hours for 7 days, which recorded the average vertical accelerations per minute. Subjects also kept a daily log of their physical activities, which was used to verify general activity habits over the week. Physical activity data were downloaded from the accelerometer and analyzed as mean counts per day divided by 1,000. After a minimum of 3 days following habitation, subjects returned for the first of the two test sessions.

**Contraction protocol.** During FF and IR, subjects performed intermittent (50% duty cycle: 5 s contract/5 s rest), isometric MVC of the ankle dorsiflexor muscles for a total of 6 min. Peak force (N) was obtained from baseline MVCs for each day and was used to scale a light-emitting diode panel that provided visual feedback to the subject. Subjects were given verbal encouragement for every contraction performed, and all contractions were performed as rapidly and forcefully as possible. All force measurements were acquired using Labview software (version 5.1, National Instruments, Austin, TX) and analyzed with specifically designed MATLAB programs (The MathWorks, Natick, MA). Baseline force data were collected at a sampling rate of 500 Hz and low-pass filtered with a 50-Hz cutoff. Force data for the entire contraction protocol were collected at a sampling rate of 25 Hz and low-pass filtered with a 10-Hz cutoff. Force data were expressed relative to baseline.

During FF, subjects performed the contraction protocol with unimpeded blood flow. In IR, the cuff was inflated to 220 mmHg 10 s before the first contraction using a rapid cuff inflator (D. E. Hokanson, Bellevue, WA) and was maintained there for the first 3 min of contractions, after which it was rapidly deflated, and contractions continued without interruption for an additional 3 min.

**Central activation.** The degree of voluntary activation of the dorsiflexors was determined by applying a supramaximal train of stimuli (50 Hz, 250 ms) when force plateaued during an MVC. The central activation ratio (CAR) was calculated as the peak force before the superimposed tetanus divided by the peak force during the superimposed tetanus (26). While some activation of the antagonist muscles may also occur as a result of the stimulus, a CAR < 1.0 was taken to indicate incomplete voluntary activation of the agonist muscle group. The CAR data were obtained at baseline and at 3 and 6 min of contractions, using a sampling rate of 500 Hz.

**Peripheral activation.** Changes during fatigue in excitability of the neuromuscular junction and muscle membrane were evaluated from changes in the CMAP, obtained in response to a single supramaximal stimulus. The CMAP peak-to-peak amplitude (mV), duration of the negative peak (ms), and area of the negative peak (mV·ms) were measured at baseline and 3 and 6 min of contractions. The CMAP waveform was acquired at 2,500 Hz and analyzed using MATLAB.

**Contractile function.** Stimulated dorsiflexion force (N) was assessed by applying a single supramaximal stimulus (twitch) and a 50-Hz, 1-s train of stimuli (tetanus). Twitch force was measured at baseline and 3 and 6 min of contractions. Baseline twitch force was obtained immediately following the third baseline MVC, to allow use of a potentiated twitch for all comparisons. Peak tetanic force, the
maximum rate of force development (RFD), the maximum rate of force relaxation (RFR), and the half-time of force relaxation (T1/2) were quantified from the tetanic train and were collected at baseline and 3 and 6 min of contractions. The RFD and RFR (% peak force/ms) were calculated from the derivative of the force trace and expressed relative to peak force. The T1/2 (ms) was measured from the last stimulation artifact of the train to the time at which tetanic force had fallen to 50% of peak. Twitch and tetanic force measures were collected at a sampling rate of 2,500 Hz and low-pass filtered with a 50-Hz cutoff. Twitch-to-tetanus ratios (Tw/Tet) were calculated as an index of low-frequency fatigue during the contraction protocols.

Statistical analyses. All statistical analyses were performed using Statistical Analysis Software (SAS Institute, Cary, NC). Age, height, mass, BMI, ABI, blood pressure, MAP, physical activity, foot-tap count, and stair climb and descent times were compared across age groups using unpaired t-tests. Baseline measures of MVC (N), tetanic force (N), RFD (% peak force/ms), RFR (% peak force/ms), T1/2 (ms), twitch force (N), Tw/Tet, CMAP amplitude (mV), CMAP duration (ms), and CMAP area (mV·ms) were compared across age groups for each contraction protocol using unpaired t-tests. Group differences in MVC force during FF and IR were evaluated using two-way repeated-measures (group, time) ANOVA on MVC for minutes 1, 2, and 3 (FF, ischemia), and minutes 4, 5, and 6 (FF, reperfusion). In the case of significant group-by-time interactions, post hoc analyses (Tukey’s) were performed to determine the time points at which the groups differed. Comparisons across groups of the Tw/Tet, RFD, and RFR, as well as the relative changes in tetanic force, T1/2, twitch force, CMAP amplitude, and CMAP area, were made at 3 and 6 min of contractions using unpaired t-tests. Measures of CAR were compared across groups at baseline and 3 and 6 min of contractions using the Wilcoxon Signed-Rank Test for nonparametric variables.

To examine whether differences in muscle strength could account for differences in fatigue between young and older adults, a subset of six young and six older men were individually matched based on strength, post hoc, without knowledge on the part of the investigator as to the fatigue responses of each individual. Each matched pair had baseline MVCs within 3% of each other. Fatigue during FF and IR in these groups was compared using two-way repeated-measures ANOVA, as for the main groups.

The level of significance was set at $P \leq 0.05$. Data in Tables 1–4 are presented as means ± SD. Data in Figs. 1–3 are presented as means ± SE. In all tables, groups sizes are indicated in parentheses, as some data are missing due to equipment failure and subject noncompliance. Ninety-five percent confidence intervals for the difference across groups, and precise $P$ values are reported, as appropriate (12).

RESULTS

Subject characteristics. Young and older subjects had similar height, mass, BMI, and ABI (Table 1). Older men had a higher brachial blood pressure and MAP compared with young men (Table 1). The physical function measures showed that older men had lower foot-tap speed and slower stair ascent and descent times compared with young men (Table 1). Both groups exhibited similar physical activity levels, as measured by the uniaxial accelerometer (Table 1).

Baseline muscle characteristics. On average, older men were weaker than young men at baseline (Fig. 1, Table 2). Older men also had lower tetanic force compared with young men, although twitch force was similar across groups (Table 2). All subjects had a baseline CAR of ±0.95, indicating nearly

| Table 2. Baseline muscle characteristics for each study day |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
|                            | Free-Flow Day               | Ischemia-Reperfusion Day     |
|                            | Young                       | Older                       | Young                       | Older                       |
| Force                      |                             |                             |                             |                             |
| MVC, N                     | 316±55 (12)                | 252±55 (11)                | 316±53 (12)                | 250±60 (11)                |
| Tetanic force, N           | 316±55 (12)                | 252±55 (11)                | 316±53 (12)                | 250±60 (11)                |
| Twitch force, N            | 85±9 (11)                  | 67±8 (11)                  | 64±7 (11)                  | 54±8 (12)                  |
| Tw/Tet                     | 0.16±0.04 (10)             | 0.19±0.09 (8)              | 0.16±0.05 (8)              | 0.19±0.06 (7)              |
| Activation                 |                             |                             |                             |                             |
| CAR                        | 1.00±0.01 (11)             | 0.99±0.02 (9)              | 1.00±0.00 (9)              | 1.00±0.01 (11)             |
| CMAP amplitude, mV         | 10.6±1.8 (11)              | 8.6±1.1 (12)               | 10.1±1.5 (12)              | 8.0±1.5 (11)               |
| CMAP area, mV·ms           | 52.7±12.9 (11)             | 39.2±8.0 (12)              | 48.6±9.5 (12)              | 37.2±9.1 (11)              |
| Contractile properties     |                             |                             |                             |                             |
| RFD, % peak force/ms       | 0.58±0.11 (10)             | 0.58±0.16 (9)              | 0.57±0.14 (9)              | 0.62±0.14 (7)              |
| RFR, % peak force/ms       | -1.25±0.13 (12)            | -1.06±0.25 (10)            | -1.26±0.20 (9)             | -0.93±0.18 (7)             |
| T1/2, relaxation, ms       | 125±11 (10)                | 149±22 (9)                 | 120±13 (9)                 | 154±27 (10)                |

Data are means ± SD; group sizes are indicated in parentheses. Older men were weaker and had slower force relaxation than young. Central activation was similar across age groups, while compound muscle action potential (CMAP) amplitude and area were lower in the older group. MVC, maximal voluntary contraction; Tw/Tet, twitch-to-tetanus ratio; CAR, central activation ratio; RFD, rate of force development; RFR, rate of force relaxation; T1/2, half-time to force relaxation.

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full central activation of the dorsiflexor muscles before the fatiguing protocols (Table 2). Older men had lower CMAP amplitude and area compared with young men (Table 2). The CMAP duration was similar between age groups at baseline ($P \geq 0.54$, data not shown). Finally, while the maximum RFD was similar across groups, both the maximal RFR and the $T_{1/2}$ of force relaxation were slower in older compared with young men (Table 2).

**FF protocol.** The repeated-measures ANOVA indicated that the older men fatigued relatively less than young men during FF ($P \leq 0.02$, Fig. 2A), with no group × time interaction ($P \geq 0.81$). Older men exhibited similar declines in tetanic and twitch forces as young men (Table 3). Young men had lower Tw/Tet compared with older men at 3 min, but there was no significant difference across age groups at 6 min of the FF protocol (Table 3). There were no differences across groups in the effect of the FF protocol on CAR or CMAP amplitude and area (Table 3). Similarly, there was no difference between young and older men in RFD during FF (Table 3). Both groups exhibited a similar degree of slowing of force relaxation (RFR, $T_{1/2}$) during FF (Table 3).

**IR protocol.** Older men fatigued less than young men during ischemia ($P < 0.001$; Fig. 2B), with a significant group × time interaction apparent at 3 min ($P < 0.001$). Both groups fatigued more at the end of ischemia compared with minute 3 of FF (older: 21 ± 13% difference; younger: 37 ± 13%; $P < 0.01$). Upon cuff deflation at minute 3, there was some force recovery during reperfusion, despite continued contractions. During reperfusion, there was less fatigue in the older compared with young men ($P < 0.001$; Fig. 2B), with no group × time interaction ($P = 0.527$). Tetanic and twitch forces declined and recovered to a similar extent in older and young men at the end of ischemia and reperfusion, respectively (Table 4). The Tw/Tet were similar in young and old at the end of ischemia, whereas young tended to have lower Tw/Tet compared with older men at the end of reperfusion, although this was not a significant difference (Table 4).

There was greater central activation failure in young compared with older men at the end of ischemia (Table 4). At the end of reperfusion, central activation recovered in the young and was similar and essentially complete in both groups (Table 4). CMAP amplitude and area fell more in young men at the end of reperfusion, compared with older men (Table 4), and this difference persisted at the end of reperfusion (Table 4).

There were no differences across age groups in the maximum RFD during the IR protocol (Table 4). In both groups, the $T_{1/2}$ and RFR were substantially and similarly slowed by the ischemic contractions (Table 4). At the end of reperfusion, there were no differences across groups in the maximal RFR, although the $T_{1/2}$ of force relaxation was prolonged in young compared with older men (Table 4).

**Strength-matched analysis.** To investigate whether age-related differences in muscle fatigue occurred as a result of differences in muscle strength, six young men (283 ± 33 N) were strength-matched to six older men (281 ± 32 N; $P = 0.32$). Older men fatigued relatively less than young men during the first 3 min ($P = 0.001$) and last 3 min ($P < 0.001$; Fig. 3A) of FF. Older men also fatigued less than young men during ischemia ($P < 0.001$) and reperfusion ($P < 0.001$; Fig. 3B). There were no significant group × time interactions ($P \geq 0.07$) during FF or IR for the strength-matched groups. Thus the overall pattern of fatigue in the strength-matched groups was similar to that of the larger study groups.

**DISCUSSION**

The overall goal of this study was to test the dependence of age-related differences in skeletal muscle fatigue on the availability of oxidative energy supply. This goal was accomplished with the use of two contraction protocols: one with intact blood flow and one with ischemic contractions followed by contractions during reperfusion. As expected, the young fatigued more than the old during intermittent, maximal contractions in which blood flow was unimpeded. However, contrary to our hypothesis, older men maintained fatigue resistance when blood flow was occluded. These results suggest that differences in oxidative energy supply do not explain age-related fatigue resistance. Under the more severe conditions of ischemia, impairments in central and peripheral activation account for some of
the differences in fatigue between young and old. When a subset of young and older men were matched for strength, older men maintained the same pattern of fatigue resistance during FF and IR, indicating that reductions in muscle strength do not account for the greater fatigue resistance of older adults during maximal intermittent, isometric contractions.

Baseline. In this study, our young and older groups were well-matched for height, mass, BMI, ABI, and physical activity level. While the older men did have higher blood pressures than the young, they were, on average, in the range of normotensive. Despite their apparent health, however, the older men exhibited some degree of physical dysfunction relative to the young men, observed as slower foot-tap and stair climb and descent speeds. The age-related slowing of foot-tap speed is consistent with earlier reports (27, 44) and is considered mainly to reflect slowing in the ability to rapidly and repeatedly recruit motor units in this important muscle group (41), although an effect of changes in antagonist muscle function cannot be ruled out at this time. In the elderly, stair climb times are sensitive to training status (4) and related to lower extremity strength and power (11). While physical activity levels were similar in our age groups, the baseline weakness of the older men may explain some of their slowed stair performance.

While some investigators have found diminished central activation in older adults (7, 52), both of our groups demonstrated full activation of the unfatigued dorsiflexors, which is consistent with previous work done in this muscle from our laboratory (27, 28, 32), as well as that of others (10, 21, 53). Thus the weakness displayed by our older group (i.e., lower MVC) was not explained by differences in central activation, but rather was likely due to decreased muscle mass. Further support of this concept is provided by the similar relative loss of MVC and tetanic force in our older group at baseline, suggesting that the source of weakness in the old was not central, but rather peripheral in this study (i.e., due to muscle atrophy). It should be noted that decreased specific strength (MVC force per unit muscle mass), which was not assessed in this study, could also explain the weakness of the older group (30, 42). However, several investigators, including ourselves, have observed similar specific strengths in young and old in the ankle dorsiflexors (27, 39), as well as in the quadriceps muscles (19, 20, 45).

The amplitude and area of the CMAP were lower in our older men at baseline, a result that has been reported previously (28, 53), although not always (27, 43), in this muscle group. It should be noted that the effects of electrode placement and

### Table 3. Muscle characteristics during free-flow protocol

<table>
<thead>
<tr>
<th></th>
<th>At Minute 3</th>
<th></th>
<th>At Minute 6</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Young</td>
<td>Older</td>
<td>P value</td>
<td>Young</td>
</tr>
<tr>
<td>Stimulated force</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetanic force, %baseline</td>
<td>74±9 (11)</td>
<td>80±13 (9)</td>
<td>0.30</td>
<td>60±12 (11)</td>
</tr>
<tr>
<td>Twitch force, %baseline</td>
<td>62±17 (11)</td>
<td>76±29 (11)</td>
<td>0.18</td>
<td>49±28 (11)</td>
</tr>
<tr>
<td>Tw/Tet</td>
<td>0.12±0.28 (10)</td>
<td>0.17±0.06 (8)</td>
<td>0.05</td>
<td>0.11±0.04 (10)</td>
</tr>
<tr>
<td>Activation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAR</td>
<td>0.98±0.04 (11)</td>
<td>1.00±0.01 (9)</td>
<td>0.44</td>
<td>0.96±0.07 (11)</td>
</tr>
<tr>
<td>CMAP amplitude, %baseline</td>
<td>93±13 (11)</td>
<td>96±15 (12)</td>
<td>0.59</td>
<td>87±12 (11)</td>
</tr>
<tr>
<td>CMAP area, %baseline</td>
<td>101±20 (11)</td>
<td>105±21 (12)</td>
<td>0.66</td>
<td>108±42 (11)</td>
</tr>
<tr>
<td>Contractile properties</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RFD, %peak force/ms</td>
<td>0.52±0.08 (10)</td>
<td>0.58±0.17 (9)</td>
<td>0.36</td>
<td>0.55±0.13 (10)</td>
</tr>
<tr>
<td>RFR, %peak force/ms</td>
<td>-0.67±0.17 (12)</td>
<td>-0.68±0.22 (10)</td>
<td>0.94</td>
<td>-0.84±0.18 (12)</td>
</tr>
<tr>
<td>T1/2 relaxation, %baseline</td>
<td>158±34 (10)</td>
<td>147±41 (9)</td>
<td>0.54</td>
<td>140±40 (10)</td>
</tr>
</tbody>
</table>

Values are means ± SD; group sizes are indicated in parentheses. Changes in tetanic force, twitch force, activation, and contractile properties were not different across groups during free flow. Young had lower Tw/Tet than old at 3 min, with a trend for a difference at 6 min of contractions.

### Table 4. Muscle characteristics during ischemia-reperfusion protocol

<table>
<thead>
<tr>
<th></th>
<th>At Minute 3 (Ischemia)</th>
<th>At Minute 6 (Reperfusion)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Young</td>
<td>Older</td>
</tr>
<tr>
<td>Stimulated force</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetanic force, %baseline</td>
<td>45±14 (9)</td>
<td>58±18 (7)</td>
</tr>
<tr>
<td>Twitch force, %baseline</td>
<td>15±14 (10)</td>
<td>22±22 (11)</td>
</tr>
<tr>
<td>Tw/Tet</td>
<td>0.05±0.06 (8)</td>
<td>0.09±0.05 (7)</td>
</tr>
<tr>
<td>Activation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAR</td>
<td>0.83±0.21 (9)</td>
<td>0.98±0.04 (11)</td>
</tr>
<tr>
<td>CMAP amplitude, %baseline</td>
<td>76±13 (11)</td>
<td>90±9 (11)</td>
</tr>
<tr>
<td>CMAP area, %baseline</td>
<td>86±12 (11)</td>
<td>99±14 (11)</td>
</tr>
<tr>
<td>Contractile properties</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RFD, %peak force/ms</td>
<td>0.54±0.16 (9)</td>
<td>0.50±0.14 (7)</td>
</tr>
<tr>
<td>RFR, %peak force/ms</td>
<td>-0.55±0.24 (9)</td>
<td>-0.37±0.20 (7)</td>
</tr>
<tr>
<td>T1/2 relaxation, %baseline</td>
<td>242±68 (5)</td>
<td>235±67 (5)</td>
</tr>
</tbody>
</table>

Values are means ± SD; group sizes are indicated in parentheses. There were no differences across groups in stimulated force during ischemia-reperfusion. Central activation failure was greater in the young than old at 3 min; this variable recovered by 6 min. Young showed lower peripheral activation than old at both 3 and 6 min. While there was no difference across groups in the maximal RFR at 3 or 6 min, or the T1/2 of force relaxation at 3 min, by 6 min there was significantly greater recovery in this measure in the older group.
differences in subcutaneous fat make the CMAP more appropriate for examining changes that occur within individuals during fatigue, as opposed to quantifying baseline differences in peripheral excitability across individuals. The duration of the CMAP was similar in both groups at baseline. Overall, baseline central and peripheral activation were comparable in our study groups.

While twitch force tended to be lower in the older group, this difference did not reach statistical significance, possibly due to the variability of this measure. At baseline, there were no differences between groups in the Tw/Tet, suggesting no intrinsic defect in excitation-contraction coupling in the elderly (16). Although the maximal RFD was not different across age groups, force relaxation following a stimulated tetanic contraction (by both T1/2 and RFR) was slower in older compared with young men, a result that is consistent with other studies (2, 28, 32, 53). Slower force relaxation in the unfatigued muscles of our older group likely reflects a shift toward a greater proportion of type I fiber area, due to motor unit remodeling (38) and relatively greater atrophy of type II fibers with advancing age (24).

**Fatigue during FF contractions.** We observed less fatigue in older compared with young men during FF contractions, a result consistent with previous studies using isometric (9, 15, 32, 50) and dynamic (32) contractions. As shown in Fig. 2, this difference emerged over time, with ~9% less fatigue in the older group at 3 min of contractions and ~12% difference at 6 min. Despite the high-intensity nature of this protocol, neither central nor peripheral activation failure was observed in the groups. In addition to the CAR measure, the lack of central fatigue was substantiated by the similar degree of voluntary (MVC) and stimulated (tetanic) fatigue within each group (5, 6).

In light of the difference in volitional fatigue, the lack of statistical difference in the fall of tetanic and twitch forces across age groups was somewhat surprising. Although the young tended to show more fatigue than the old in the stimulated measures, these differences were not significant, possibly due to the variability of the stimulated measures in these subjects. The Tw/Tet was somewhat lower in the young group than the older group during FF, suggesting greater changes in the intracellular environment, including calcium kinetics (8), in the young. However, the lack of difference across groups in RFD, RFR, or T1/2 of force relaxation at fatigue (Table 3) suggests that intracellular differences were of a modest degree. It is curious that, in both groups, some recovery of the relaxation parameters toward baseline levels occurred between minutes 3 and 6 of FF. This effect has been reported previously for twitch contractions during a fatigue task composed of maximal concentric and eccentric isokinetic contractions at 50°/s (3). The mechanism of this recovery is not clear at this time, but it is useful to note that it occurred in both age groups.

The 50% duty cycle of this protocol allowed reperfusion between contractions. Despite reports of decreased blood flow in older muscle at rest (13, 14) and during knee extension and cycle ergometry (34, 49), the enhanced fatigue resistance of our older group suggests that it was unlikely that blood flow was impaired in these subjects. Were this the case, limitations in reperfusion between contractions would likely have resulted in more fatigue in the old. Overall, the moderate degree of fatigue generated during intermittent MVCs arose from differences within the muscle cells. These results confirm those of earlier studies that indicated an age-related enhancement of fatigue resistance during intermittent, maximal isometric contractions (9, 15, 28, 32, 50).

**Fatigue during ischemic contractions.** The purpose of inducing ischemia during contractions in the present study was to test whether the increased reliance on oxidative metabolism that our laboratory has previously observed (28, 31) explains the age-related difference in fatigue resistance. Older adults have shown a relatively greater reliance on oxidative phosphorylation and a lower reliance on anaerobic glycolysis during fatiguing tasks using submaximal (28) and maximal (31) isometric contractions. Therefore, by essentially eliminating oxidative metabolism with ischemia, both age groups would necessarily rely more on anaerobic sources of ATP (25), the by-products of which are known to impair force production (8, 28, 40). In contrast to our expectation, the fatigue resistance of the older group was even more apparent during ischemia. Thus,
we must reject our hypothesis that the oxidative advantage (28, 31) of older muscle is necessarily the primary source of its fatigue resistance.

In general, muscle fatigue is exacerbated dramatically when blood flow is limited by ischemia (22, 48, 51); others have shown that force declines continuously until the end of exercise under these conditions (48, 51). We observed a similar effect of ischemia on muscle force in both of our study groups (Fig. 2); fatigue at 3 min of ischemia was more pronounced than at 3 min of FF. During ischemia, the excess fatigue of the young men was accompanied by greater central (CAR) and peripheral (CMAP amplitude and area) activation failure compared with the older men. Because decreased CMAP amplitude may be observed during fatigue without a net change in excitability, as reflected by CMAP area (46), it was important to quantify peripheral activation failure using both of these measures. Due to the nonlinear nature of the relationship between CMAP amplitude and twitch force in the unfatigued muscle (unpublished observations), it is difficult to know how much the peripheral activation failure contributed to fatigue in the young. Overall, it appears that, when conditions become sufficiently severe, as in ischemia, central and peripheral activation failure compounds the intramuscular failure of force production observed in FF in the young.

Fatigue during reperfusion. In the present study, reperfusion resulted in some recovery of force in both groups. Libonati et al. (36) observed force recovery in the forearm muscle following reintroduction of blood flow after a period of occlusion. In the present study, the recovery of force during reperfusion contractions reached a level that was similar to the force level at the end of FF (Fig. 2). At the end of reperfusion, central activation failure was no longer evident in the young subjects. However, peripheral activation (CMAP amplitude and area) was lower in the young men than older men at this time, although the difference in CMAP area appeared to be due to potentiating in the old, rather than impairment in the young. Low-frequency fatigue (decreased Tw/Tet) also tended to be greater in the young than the old at the end of reperfusion. While the maximal RFR was not different between groups, the T$_{1/2}$ of force relaxation was relatively more prolonged in the young compared with old at the end of the reperfusion period. Together, these results suggest that greater intracellular perturbations remained in the young than the old during the reperfusion phase of this contraction protocol. It should be noted that a portion of the residual differences between young and old could be due to differences in fatigue at the start of the reperfusion period, a possibility that is supported by the lack of a group × time interaction during this period.

Effects of strength. Some investigators have suggested that fatigue resistance in the elderly may be the result of less vascular occlusion during contractions, due to diminished muscle mass and strength (15, 28). At the same relative force, older, weaker adults would produce less absolute force compared with young adults, resulting in lower intramuscular pressure and less vascular occlusion during a contraction. As a result, there may be better replenishment of substrates and oxygen, more efflux of metabolic by-products, and less fatigue in weaker muscle. However, we found that older men exhibited the same pattern of fatigue resistance compared with strength-matched young men during intermittent maximal, isometric contractions (Fig. 3). Recently, our laboratory observed full vascular occlusion in the dorsiflexor muscles during isometric contractions above ~60% MVC in subjects with a twofold range in strength (54). Therefore, it may be that muscle size and strength plays a role in fatigue only during contractions at intensities below this threshold. However, Hunter et al. (23) recently observed greater endurance in strength-matched older adults during a sustained, submaximal (20% MVC) isometric contraction. Together, these studies do not support the hypothesis that decreases in muscle size and strength account for the enhanced fatigue resistance of healthy, older adults.

Conclusions. During maximal contractions, older adults exhibited enhanced resistance to skeletal muscle fatigue that was independent of blood flow and muscle strength. In FF conditions, the source of this fatigue resistance was within the muscle, while the more severe conditions of ischemia-induced central and peripheral activation failure in the young that further exacerbated their fatigue compared with the old.

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