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Fatigability of the Knee Extensor Muscles during High-Load Fast and Low-Load Slow Resistance Exercise in Young and Older Adults

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Fatigability of the Knee Extensor Muscles during High-Load Fast and Low-Load Slow Resistance Exercise in Young and Older Adults

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Abstract
Resistance exercise training is a cornerstone in preventing age-related declines in muscle mass and strength, and fatigability of limb muscle is important to this adaptive response. It is unknown, however, whether fatigability and the underlying mechanisms differ between different resistance exercise protocols in young and older adults. The purpose of this study was to quantify the fatigability of the knee extensors and identify the mechanisms in 20 young (22.2 ± 1.3 yr, 10 women) and 20 older adults (73.8 ± 5.4 yr, 10 women) elicited by a single session of high- and low-load resistance exercise. One leg completed a high-load protocol with contractions performed as fast as possible (HL-fast, ~80% 1 Repetition Max, 1RM), and the contralateral leg a low-load protocol performed with slow contractions (LL-slow, ~30% 1RM, 6 s concentric, 6 s eccentric). Each exercise involved four sets of eight repetitions. Before and immediately following each set, maximal voluntary isometric contractions (MVC) were performed, and voluntary activation and contractile properties quantified using electrical stimulation. The reduction in MVC was greater following the LL-slow (20%) than the HL-fast (12%, $P = 0.004$), with no age or sex differences. Similarly, the reduction in the amplitude of the involuntary electrically-evoked twitch was greater in the LL-slow (14%) than the HL-fast (7%, $P = 0.014$) and correlated with the reduction in MVC ($r = 0.546$, $P < 0.001$), whereas voluntary activation decreased only for the LL-slow protocol (5%, $P < 0.001$). Thus, low-load resistance exercise with slow contractions induced greater fatigability within the muscle than a more traditional high-load resistance protocol for both young and older men and women.

Keywords
Aging, resistance exercise, muscle fatigue, contractile properties

1. Introduction
Adult aging is accompanied by decrements in neuromuscular function that can lead to a decreased ability to perform daily activities and a loss of independence in older adults. A large portion of the loss in function is attributed to the decline in the force and power generating capacity that occurs to a large extent from the age-related loss of muscle mass (Doherty, 2003; Larsson et al., 2019), particularly the atrophy of muscle expressing the fast myosin heavy chain isoforms (Lexell, 1995; Nilwik et al., 2013; Sundberg et al., 2018a; Teigen et al., 2020). Resistance exercise training, most commonly high-load resistance training (>70% 1 Repetition Maximum, 1RM), is a cornerstone in the prevention of the age-related decline in muscle mass, strength, and function (Aagaard et al., 2010; Borde et al., 2015; Fragala et al., 2019). However, high-load resistance exercise can lead to pain and discomfort, for example in the tibio-femoral joint in older adults and can be intolerable or contraindicated in some chronic illnesses and musculoskeletal injuries that increase in prevalence with aging. As a result, there is considerable interest from both a basic and applied science perspective in identifying whether low-load resistance exercise training paradigms can be manipulated to elicit similar, or near similar, adaptations in muscle mass and strength compared to traditional high-load resistance training.

One potential approach to augment the increase in muscle mass and strength with low-load resistance exercise training is to perform a slow, controlled movement with no rest between contractions (Burd et al., 2012; Watanabe et al., 2014). For example, the increase in protein synthesis rates were greater in young men after performing low-load (30% 1RM) resistance exercise with a 6 s concentric and 6 s
eccentric phase compared with a work matched exercise performed with the same load but a 1 s concentric and 1 s eccentric phase (Burd et al., 2012). In agreement with this finding, 12 weeks of low-load (30% 1RM) resistance exercise training with a slow, controlled movement and no rest between contractions (3 s concentric, 1 s hold and 3 s eccentric per cycle) elicited a 5% increase in the cross-sectional area of the knee extensor muscles of older adults (60–77 years old) whereas no change in muscle size was observed following the same exercise training but performed with faster contractions (Watanabe et al., 2014). The mechanisms for the augmented protein synthesis and hypertrophic response to low-load, slow resistance training are unknown; however, it has been proposed that low-load, slow resistance exercise with no rest between contractions may accelerate fatigability (Burd et al., 2012; Watanabe et al., 2014). The increased fatigability is thought to either increase (1) mechanical stress from the compensatory increase in motor unit recruitment to maintain the load as the muscle fibers fatigue and/or (2) metabolic stress from the accumulation of fatigue-inducing metabolites that may provide an additional signal for the neuromuscular system to adapt (Schoenfeld, 2013). Despite the potential importance of fatigability in the adaptive response to resistance exercise training, to our knowledge there are no studies that 1) quantify the fatigability elicited by low-load, slow resistance exercise, 2) assess the fatigability and potential mechanisms for a low-load, slow resistance protocol compared with the more traditional high-load, resistance exercise, or 3) determine whether fatigability differs between young and older men and women during these two resistance exercise protocols.

Age differences in fatigability between the low-load, slow resistance protocol and high-load, resistance exercise are possible given that fatigability with aging varies with the velocity of the contraction (Hunter, 2018). Healthy older adults (~60–75 yr) for example, are typically less fatigable than young for maximal and submaximal isometric contractions for the upper and lower limb muscles (Callahan et al., 2009; Hunter et al., 2005; Kent-Braun, 2009; Yoon et al., 2013), although the fatigue resistance with advanced age diminishes for slow dynamic contractions (Callahan et al., 2009; Yoon et al., 2013). In contrast, older adults are more fatigable than young adults for dynamic contractions performed at low loads with moderate- to high-velocities (Callahan and Kent-Braun, 2011; Dalton et al., 2015; McNeil and Rice, 2007; Senefeld et al., 2017). The mechanisms for the greater fatigability of older adult during these dynamic contractions are not fully understood, but most of the data indicate that the mechanisms are primarily within the muscle (Dalton et al., 2010; Sundberg et al., 2018a; Sundberg et al., 2018b; Sundberg et al., 2019). Furthermore, most studies have assessed fatigability with isolated concentric, eccentric, or isometric contractions. It is unknown whether there are age differences in fatigability during resistance exercises that are used to ameliorate age-related declines in neuromuscular function and incorporate both concentric and eccentric phases of contraction.

Thus, the purpose of this study was to compare the fatigability elicited by a low-load, slow resistance exercise protocol (LL-slow) and a traditional, high-load protocol with contractions performed as fast as possible (HL-fast) in the knee extensor muscles of young and older men and women. We hypothesized that (1) both young and older adults would exhibit greater fatigability (i.e., reductions in maximal isometric force) following the LL-slow compared with the HL-fast protocol; and (2) there would be minimal age differences in fatigability for the LL-slow protocol, but older adults would be more fatigable than young for the HL-fast protocol. To determine where along the motor pathway fatigue occurred during the two resistance exercise protocols, we coupled transcutaneous peripheral electrical stimulation with surface electromyography (EMG) of the knee extensor muscles. We quantified
fatigability as the reduction in the maximal voluntary isometric contraction force (MVC), which is a gold standard measurement of muscle fatigue (Gandevia, 2001). Both males and females were assessed, although we did not expect to observe sex differences in fatigability between the protocols because of the minimal differences between men and women for dynamic contraction tasks in the lower limb (Hunter, 2016a; Hunter, 2016b; Senefeld et al., 2018; Sundberg et al., 2017).

2. Methods
2.1. Participants and ethical approval
Twenty young (19–24 years, 22.2 ± 1.3 years, 10 women) and 20 older adults (64–85 years, 73.8 ± 5.4 years, 10 women) volunteered and provided their written informed consent to participate in this study. All participants were healthy, community dwelling adults who were free of any known neurological, musculoskeletal, or cardiovascular diseases. All experimental procedures were approved by the Marquette University Institutional Review Board and were conducted in accordance with the principles in the Declaration of Helsinki.

2.2. Experimental approach
Participants reported to the laboratory on two occasions, once to conduct one repetition maximum testing (1RM) and familiarization to the study procedures and once for the experimental session to measure fatigability of the knee extensors in response to two resistance exercise protocols. The resistance exercise protocols involved a traditional high-load protocol with contractions performed as fast as possible (HL-fast, ~80% 1RM, ~1-s concentric and ~1-s eccentric) and a low-load protocol performed with slow contractions (LL-slow, ~30% 1RM, 6-s concentric, 6-s eccentric). Both protocols involved 4 sets of 8 contractions so that the number of contractions were matched. This approach was taken because matching protocols for total training volume (repetitions x load) or mechanical work (J) would have resulted in ~2.5-fold more repetitions and ~15-fold greater times under tension in the LL-slow compared with HL-fast. Furthermore, matching for a set number of repetitions is a more practical approach to translate the protocols into a clinical exercise setting for older adults. Using a different method would have resulted in considerable differences in the number of repetitions between protocols (e.g., work matched) and potentially between participants (e.g., performed to failure).

For both sessions and resistance exercise protocols, participants were seated upright in a custom-instrumented leg extension machine (Hammer Strength Select Leg Extension, Life Fitness, Rosemont, IL). The seat and lever arm were adjusted so that 1) the axis of rotation of the machine's lever arm was aligned with the axis of rotation of the participant's knee (tibio-femoral joint) and 2) the starting knee position was at 90° flexion. Extraneous movements and changes in hip angle were minimized by securing the participant to the seat at the hips and shoulders with a custom four-point restraint system as done previously (Sundberg and Bundle, 2015). To ensure the measured mechanical performances were generated primarily by the knee extensor muscles, participants were prohibited from grasping the dynamometer with their hands.

2.2.1. 1 Repetition maximum testing (1RM) and familiarization session (session 1)
The session began with a standardized warmup consisting of five-minutes of cycling (Schwinn Bikes, Vancouver, WA) followed by knee extensions lifting a light load (~4.5 kg). After the warmup, the participant's unilateral 1RM was assessed for each leg and determined as the greatest load (kg) lifted
through a range of motion (ROM) of at least 65°. Completion of the 65° ROM was verified by measuring the angular displacements with a string potentiometer (SP1–50, Measurement Specialties, Berwyn, PA) attached to the distal end of the leg extension machine's lever arm as described previously (Sundberg and Bundle, 2015). The load for the 1RM assessment started at a light intensity and increased incrementally by 2–9 kg depending on the ease at which the participant successfully lifted the previous load. Participants were provided strong verbal encouragement during each attempt and given at least two attempts to lift the load through the 65° ROM.

Following the completion of the 1RM assessment, participants were habituated to electrical stimulation of the quadriceps muscles and femoral nerve and practiced performing brief 2–3 s maximum voluntary isometric contractions (MVC) with the knee extensors. Additionally, participants practiced completing eight sequential repetitions for both resistance exercise protocols to ensure they were able to achieve the 65° ROM at the calculated loads. All participants were able to complete the 30% 1RM load for the LL-slow protocol, however, eight older participants were unable to complete the 80% 1RM load for the HL-fast protocol. For these participants, the load was lowered in 5% increments until they were able to complete eight sequential repetitions through the 65° ROM. As a result, three older women performed the HL-Fast protocol with 75% 1RM and five (three older women and two older men) with 70% 1RM.

2.2.2. Experimental session (session 2)

The experimental session began with electrical stimulation of the femoral nerve and knee extensor muscles to identify 1) the electrode placement that elicited the maximum peak-to-peak compound muscle action potential (maximum M-wave: $M_{\text{max}}$) of the vastus lateralis (VL) and vastus medialis (VM) and 2) the peak twitch force. Following the electrical stimulations, participants performed a minimum of three brief unilateral MVCs (2–3 s) without stimulations. Participants were provided strong verbal encouragement and visual feedback on their performance. Each MVC was interspersed with at least 2 min rest, and MVC attempts were continued until the two highest values were within 5% of each other. To establish the baseline measures for quantifying fatigability and to localize the sites of fatigue along the motor pathway, participants then performed four MVCs coupled with electrical stimulation to assess voluntary activation and involuntary contractile properties of the muscle. Briefly, participants performed a MVC with 100 Hz paired pulse stimulation (doublet) delivered to the knee extensor muscles during and immediately following the MVC (<5 s). Each MVC attempt was interspersed with at least 2 min rest, and after all MVCs, participants completed one of the two unilateral resistance exercise protocols as described below.

Following completion of the first protocol, the participant was removed from the leg extension machine and required to rest for at least 10 min before repeating the experimental procedures with the alternate resistance exercise protocol on the contralateral leg. This within-subject unilateral research design was chosen to mitigate the confounding effects of the large inter-individual variability in fatigability that is commonly observed between participants of a similar age cohort (Hunter et al., 2016; Sundberg et al., 2018b). The resistance exercise protocol for each leg was counterbalanced based on 1) each participant's single-leg knee extension 1-RM to minimize the potential effects of differences in baseline strength between legs and 2) the order of testing for each protocol to minimize the potential crossover effects on fatigability.
2.2.3. Resistance exercise protocols

For each resistance exercise protocol participants performed 4 sets of 8 repetitions with each set interspersed by 3 min rest. For the LL-slow protocol, participants were instructed to lift and lower the 30% 1RM load at a cadence corresponding with a 6 s concentric phase and 6 s eccentric phase with no rest between repetitions (Burd et al., 2012). To ensure adherence to the slow and controlled cadence, participants were provided real-time visual feedback via a custom array consisting of two columns each with 14 light-emitting diodes (LEDs). One array column was controlled by an internal adjustable timing circuit preset to illuminate and darken the LEDs (Barrett and Sundberg, 2017) at the desired 6 s concentric and 6 s eccentric cadence. The second column was controlled by the voltage changes from a string potentiometer (SP1–50, Measurement Specialties, Berwyn, PA) connected to the knee extension machine’s lever arm and provided feedback depicting the participant’s actual displacements as done previously (Sundberg and Bundle, 2015). Participants were instructed to match the progress of the lights displaying their displacement with the complementary array depicting the desired cadence. The preset 65° ROM resulted in an interdiode resolution for the array of 5°.

For the HL-fast protocol, participants were exhorted to kick out as fast as possible through the 65° ROM and were provided visual feedback on their limb displacement via the LED array. To quantify fatigability and localize the sites of fatigue along the motor pathway, participants performed a MVC coupled with electrical stimulation immediately following each set of eight repetitions (~10s). The forces and displacements during both resistance exercise protocols were sampled continuously, and the mechanical outputs analyzed contraction-by-contraction for the concentric phase of the limb movement cycle. Representative raw data traces from the experimental session are shown in Fig. 1.

Fig. 1. Representative data from the HL-fast (A) and LL-slow (B) resistance exercise protocols performed by a 72-year-old woman. Participants performed four MVCs coupled with electrical stimulation delivered to the knee extensor muscles to obtain baseline voluntary activation and involuntary contractile properties prior to performing the four sets of resistance exercise. To quantify fatigability and localize the sites of fatigue along the motor pathway, MVCs coupled with electrical stimulation were performed immediately following each set of resistance exercise. For ease of comparison between the exercise protocols, the x-axis is the same for the two protocols resulting in inclusion of all 8 repetitions for the HL-fast and only 2 repetitions for the LL-slow.
2.3. Measurements and data analysis

2.3.1. Mechanics during resistance exercise
Force outputs during the resistance exercise was measured with a linear force transducer (S-type load cell, SSM-AJ-2000 N, Interface Force Measurement Solutions, Scottsdale, AZ) mounted in the leg extension machine's steel cable pulley system via two eye bolts. Angular displacements were measured by the voltage changes from a string potentiometer connected to the LED feedback array. Force and position signals were digitized at 1000 Hz with a Power 1401 A/D converter, stored online with Spike 2 software (Cambridge Electronics Design, Cambridge, UK) and analyzed with IGOR Pro, version 8 (WaveMetrics Inc., Oswego, OR, USA). Contraction-by-contraction mechanical power outputs (W) were calculated as the product of the measured force output (N), the first derivative of the angular displacements (radians·s$^{-1}$), and the leg extension machine's moment arm (m) and averaged over the concentric phase of the knee extension cycle. To quantify the reductions in power during the HL-fast protocol, contraction-by-contraction power outputs were also expressed relative to the highest power output generated within the first four repetitions of the first set for each individual. Additionally, to quantify the differences between the LL-slow and HL-fast protocols from both the change in force and time the muscle was active, contraction-by-contraction mechanical impulse (N·s) was calculated as the integral of force over the entire knee extension movement cycle (i.e., including both concentric and eccentric phases).

2.3.2. Force output during MVCs
Force output during all MVC attempts was measured with a linear force transducer (S-type load cell, SSM-AJ-2000 N) attached to the frame beneath the seat of the leg extension machine. To accommodate varying leg lengths and seat positions, the force transducer was mounted to the frame with a custom-built, dual channel system constructed of steel. The positioning of the force transducer was adjusted with the dual channel system for each participant and secured to the leg with a Velcro strap proximal to the malleoli. Voltage changes from the analog force signals were sampled at 1000 Hz with a Power 1401 analog-to-digital converter and stored online using Spike 2 software (Cambridge Electronics Design, Cambridge, UK). The force during each MVC was quantified as the average value over a 0.5 s interval centered on the peak force of the contraction. The baseline MVC value for each participant was the median force output recorded from the isometric MVCs performed with stimulations before the resistance exercise protocols. To compare the changes in MVC between the young and old men and women following each set of resistance exercise, the MVC values were expressed as a percentage of the individual-specific baseline MVC value.

2.3.3. Surface electromyography (EMG)
Wireless surface EMG electrodes (Trigno™ DELSYS Inc., Natick, MA) were adhered to the skin overlying the muscle bellies of the vastus medialis and vastus lateralis according to recommended placements (Hermens et al., 2000). Analog EMG signals were amplified (909×), band pass filtered (10-850 Hz, DELSYS Inc., Natick, MA), digitized at 2000 Hz with a Power 1401 analog-to-digital converter and stored online with Spike 2 software (Cambridge Electronics Design, Cambridge, UK). The amplitude of the EMG was determined contraction-by-contraction as the root mean square (RMS) from the first 30° of the 65° ROM to ensure every contraction could be included in the EMG analysis and analyzed over the same ROM. To compare the EMG activity between the resistance exercise protocols for young and old
men and women, the RMS EMG was normalized to the EMG from 1) the first contraction of the first set for each resistance exercise protocol and 2) the MVC.

2.3.4. Femoral nerve stimulation and M-wave
The femoral nerve was stimulated with a constant-current, high-voltage stimulator (DS7AH, Digitimer, Welwyn Garden City, Hertfordshire, UK) to obtain $M_{\text{max}}$ of the vastus lateralis and vastus medialis as described previously (Sundberg et al., 2018b). The cathode was placed over the nerve high in the femoral triangle, and the anode was placed over the greater trochanter. Single 200-μs square-wave pulses were delivered with a stimulus intensity beginning at 50 mA and increased incrementally by 50–100 mA until both the unpotentiated resting twitch amplitude and $M_{\text{max}}$ for all three quadriceps muscles no longer increased. The intensity was then increased by an additional 20% to ensure the stimuli were supramaximal. The baseline peak-to-peak amplitude ($M_{\text{max}}$) and area of the m-wave were reported as the median value obtained from three stimulations performed at rest prior to performing the baseline MVCs. To assess whether impaired neuromuscular propagation was contributing to fatigue, the compound muscle action potential (m-wave amplitude and area) (Fuglevand et al., 1993) was elicited within 10 s after completion of the fourth set of each resistance exercise protocol and compared to the individual-specific baseline value.

2.3.5. Muscle stimulation and contractile properties
Because muscle stimulation is more tolerable than femoral nerve stimulation, we used transcutaneous electrical stimulation of the knee extensor muscles for the assessment of voluntary activation and involuntary contractile properties. Custom pad electrodes (6 × 8 cm) were secured to the skin overlying the knee extensor muscles with the cathode placed ~8–12 cm proximal to the superior border of the patella and the anode ~10–13 cm proximal to the cathode. The stimulator intensity was determined using single pulse stimuli (400 V, 200 μs duration) delivered transcutaneously with a constant current stimulator (DS7AH, Digitimer, Hertfordshire, UK). The stimulator intensity began at 50 mA and increased incrementally by 50–100 mA until a plateau in the twitch force was observed. The intensity was then increased an additional 20% to ensure the stimuli were supramaximal. This stimulator intensity was used as a 100 Hz paired pulse stimulation (doublet) for all voluntary activation and contractile property assessments.

Contractile properties of the knee extensors were quantified with the potentiated resting twitches delivered immediately after (<5 s) the MVCs. The baseline values for each participant were calculated as the median from the four MVCs performed prior to the resistance exercise and were reported for the amplitude of the potentiated resting twitch (N), the half relaxation time (ms), and the peak rate of force development (N·s$^{-1}$). The peak rate of force development ($dF/dt$) was quantified with the derivative of the force signal as the highest rate of force increase over a 10 ms interval. To assess whether disruptions in cross-bridge function and/or excitation contraction coupling contributed to fatigue, we measured the changes in the potentiated resting twitch immediately following each set of resistance exercise.

2.3.6. Voluntary activation
Voluntary activation of the knee extensors was assessed using the interpolated twitch technique (Gandevia, 2001; Merton, 1954) during each MVC that was coupled with transcutaneous electrical muscle stimulation and was quantified in accordance with Eq. (1):
Voluntary Activation(%) = \left(1 - \frac{\text{SIT}}{\text{RT}}\right) \times 100

where SIT is the amplitude of the superimposed twitch force elicited by the stimulation during the MVC and RT is the potentiated resting twitch electrically evoked immediately after the MVC (<5 s). The reported baseline voluntary activation for each participant was the median from the 4 MVCs performed before the resistance exercise protocols. To assess whether a reduced ability of the nervous system to voluntarily activate the muscle contributed to fatigue (central fatigue), voluntary activation immediately following each set of resistance exercise was compared to the individual specific baseline values.

2.4. Statistical analysis

Individual univariate ANOVAs were performed on the anthropometric measurements and baseline values of strength and neuromuscular function with age (young or older), sex (men or women), and training type (HL-fast or LL-slow) as the fixed factors. Repeated measure ANOVAs were performed on the measure of fatigability (reduction in MVC force) and the mechanistic measurements (voluntary activation, M-wave, RMS EMG, and involuntary potentiated twitch amplitude) for each exercise protocol separately with age (young and older) and sex (men and women) as the between subject factors. The relative changes in MVC force and the mechanistic measurements from the beginning to the end of the fourth set of exercise were also compared with an individual univariate ANOVA with age, sex, and training protocol as the fixed factors. Simple linear regression analyses were performed between the reductions in MVC force and the mechanistic measurements to identify the primary site of fatigue along the motor pathway. Significance was determined at \( P < 0.05 \), and all statistical analyses were performed with SPSS Statistics software (version 27; IBM, Inc., Chicago, IL). Data are reported as mean ± SD in the text as well as the tables and displayed as mean ± SEM in the figures.

3. Results

Baseline measures of strength and neuromuscular function, such as MVC force (\( P = 0.626, \eta_p^2 = 0.00 \)), involuntary potentiated twitch amplitude (\( P = 0.996, \eta_p^2 = 0.00 \)), and voluntary activation (\( P = 0.641, \eta_p^2 = 0.00 \)), did not differ between the legs performing the two resistance exercise protocols. As a result, the baseline measures reported in Table 1 are the combined values from both legs.

Table 1. Anthropometrics and baseline neuromuscular function of the knee extensor muscles.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Units</th>
<th>Young</th>
<th>Old</th>
<th>P-Value</th>
<th>Age</th>
<th>Sex</th>
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<td></td>
<td></td>
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<td>Women (10)</td>
<td></td>
<td>Men (10)</td>
<td>Women (10)</td>
</tr>
<tr>
<td>Age</td>
<td>yr</td>
<td>21.6 ± 1.3</td>
<td>22.0 ± 0.8</td>
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<td>74.4 ± 4.7</td>
<td>72.6 ± 5.9</td>
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<td>Height</td>
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<td>167.5 ± 5.4</td>
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<td>173.5 ± 5.8</td>
<td>162.8 ± 4.2</td>
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<td></td>
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<tr>
<td>Weight</td>
<td>kg</td>
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<td>BMI</td>
<td>kg·m⁻²</td>
<td>24.5 ± 2.7</td>
<td>22.6 ± 1.1</td>
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<td>Voluntary Isometric MVC</td>
<td>N</td>
<td>670 ± 130</td>
<td>364 ± 77</td>
<td></td>
<td>384 ± 83</td>
<td>258 ± 54</td>
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<td>&lt;0.001</td>
<td></td>
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<td>&lt;0.001</td>
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<tr>
<td>Voluntary Activation</td>
<td>%</td>
<td>92.3 ± 6.0</td>
<td>88.8 ± 8.9</td>
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Electrical Stimulation - Muscle

Twitch Amplitude  N  334 ± 60  218 ± 36  252 ± 51  171 ± 41  <0.001  <0.001
Rate of Force Development  N·s⁻¹  6820 ± 1099  4384 ± 832  5053 ± 1172  3352 ± 1112  <0.001  <0.001
1/2 Relaxation Time  ms  68 ± 17  96 ± 30  89 ± 19  129 ± 39  <0.001  <0.001

Electrical Stimulation - Nerve

VL Mₘₐₓ Amplitude  mV  8.1 ± 1.9  4.2 ± 1.4  3.5 ± 1.1  2.8 ± 1.6  <0.001  <0.001
VM Mₘₐₓ Amplitude  mV  7.4 ± 2.1  5.6 ± 2.1  4.7 ± 2.0  4.3 ± 1.8  <0.001  0.013

The measurements from the maximal voluntary isometric contractions (MVC) and electrical stimulation are the median values obtained from baseline and are combined from both legs. The maximum m-wave (Mₘₐₓ) for the vastus lateralis (VL) and vastus medialis (VM) are the peak-to-peak maximal compound muscle action potential amplitude. Significant main effects of age and sex (P < 0.05) are indicated in bold. The values are the mean ± SD.

3.1. Mechanics during resistance exercise

The mechanical outputs and loads lifted during the LL-slow and HL-fast resistance exercise protocols are presented in Table 2. The 1RM was 89% greater in young (61.0 ± 16.2 kg) compared with older adults (32.2 ± 8.2 kg, P < 0.001, η² = 0.75) and 48% greater in men (55.6 ± 20.4 kg) compared with women (37.5 ± 13.1 kg, P < 0.001, η² = 0.55). Irrespective of age or sex, the load lifted during the HL-fast protocol (36.3 ± 15.9 kg) was ~2.6 times greater than the load lifted during the LL-slow protocol (13.9 ± 5.9 kg, P < 0.001, η² = 0.84). Because eight older participants (6 women and 2 men) were unable to complete eight sequential repetitions with the 80% 1RM load, the relative load used for the HL-fast protocol was ~4% lower in older (76.2 ± 4.6% 1RM) compared with young adults (80.0 ± 0.2% 1RM, P = 0.001, η² = 0.28) but did not differ between men (78.8 ± 3.3% 1RM) and women (77.4 ± 4.1% 1RM, P = 0.164, η² = 0.05).

Table 2. Mechanical outputs and 1 RM for the HL-Fast and LL-slow resistance exercise protocols.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Units</th>
<th>Young</th>
<th>Old</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Men (10)</td>
<td>Women (10)</td>
<td>Men (10)</td>
</tr>
<tr>
<td>1RM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HL-Fast</td>
<td>kg</td>
<td>71.9 ± 12.7</td>
<td>49.3 ± 7.3</td>
<td>38.6 ± 5.7</td>
</tr>
<tr>
<td>LL-Slow</td>
<td>kg</td>
<td>74.3 ± 14.6</td>
<td>48.4 ± 6.7</td>
<td>37.6 ± 5.6</td>
</tr>
<tr>
<td>Absolute Training Load</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HL-Fast</td>
<td>kg</td>
<td>57.6 ± 10.2</td>
<td>39.5 ± 5.9</td>
<td>29.9 ± 4.2</td>
</tr>
<tr>
<td>LL-Slow *</td>
<td>kg</td>
<td>22.1 ± 4.4</td>
<td>14.3 ± 1.9</td>
<td>11.2 ± 1.7</td>
</tr>
<tr>
<td>Relative Training Load</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HL-Fast</td>
<td>% 1RM</td>
<td>80.0 ± 0.1</td>
<td>80.0 ± 0.2</td>
<td>77.6 ± 4.4</td>
</tr>
<tr>
<td>LL-Slow *</td>
<td>% 1RM</td>
<td>29.8 ± 0.3</td>
<td>29.6 ± 0.4</td>
<td>29.6 ± 0.6</td>
</tr>
<tr>
<td>Time for 8 Repetitions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HL-Fast</td>
<td>s</td>
<td>11.9 ± 1.8</td>
<td>16.3 ± 1.7</td>
<td>14.5 ± 3.2</td>
</tr>
<tr>
<td>LL-Slow *</td>
<td>s</td>
<td>95.5 ± 0.4</td>
<td>95.7 ± 0.5</td>
<td>95.4 ± 0.7</td>
</tr>
</tbody>
</table>
As expected, the forces generated during the HL-fast protocol (357 ± 170 N) were ~2.7 times greater than during the LL-slow protocol (133 ± 55 N, P < 0.001, η² = 0.85) and were greater for both exercise protocols in young compared with older adults (P < 0.001, η² = 0.77) and men compared with women (P < 0.001, η² = 0.54). Because the cadence was controlled during the LL-slow protocol, the velocities did not differ between the young (12.8 ± 1.0°/s) and older adults (12.9 ± 0.8°/s, P = 0.568, η² = 0.01) or between the men (12.9 ± 0.9°/s) and women (12.8 ± 0.9°/s, P = 0.889, η² = 0.00). The contraction velocities, however, were ~8.8 times slower during the LL-slow (12.8 ± 0.9°/s) compared with the HL-fast protocol (112.0 ± 36.1°/s, P < 0.001, η² = 0.92). The velocities achieved during the HL-fast protocol were ~32% greater in young (127.2 ± 40.7°/s) compared with older adults (96.7 ± 22.9°/s, P < 0.001, η² = 0.34) and ~48% greater in men (133.5 ± 35.5°/s) compared with women (90.5 ± 21.0°/s, P < 0.001, η² = 0.50). Due to the large differences in velocity between the two exercise protocols, the average time to complete eight repetitions during the LL-slow protocol (95.5 ± 0.6 s) was ~6.4 times longer than the HL-fast protocol (14.9 ± 3.3 s, P < 0.001, η² = 1.00). The longer contractile durations resulted in an ~3.4 times greater impulse per contraction in the LL-slow (1225 ± 6 N·s) compared with HL-fast protocol (357 ± 136 N·s, P < 0.001, η² = 0.84), for both young and old adults, despite the lower forces in the LL-slow protocol (Fig. 2). For the HL-fast protocol, the impulse per contraction was 1.8 times greater in young (459 ± 102 N·s) compared with older adults (255 ± 74 N·s, P < 0.001, η² = 0.59), but due to the longer contractile durations in women, there were no differences between men (372 ± 123 N·s) and women (342 ± 149 N·s, P = 0.293, η² = 0.03). The impulse for the LL-slow protocol was ~1.9 times greater in young (1616 ± 493 N·s) compared with older adults (834 ± 206 N·s, P < 0.001, η² = 0.70) and ~1.5 times greater in men (1462 ± 612 N·s) compared with women (988 ± 340 N·s, P < 0.001, η² = 0.46).
Fig. 2. Contraction-by-contraction absolute power output (A) and impulse (B) from the HL-fast (diamonds) and LL-slow protocols (circles) of young and older adults. Irrespective of age or sex, the absolute power outputs were ~24 times greater during the HL-fast compared with the LL-slow protocol ($P < 0.001$). In contrast, mechanical impulse was ~3.4 times greater per contraction in the LL-slow compared with HL-fast protocol ($P < 0.001$), due to the ~6 times greater contractile durations.

The mechanical power outputs generated during the concentric phase of the HL-fast protocol (262 ± 193 W) were ~24 times greater than during the LL-slow protocol (11 ± 4 W, $P < 0.001$, $\eta^2_p = 0.88$) as a result of both the higher forces and velocities in the HL-fast protocol. The power outputs during the HL-fast protocol were also ~2.9 times greater in young (389 ± 196 W) compared with older adults (135 ± 59 W, $P < 0.001$, $\eta^2_p = 0.80$; Fig. 2) and ~2.4 times greater in men (370 ± 215 W) compared with women (154 ± 75 W, $P < 0.001$, $\eta^2_p = 0.74$). For the LL-slow protocol, the age and sex differences in power output were reduced to ~2 times greater in the young (14 ± 4 W) compared with the older
adults (7 ± 2 W, \( P < 0.001, \eta^2 = 0.73 \)) and ~1.6 times greater in men (13 ± 5 W) compared with women (8 ± 2 W, \( P < 0.001, \eta^2 = 0.56 \)). As intended, the power output did not change across the four sets for the LL-slow protocol (\( P > 0.05 \)). In contrast, the power decreased by the eighth contraction of each set for the HL-fast protocol (\( P < 0.001 \)), and the relative reduction in power by the final contraction of the fourth set was greater in older (43 ± 21%) compared with young adults (28 ± 22%, \( P = 0.021, \eta^2 = 0.14 \)) and greater in women (45 ± 21%) compared with men (26 ± 20%, \( P = 0.004, \eta^2 = 0.20 \)).

3.2. MVC force
3.2.1. Baseline
MVC force of the knee extensor muscles was 61% greater in young (517 ± 187 N) compared with older adults (321 ± 94 N, \( P < 0.001, \eta^2 = 0.56 \)) and 69% greater in men (527 ± 180 N) compared with women (311 ± 85 N, \( P < 0.001, \eta^2 = 0.60 \); Table 1).

3.2.2. Fatigue
Irrespective of age or sex, the MVC force immediately following each set of resistance exercise decreased across the four sets for both the HL-fast (\( P < 0.001, \eta^2 = 0.30 \)) and LL-slow resistant exercise protocols (\( P < 0.001, \eta^2 = 0.55 \); Fig. 3). The relative decrease in MVC force following the fourth set was greater for the LL-slow (20 ± 13%) compared with the HL-fast (12 ± 12%, \( P = 0.004, \eta^2 = 0.11 \)), with no effect of age (\( P = 0.265, \eta^2 = 0.02 \)), sex (\( P = 0.550, \eta^2 = 0.01 \)), or any other interactions (\( P > 0.05 \)).
3.3. Involuntary electrically-evoked twitch amplitude

3.3.1. Baseline
The amplitude of the involuntary potentiated twitch force was \( \sim31\% \) greater in young \((277 \pm 77 \text{ N})\) compared with older adults \( (212 \pm 62 \text{ N}, P < 0.001, \eta^2_p = 0.32) \) and \( \sim51\% \) greater in men \((293 \pm 69 \text{ N})\) compared with women \((194 \pm 45 \text{ N}, P < 0.001, \eta^2_p = 0.53; \text{Table 1})\).

3.3.2. Fatigue
Irrespective of age or sex, the amplitude of the involuntary potentiated twitch of the quadriceps muscles immediately following each set of resistance exercise decreased across the four sets for both the HL-fast \( (P < 0.001, \eta^2_p = 0.17) \) and LL-slow resistant exercise protocols \( (P < 0.001, \eta^2_p = 0.40; \text{Fig. 4})\).
The relative decrease in the twitch amplitude following the fourth set was twofold greater for the LL-slow (14 ± 12%) compared with the HL-fast (7 ± 11%, \( P = 0.014, \eta_p^2 = 0.08 \)), with no effect of age (\( P = 0.329, \eta_p^2 = 0.01 \)), sex (\( P = 0.385, \eta_p^2 = 0.01 \)), or any other interactions (\( P > 0.05 \)). Linear regression analysis revealed that the relative reduction in the involuntary potentiated twitch amplitude was associated with the relative reduction in the MVC (\( r = 0.546, P < 0.001 \)).

**Fig. 4.** Potentiated twitch amplitudes (A) and voluntary activation (B) measured after each set of resistance exercise. The amplitude of the potentiated twitch following each set of resistance exercise decreased across the four sets for both the HL-fast (\( P < 0.05 \)) and LL-slow protocols (\( P < 0.05 \)), whereas voluntary activation decreased across the four sets only in the LL-slow protocol. The relative decrease in the twitch amplitude following the fourth set was twofold greater for the LL-slow compared with the HL-fast (\( P < 0.05 \)). In contrast, the voluntary activation levels after the fourth set of exercise did not differ between the protocols (\( P > 0.05 \)). Linear regression analysis revealed that the relative reduction in MVC was associated with both the relative reduction in the potentiated twitch amplitude (\( r = 0.546, P < 0.05 \)) and the reduction in voluntary activation (\( r = 0.356, P < 0.05 \)). *Significantly different from HL-fast (\( P < 0.05 \)). Values are the mean ± SEM.

### 3.4. Voluntary activation

#### 3.4.1. Baseline

Voluntary activation of the knee extensor muscles did not differ in older (91 ± 5%) compared with young adults (91 ± 8%, \( P = 0.692, \eta_p^2 = 0.00 \)) or in women (90 ± 7%) compared with men (92 ± 5%, \( P = 0.187, \eta_p^2 = 0.03 \); Table 1).

#### 3.4.2. Fatigue

Irrespective of age or sex, the ability to voluntarily activate the muscle immediately following each set of resistance exercise decreased across the four sets for the LL-slow (\( P < 0.001, \eta_p^2 = 0.17 \)) but did not change for the HL-fast protocol (\( P = 0.218, \eta_p^2 = 0.04 \), Fig. 4). However, the voluntary activation levels after the fourth set did not differ between LL-slow (86 ± 8%) and HL-fast protocols (88 ± 8%, \( P = 0.216, \eta_p^2 = 0.02 \)) nor did the percent change in voluntary activation from baseline to the end of the fourth set...
Linear regression analyses revealed that the reduction in voluntary activation was associated with the relative reduction in the MVC \((r = 0.356, P = 0.001)\) but was not associated with the relative reduction in the involuntary potentiated twitch amplitude \((r = 0.088, P = 0.443)\).

### 3.5. M-wave amplitude \((M_{\text{max}})\)

#### 3.5.1. Baseline

The peak-to-peak amplitude of the m-wave \((M_{\text{max}})\) for the VL was lower in the older \((3.1 \pm 1.4 \text{ mV})\) compared with young adults \((6.2 \pm 2.6 \text{ mV}, P < 0.001, \eta_{p}^2 = 0.52)\) and in women \((3.5 \pm 1.7 \text{ mV})\) compared with men \((5.8 \pm 2.8 \text{ mV}, P < 0.001, \eta_{p}^2 = 0.38; \text{Table } 1)\). Similarly, \(M_{\text{max}}\) for the VM was lower in the older \((4.5 \pm 1.9 \text{ mV})\) compared with young adults \((6.5 \pm 2.3 \text{ mV}, P < 0.001, \eta_{p}^2 = 0.20)\) and in women \((4.9 \pm 2.0 \text{ mV})\) compared with men \((6.1 \pm 2.5 \text{ mV}, P = 0.015, \eta_{p}^2 = 0.08)\).

#### 3.5.2. Fatigue

\(M_{\text{max}}\) did not change immediately following the fourth set of exercise compared with baseline for the LL-slow \((VL, P = 0.392, \eta_{p}^2 = 0.02; VM, P = 0.242, \eta_{p}^2 = 0.04)\) or HL-fast protocols \((VL, P = 0.663, \eta_{p}^2 = 0.01; VM, P = 0.255, \eta_{p}^2 = 0.04)\).

### 3.6. EMG amplitude (RMS)

The RMS EMG for both the VM and VL increased across the eight repetitions in all four sets for both the HL-fast and the LL-slow protocols \((P < 0.05; \text{Fig. } 5)\). The increase in RMS EMG during the exercise was greater for the young compared with the older adults in all four sets for both protocols \((P < 0.05)\) and was greater in the LL-slow compared with the HL-fast irrespective of age or sex \((P < 0.05)\). The RMS EMG expressed relative to the MVC \((\% \text{ MVC})\) remained more than 50% lower in all four sets for the LL-slow compared with the HL-fast protocol \((P < 0.05)\).

### Fig. 5

Contraction-by-contraction RMS EMG from the vastus lateralis expressed relative to the RMS EMG from the first contraction in set 1 (A) and from the MVC (2). The EMG amplitude increased across all four sets for the HL-fast and LL-slow protocols for both young and older adults \((P < 0.05)\). The increase in RMS EMG during the
resistance exercise was greater for the young compared with the older adults for both protocols \(P < 0.05\), and greater in the LL-slow compared with the HL-fast irrespective of age or sex \(P < 0.05\). The RMS EMG expressed relative to the MVC remained over 50% lower in the LL-slow compared with the HL-fast protocol \(P < 0.05\). Values are the mean ± SEM.

4. Discussion

This study determined whether there were differences in fatigability of the knee extensor muscles between a low-load, slow resistance exercise protocol (LL-slow) and a high-load protocol with contractions performed as fast as possible (HL-fast) in young and older men and women. The novel findings were that the LL-slow protocol induced a greater reduction in maximal isometric force (i.e., greater fatigability) than the HL-fast (20% vs. 12% reduction) for all groups. There was a concomitant reduction in the electrically evoked twitch amplitude that was twice as large for the LL-slow than the HL-fast protocol, and a significant association between fatigability and the reduction in twitch amplitude for the LL-slow and HL-fast. However, there was no reduction in M-wave amplitude \(M_{\text{max}}\) and a small reduction in voluntary activation, but only for the LL-slow protocol (5%). Collectively, the greater fatigability of the LL-slow protocol was primarily due to mechanisms within the muscle impairing contractile function of the knee extensor muscles, which may have also indirectly induced inhibitory feedback to the central nervous system and reduced some activation. Furthermore, in contrast to our hypothesis, there were no age-differences in fatigability of the MVC after the HL-fast protocol or the LL-slow protocol for men or women, although the older adults showed greater reductions in power during the HL-fast protocol.

A novel finding was the low-load slow contraction protocol (LL-slow) induced almost twice the fatigue of the MVC than the high-load protocol with contractions performed as fast as possible (HL-fast). Despite the focus on the potential for fatigability to induce protein synthesis in response to the LL-slow protocol in young men (Burd et al., 2012), no previous study has 1) quantified the magnitude of fatigability in response to this protocol, 2) compared the fatigability to a more traditional high-load protocol, or 3) identified the contribution of neural and muscular mechanisms to fatigability in these resistance exercise protocols. We matched the number of repetitions between the two protocols (4 sets of 8 repetitions), which resulted in ~63% lower forces and total exercise volume (load x repetitions) in the LL-slow compared with HL-fast exercise protocol; yet, the LL-slow still induced greater reductions in MVC (Fig. 3). The greater fatigability in the LL-slow protocol is most likely explained by both the lack of rest between sequential contractions and the ~6-fold greater time the muscle was under tension (Table 2, Fig. 2). Accordingly, impulse (product of the force and duration of the concentric and eccentric contractions) was 3.4 times greater per contraction cycle in the LL-slow than HL-fast protocol for all groups, despite a lower load lifted during the LL-slow protocol.

The primary mechanism contributing to the differences in fatigability between the protocols was from factors originating within the muscle. This was evidenced by a twofold greater reduction in the involuntary electrically evoked twitch amplitude for the LL-slow (14%) compared with the HL-fast protocol (7%), that was associated with the reduction in MVC force (Fig. 4). Although the specific cellular mechanisms cannot be identified by changes in the involuntary twitch properties, the leading mechanism thought to be responsible for fatigue within the muscle is the accumulation of metabolites, primarily acidosis \(H^+\) and inorganic phosphate \(P_i\), which directly inhibit both cross-bridge function
and excitation–contraction coupling (Debold et al., 2016; Kent-Braun et al., 2012; Sundberg and Fitts, 2019). Indeed, it was recently observed that fatigability during a dynamic knee extension exercise of young and older adults was closely associated with the accumulation of H\(^+\) and P\(_i\) (Sundberg et al., 2019). Thus, it is plausible that the lack of relaxation between contractions coupled with the ~6-fold greater time the muscle was active in the LL-slow compared with the HL-fast protocol reduced the opportunity for blood flow and O\(_2\) delivery to the working muscle resulting in a greater accumulation of metabolites that disrupted contractile function with the muscle.

Voluntary activation, measured with the interpolated twitch technique, also declined after the LL-slow protocol, whereas no reduction in voluntary activation occurred in response to the HL-fast protocol. The reduction in MVC was associated with the reduction in voluntary activation suggesting that some of the increased fatigability for the LL-slow protocol was explained by a reduced ability of the nervous system to voluntarily activate the muscle. Notably, the reduction in voluntary activation was only evident in the LL-slow protocol that also exhibited the greatest reduction in both MVC force (fatigability) and the involuntary twitch amplitude. A loss of neural drive during a fatiguing task can result from decreased descending drive and/or increased inhibition of motor pathways (Taylor et al., 2016). The decline in volitional drive to the muscle with the LL-slow protocol could have been due to the increased activation of group III and IV afferents that occurs in response to metabolite accumulation during fatiguing exercise (Amann et al., 2009; Gandevia et al., 1996; Hilty et al., 2011; Kennedy et al., 2015; Taylor et al., 1996). This small afferent (group III/IV) feedback can directly or indirectly decrease the output from spinal motoneurons and reduce motor neuron discharge rates which may lead to reduced voluntary activation (e.g. (Bigland-Ritchie et al., 1986; Duchateau and Hainaut, 1993; Woods et al., 1987)). The lack of association in our data between the reduction in the twitch amplitude and voluntary activation \((r = 0.088)\), however, suggests that the group III/IV afferents may have been acting to reduce activation in response to ischemia and/or pain (Taylor et al., 2016), rather than via the metabolites that directly interfere with contractile function.

The global EMG activity increased throughout the four sets of contractions for both protocols with a larger relative increase from baseline for the LL-slow than the HL-fast protocol. EMG activity will increase during a submaximal fatiguing task, primarily due to increased motor unit recruitment and a change in discharge rates of the active motor units, as a compensatory mechanism used by the nervous system to maintain a constant load or force output as the muscle fibers become fatigued (Enoka and Duchateau, 2017; Riley et al., 2008). The EMG activity (relative to MVC) was higher at the start of the HL-fast protocol compared with the LL-slow protocol (Fig. 5) because of the requirement to recruit most of the motor unit pool to lift the high loads. Thus, the increase in EMG for the HL-fast protocol was likely due primarily to an increase in motor unit discharge rate, whereas the LL-slow task due to both motor unit recruitment and a change in discharge rates.

Despite significant fatigue at the end of the fourth set of the LL-slow protocol, the EMG activity was only ~50% of MVC, and for the HL-fast protocol considerably higher (>100%). Consistent with our findings, low-force sustained contractions also have low EMG (%MVC) even at task failure (Fuglevand et al., 1993; Yoon et al., 2008). The lower activation at the end of the protocol was not due to failed neuromuscular transmission across the neuromuscular junction, because the compound muscle action potential \((M_{\text{max}})\) was not different between tasks at baseline and remained similar after both the
LL-slow and HL-fast protocols. Thus, the lower EMG for the LL-slow protocol may have occurred because 1) the task was not performed to failure and did not require all motor units to be recruited and discharging maximally or 2) an inability to activate some motor units at the same rate either from decreased descending drive or inhibitory feedback that lowered the activation of the motor neuron pool.

5. Minimal age and sex differences in fatigability

There was no sex difference in fatigability or the change in voluntary activation and potentiated twitch. Baseline $M_{\text{max}}$ was lower in the women than the men, and older adults compared with the young, which is consistent with previous findings for the quadriceps (Piasecki et al., 2016; Sundberg et al., 2018b). As expected, women had slower contractile properties than the men (RFD and relaxation times) for both age groups at baseline (Senefeld et al., 2018; Sundberg et al., 2018b), although these differences did not result in a sex difference in fatigability of the MVC in response to the LL-slow or HL-fast resistance protocols. The lack of difference in fatigability between the men and women for both age groups is consistent with the minimal sex differences in fatigability observed for dynamic contraction tasks (Hunter, 2016b). However, of note, when the power output of the concentric phase of the HL-fast protocol was analyzed, the women showed greater fatigability than the men, despite no difference in the reduction in MVC. This was likely because the women slowed more than the men in both age groups during the concentric phase of the HL-Fast protocol. Whether this sex difference in fatigability would remain if the durations of the concentric and eccentric phase of the contractions were controlled is unknown and worth further investigation.

As expected, there was a minimal age difference in fatigability for the LL-slow protocol. Old adults are typically less fatigable than young (more fatigue resistant) for isometric contractions, but this diminishes even during slow contractions at ~60 deg./s (Callahan et al., 2009; Yoon et al., 2013). In contrast to our expectations, we found no age difference in the decline in MVC for the HL-protocol. Typically, the fatigability of the knee extensors of older adults is larger for fast-velocity contractions than young adults (Callahan and Kent-Braun, 2011; Senefeld et al., 2017; Sundberg et al., 2018b), with minimal differences in moderate- to-slow contractions that are less than ~270°/s when the velocity is held constant (Callahan et al., 2009; Callahan and Kent-Braun, 2011). Our protocols held the load constant during each protocol as typically occurs with resistance training and during the HL-fast protocol the velocity varied so that the old adults contracted more slowly than the young (Table 2). The contraction velocities achieved during the HL-fast protocol were 30% faster for the young compared with the older adults (131°/s vs 101°/s respectively). Regardless, analysis of the concentric phase of the HL-fast protocol showed the relative reduction in power for the old adults was greater than the young adults and is consistent with the age difference in fatigability of fast-velocity concentric protocols (Callahan and Kent-Braun, 2011; Senefeld et al., 2017; Sundberg et al., 2018b). Both our fatiguing protocols however, involved concentric and eccentric contractions and the timing of contractions was not controlled in the HL-Fast protocol. Furthermore, fatigability as a loss of power could not be compared between the protocols because the velocity was held constant for the LL-slow protocol. Thus, despite the age-related differences in power during the concentric phase of the HL-fast protocol, the reduction in MVC did not differ between the young and old adults.
The age differences in contraction velocity during the HL-fast protocol across both sexes likely reflect a larger relative area of fibers expressing the fast myosin heavy chain isoforms in the older muscle compared with the young (Hunter et al., 1999; Nilwik et al., 2013; Sundberg et al., 2018a). The slow velocities for both age groups were due to the high loads lifted, and while the initial relative load had to be lowered from 80% 1RM in some older adults (~4% lower on average, Table 2), it probably did not influence the age difference in fatigability. Practically, these results highlight that a target of eight contractions for an 80% 1RM resistance training protocol can be achieved for young men and women but is not realistic for some older adults.

6. Conclusion
The knee extensor muscles of young and older men and women were more fatigable (larger reductions in MVC force) after a single session of low-load (LL-slow) compared with high-load resistance exercise (HL-fast). The greater fatigability in response to the LL-slow protocol was primarily attributed to disruptions in contractile function, with small contributions from a reduced ability of the nervous system to voluntarily activate the muscle. The clinical and practical relevance of these findings is considerable and prompts studies into whether low-load resistance exercise training can elicit similar neuromuscular adaptations to high-load training for older adults aiming to improve fatigability and offset age-related declines in muscle strength and size.

CRediT authorship contribution statement
J.D.D., C.W.S., S.K.H. conceived and designed the experiments; J.D.D. and M.K. performed the experiments; J.D.D. and C.W.S. analyzed the data; J.D.D., C.W.S., and S.K.H. interpreted the results of the experiments. J.D.D. and C.W.S. prepared the figures and tables. J.D.D., C.W.S and S.K.H drafted, edited, and revised the manuscript. All authors approved the final version of the manuscript and agree to be accountable for all the aspects of the work.

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Declaration of competing interest
No conflicts of interests, financial or otherwise, are declared by the authors.

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