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Muscle power failure in mobility-limited older adults: preserved single fiber function despite lower whole muscle size, quality and rate of neuromuscular activation

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Abstract

This study investigated the physiological and gender determinants of the age-related loss of muscle power in 31 healthy middle-aged adults (aged 40–55 years), 28 healthy older adults (70–85 years) and 34 mobility-limited older adults (70–85 years). We hypothesized that leg extensor muscle power would be significantly lower in mobility-limited elders relative to both healthy groups and sought to characterize the physiological mechanisms associated with the reduction of muscle power with aging. Computed tomography was utilized to assess mid-thigh body composition and calculate specific muscle power and strength. Surface electromyography was used to assess rate of neuromuscular activation and muscle biopsies were taken to evaluate single muscle fiber contractile properties. Peak muscle power, strength, muscle cross-sectional area, specific muscle power and rate of neuromuscular activation were significantly lower among mobility-limited elders compared to both healthy groups ($P \leq 0.05$). Mobility-limited older participants had greater deposits of intermuscular adipose tissue ($P < 0.001$). Single fiber contractile properties of type I and type IIA muscle fibers were preserved in mobility-limited elders relative to both healthy groups. Male gender was associated with greater decrements in peak and specific muscle power among mobility-limited participants. Impairments in the rate of neuromuscular activation and concomitant reductions in muscle quality are important physiological mechanisms contributing to muscle power deficits and mobility limitations. The dissociation between age-related changes at the whole muscle and single fiber level suggest that, even among older adults with overt mobility problems, contractile properties of surviving muscle fibers are preserved in an attempt to maintain overall muscle function.

Keywords

Aging; Mobility; Muscle power; Single muscle fiber properties

Introduction

Lower extremity muscle power, the product of dynamic muscular force and contraction velocity, declines earlier and more rapidly with advancing age compared to muscle strength (Metter et al. 1997; Skelton et al. 1994). Peak muscle power has also emerged as an independent and potent predictor of physical performance, functional mobility, and risk of falling in older adults (Bassey et al. 1992; Bean et al. 2002; Kuo et al. 2006; Skelton et al. 1994; Suzuki et al. 2001). Despite this evidence, limited knowledge exists on the major physiological determinants of lower extremity muscle power with advancing age. A more definitive understanding of these mechanisms is necessary and may provide more discriminant information on the specific factors that mediate mobility limitations in older persons.

Similar to the age-related loss of muscle strength, deficits in muscle power production are related to the consequences of sarcopenia (Evans 1995). The progressive muscle atrophy

with aging is associated with a loss of overall muscle power and changes in the force and power generation of the remaining muscle fibers (Brooks and Faulkner 1994). While many cross-sectional studies have suggested that the loss of muscle performance is a direct result of the reduction in muscle mass (Doherty 2003; Frontera et al. 1991), several longitudinal studies have indicated a dissociation between the loss of muscle mass and the corresponding reduction in muscle performance among older adults (Delmonico et al. 2009; Goodpaster et al. 2006; Hughes et al. 2001). In healthy older adults, changes in muscle mass explained only 5% of the corresponding reduction in muscle strength in older men and women after 10 years of follow-up (Hughes et al. 2001). Similarly, compared to the corresponding decline in muscle mass, a threefold greater loss of muscle strength was observed in high-functioning older men and women after a 3 year follow-up period. This dissociation between the magnitude of muscle loss and the corresponding reduction in muscle performance with advancing age indicate that several additional physiological mechanisms that accompany the phenomenon of sarcopenia may specifically influence muscle function and power production in older adults. Recent evidence has shown that an increased adipose tissue accumulation around and between muscle fibers concomitant with a reduced muscle cross-sectional area (CSA) occurs with aging, and this skeletal muscle attenuation is inversely associated with muscle performance in older adults (Delmonico et al. 2009; Goodpaster et al. 2001). Marked age-related changes in the nervous system may also have a substantial role in the age-associated decline in muscle power generation (Aagaard et al. 2010). These include loss of motor neurons and concomitant remodeling of motor units through collateral reinnervation (Lexell 1997), impairment of neuromuscular activation observed as decreased maximal motor unit firing rates (Kamen et al. 1995) and uncoordinated patterns of intermuscular neural activation (Hakkinen et al. 1998).

In addition, changes in individual muscle fiber composition and intrinsic contractile properties may influence the decline in muscle power among older adults. Cross-sectional observations suggest that reductions in muscle power may be related to muscle fiber composition and, in particular, the selective atrophy of type II muscle fibers with aging (Larsson et al. 1979; Martin et al. 2000). Specific changes in the intrinsic ability of aged muscle to generate force have also been observed. A decreased specific force (force normalized per CSA) and unloaded shortening velocity in type I and IIA fibers in older males compared to young controls have been previously reported (Frontera et al. 2000b; Larsson et al. 1979). Conversely, recent longitudinal evidence has demonstrated that despite reductions in whole muscle CSA, single muscle fiber contractile function is preserved with advancing age (Frontera et al. 2008). Level of mobility, physical activity and immobilization have also been shown to have a significant influence on the contractile properties of individual muscle fibers among older adults (D'Antona et al. 2003, 2007). Further evaluation of the relationships between the intrinsic force and shortening velocity characteristics of aging skeletal muscle and their associations with whole muscle peak power is also warranted.

Important gender-related differences in lower extremity muscle power have also been reported. Across all age groups, females produce significantly lower muscle power compared to males (Bassey et al. 1992; Caserotti et al. 2001; Metter et al. 1997). In addition, significant gender differences in the magnitude of muscle power loss with advancing age have been identified. Among 65- to 85-year-old males and females, maximal leg extension power was found to deteriorate at a rate of 3% per year in men and 1.7% per year in women (Skelton et al. 1994). Several studies have reported gender differences in the physiological domains that may directly influence muscle power loss with aging. Divergent changes in muscle mass (Doherty 2001; Goodpaster et al. 2006), impairments in muscle contraction velocity (Caserotti et al. 2001; Petrella et al. 2005), alterations in neuromuscular function (Doherty 2001; Kent-Braun and Ng 1999) and differences in single muscle fiber

characteristics have been identified between older men and women with advancing age (Frontera et al. 2000b). However, a more integrated understanding of these underlying physiological mechanisms and their contribution to the gender-specific differences in muscle power is also necessary.

The purpose of this study was to provide a comprehensive examination of the major age-related physiological mechanisms that contribute to peak muscle power production among three distinct populations: healthy middle-aged adults, healthy older adults and older adults with mobility limitations. Given the strong association between measures of functional performance and leg extensor power output, we hypothesized that leg muscle power would be significantly lower in mobility-limited older adults relative to both healthy groups. As previous epidemiologic evidence has shown that muscle power is largely preserved until approximately age 40 years (Metter et al. 1997), we employed this experimental design to investigate differences in muscle power generation within a more focused age range that would provide greater specificity to our potential findings. To delineate the major physiological mechanisms contributing to muscle power deficits with advancing age, we conducted a comparative assessment of lower extremity muscle power, strength, muscle size and quality, rate of neuromuscular activation and also evaluated intrinsic single muscle fiber contractile properties. In addition, because of the significant gender differences that exist for leg muscle power, we also characterized the influence of gender on the determinants of lower body power production within these populations.

Materials and methods

Study participants

This study employed a cross-sectional design and participants were recruited into three experimental groups: healthy middle-aged adults (aged 40–55 years), healthy older adults (aged 70–85 years) and older adults with mobility limitations (aged 70–85 years). Subjects were recruited from the Greater Boston area through local advertisements, community newsletters, and were initially screened for eligibility in-person or by telephone.

Participants considered for either healthy group were community dwelling, not taking any prescribed medications, and scored between 10 and 12 on the Short Physical Performance Battery test (SPPB) (Guralnik et al. 1994, 1995, 2000). Older mobility-limited subjects were community-dwelling and demonstrated objective functional limitations as evidenced by an SPPB score ≤9. The SPPB characterizes lower extremity function by assessing gait speed, balance and strength and has been validated in large-scale epidemiologic studies. The SPPB classifications used in the current investigation were based on a series of performance-based normative data developed from previous community-based population studies (Guralnik et al. 1994, 1995, 2000). In these studies, SPPB scores of ≤9, when compared to the best performing reference range of scores between 10 and 12, were indicative of significant mobility-deficits and highly predictive of subsequent disability, institutionalization and mortality (Guralnik et al. 2000).

After meeting the initial study eligibility criteria, all eligible subjects completed a medical history questionnaire and underwent a physical examination and medical screening by the study physician. Subjects were excluded from participation if they had a body mass index (BMI) less than 19 kg/m^2 or greater than 33 kg/m^2, acute or terminal illness, myocardial infarction or upper/lower extremity fracture in the previous 6 months, unstable cardiovascular disease or other medical condition, upper or lower extremity amputation, cognitive impairment according to the Folstein Mini-Mental State Examination (MMSE) (score < 23) (Folstein et al. 1975), current participation or participation during the previous 6 months in any regular endurance or resistance training exercise (>3×/week), or

unwillingness to complete the study requirements. Other exclusion criteria included uncontrolled hypertension (>150/90 mmHg), the presence of neuromuscular disease or medications affecting neuromuscular function, anti-coagulation therapy, hormone replacement therapy, and women who were pregnant, planning to become pregnant, or breastfeeding. Participants who presented with lower extremity joint pain were also excluded. Subjects meeting the study entry criteria and given medical clearance by the study physician and written approval from their primary care physician were deemed eligible for participation. Prior to enrollment all volunteers signed an informed consent form and were made aware of all potential risks associated with the study procedures. This study was approved by the Tufts Medical Center and Tufts University Health Sciences Institutional Review Board.

Lower extremity muscle strength, power and rate of neuromuscular activation

Strength and power testing took place on two occasions, at the same time of day separated by approximately 1 week. Each participant was given the opportunity to familiarize themselves with the testing equipment through the use of a visual demonstration and practice at low resistances. Participants were seated on the bilateral leg press apparatus with knees flexed to 90° and hips flexed to approximately 110° (Leg Press A420, Keiser Corporation, Fresno, CA). Knee angle was measured using an electrogoniometer (ADInstruments, Colorado Springs, CO). Force, position, and velocity of each piston were sampled at 400 Hz and saved to disk for offline analysis. Using software provided by the manufacturer, these data were then converted to force, position and velocity at the footplate (Software Release 7.8, Keiser Corporation, Fresno, CA).

Leg extensor muscle strength was quantitatively assessed using the one-repetition maximum (1RM) technique and was defined as the maximum load that could be moved only once throughout the full range of motion (ROM) while maintaining proper form (Callahan et al. 2007). Subjects were instructed to perform several warm-up repetitions at minimal resistance to familiarize themselves with the apparatus. Each participant's ROM was determined during performance of a minimally loaded repetition prior to each test. An ultrasonic system measuring position, and therefore relative motion, aided examiners in establishing a subject's ROM by observing the excursion of a lighted bar on the output screen during performance of the measure with minimal resistance. Starting at a relatively low level, the examiner progressively increased the resistance after each successful repetition until the participant could no longer move the lever arm one time through their full ROM (optimally within 6–8 repetitions). Subjects performed the concentric phase, maintained full extension, and performed the eccentric phase of each repetition over approximately 2, 1, and 2 s, respectively. To aid in accurate establishment of the 1RM, the subject's self-perceived level of exertion was also assessed after each successful repetition using the Borg scale (Borg 1970). If the subject's rating was $\leq$15, a rest period of 30–60 s was provided between repetitions. A rest period of 2 min was provided if the subject's rating was $\geq$15.

After measurement of the 1RM, assessment of leg extensor peak muscle power was made after a 5 min rest period. Performance of this multiple attempt peak power test has been previously described and validated (Callahan et al. 2007). Briefly, each participant was instructed to complete a total of five repetitions each separated by 30 s as quickly as possible through their full ROM at 70% of the 1RM. The highest measured power output was recorded as the leg extensor peak power. From the two data collection sessions, the highest value for 1RM and peak power was used as the baseline value.

Muscle activation of the vastus lateralis was assessed by surface electromyography (EMG) using a commercially available data acquisition system (Delsys Bagnoli-8, Delsys, Boston,

MA) by placing single differential surface electrodes (Delsys 2.1, Delsys, Boston, MA) with 1 cm inter-electrode distance over the muscle belly. We have reported these methods previously (Clark et al. 2011). Muscle activation was quantified on the second baseline visit during the multiple attempt peak power test performed at 70% of 1RM. Participants also exerted an isometric maximal voluntary effort with their legs constrained to the starting position of the leg press. Vastus lateralis EMG was recorded at a sampling rate of 1 kHz using a Powerlab/16SP A/D system and Chart software (ADInstruments, Colorado Springs, CO) and data were analysed using a custom analysis program created in MATLAB (version 7.0, The Mathworks, Natick, MA). The EMG was de-biased and then filtered using a zero-phase lag first-order Butterworth band-pass filter (10–200 Hz). EMG were then normalized by expressing EMG amplitude relative to peak EMG acquired during maximal voluntary isometric contraction (defined by the root-mean-square average over the 100 ms window with greatest activation magnitude). The measure of neuromuscular activation evaluated in this study was the rate of vastus lateralis activation. For each separate repetition, the derivative of the normalized EMG signal was calculated to indicate the change in activation as a function of time. Rate of neuromuscular activation was then calculated as the mean of the derivative between the onset of activation (determined as resting EMG amplitude plus three standard deviations) and the onset of movement. This analysis approach standardizes the units of rate of activation to "percent of maximal voluntary EMG per millisecond" in order to facilitate comparison across participants and study groups. For each subject, the rate of activation was averaged across trials 2, 3 and 4. Trial 1 was considered a practice trial while trial 5 was eliminated due to the potential effects of short-term fatigue. A composite analysis (rate of neuromuscular activation from the vastus lateralis, vastus medialis and rectus femoris muscles) has been previously reported from the current study cohort in an investigation that quantified the specific associations between the rate of lower limb neuromuscular activation with leg power and measures of functional performance (Clark et al. 2011). In this investigation, we report the EMG data from the vastus lateralis muscle for each study group and examine gender differences across participants.

Computed tomography

A computed tomography (CT) scan of the nondominant thigh was performed at the midpoint of the femur for each subject. The length of the femur was determined from a coronal scout image as the distance between the intercondylar notch and the trochanteric notch. Scans were obtained using a Siemens Somotom Scanner (Erlangen, Germany) operating at 120 kV and 100 mA, with slice width of 10 mm and a scanning time of 1 s. All scans were analyzed by a single investigator in a blinded manner using SliceOmatic v4.2 software (Montreal, Canada). Images were reconstructed on a 512 × 512 matrix with a 25-cm field of view. From the images, the CSAs for normal density muscle, low density muscle and intermuscular adipose tissue were measured using manual tracing. Muscle CSA was measured in the range of 0–100 Hounsfield units (HU) and calculated as the sum of low-density muscle and normal-density muscle CSA. Adipose tissue areas were measured in the range of −190 to −30 HU. Intermuscular adipose tissue was defined as adipose tissue lying between and among muscle groups. These methods have been previously described (Goodpaster et al. 2001; Kelley et al. 1991).

Specific muscle power and strength

The absolute leg extensor peak power and 1RM values obtained were adjusted for total muscle CSA to yield estimates of specific peak power (W/cm^2) and specific leg extensor strength (N/cm^2) (Goodpaster et al. 2001; Reid et al. 2008).

Muscle biopsy and single muscle fiber experiments

Muscle biopsies were taken from the vastus lateralis muscle at the level of the CT scan using a 5-mm Duchenne biopsy needle and suction (Bergström 1962; Evans et al. 1982). The specimen was placed in relaxing solution (see below) at 4°C within 1–2 min of being obtained. Bundles of 30 fiber segments were dissected free from the samples and then tied with surgical silk to glass capillary tubes at slightly stretched lengths. The fiber segments were chemically skinned for 24 h in relaxing solution containing 50% (vol/vol) glycerol at 4°C and were subsequently stored at −20°C for up to 4 weeks before use.

A detailed explanation of the general methods used for the single muscle fiber experiments in this study has been published by others (Larsson and Moss 1993). Briefly, on the day of an experiment, fiber segments were placed for 30 min in relaxing solution containing 0.5% Brij-58 (poly-oxyethylene 20 cetyl ether; Sigma, St. Louis, MO) before mounting in an experimental apparatus, similar to that described previously (Moss 1979). A fiber segment length of 1–2 mm was left exposed to the solution between connectors leading to a force transducer (model 400A; Aurora Scientific, Aurora, ON, Canada) and a DC torque motor (model 308B; Aurora Scientific). The apparatus was mounted on the stage of an inverted microscope (Olympus IX70, Tokyo, Japan). While the fiber segments were in relaxing solution, sarcomere length (SL) was set to 2.75–2.85 μm by adjusting the overall segment length.

The sarcomere length, the segment diameter, and the length of segment between the connectors were measured with an image analysis system (Image-Pro Plus, Media Cybernetics, Silver Spring, MD). Fiber depth was measured by recording the vertical displacement of the microscope nosepiece while focusing on the top and bottom surfaces of the fiber. The focusing control of the microscope was used as a micrometer. In our hands the coefficient of variation for three measurements done by the same observer is 0.5% for diameter and 3.7% for depth. Fiber CSA was calculated from the diameter and depth, assuming an elliptical circumference. Maximum force (P_0) was adjusted for fiber CSA after adjusting fiber area for the 20% swelling that is known to occur during skinning (Godt and Maughan 1977; Moss 1979).

Relaxing and activating solutions contained (in mM) 4 MgATP, 1 free Mg^{2+}, 20 imidazole, 7 EGTA, 14.5 creatine phosphate, and KCl to adjust the ionic strength to 180 mM. The pH was adjusted to 7.0. The concentrations of free Ca^{2+} were 10^{-9} M (relaxing solution) and $10^{-4.5}$ M (maximum activating solution) and are expressed as pCa (−log [Ca^{2+}]). Apparent stability constants for Ca^{2+}-EGTA were corrected for temperature (15°C) and ionic strength (180 mM) (Fabiato 1988). A computer program was used to calculate the concentrations of each metal, ligand, and metal–ligand complex (Fabiato 1988).

Immediately preceding each activation, the fiber was immersed for 10–20 s in a solution with a reduced Ca^{2+}-EGTA buffering capacity. This solution was identical to the relaxing solution except that EGTA was reduced to 0.5 mM, which resulted in a faster attainment of steady tension during subsequent activation. Maximum active force (P_0) was calculated as the difference between the total force in activating solution (pCa 4.5) and the resting tension measured in the same segment while in the relaxing solution. All contractile measurements were carried out at 15°C. Fibers with visible tears and fibers demonstrating a loss of force >10% of the baseline value were not used for the analysis. Maximum unloaded shortening velocity (V_0) was measured using the slack test (Edman 1979).

After mechanical measurements, each fiber was placed in SDS sample buffer in a plastic microfuge tube and stored at –20°C for up to 1 week or at –80°C if the gels were to be run later. The myosin heavy chain (MyHC) composition of single fibers was determined by

SDS-PAGE (Laemmli 1970). The acrylamide concentration was 4% (wt/vol) in the stacking gel and 6% in the running gel, and the gel matrix included 30% glycerol. Sample loads were kept small (equivalent to ~0.05 mm of fiber segment) to improve the resolution of the MyHC bands (types I, IIA, IIB). The conditions in which the SDS-PAGE were run include constant current (24 mA) for 5.5 h. Proteins were identified using a combination of human myosins from vastus lateralis muscles and from reports in the literature (Larsson and Moss 1993).

Statistical analysis

Data analysis was conducted using SAS statistical software (Version 9.2, SAS Institute Inc., Cary, NC) and all variables were examined for normality both graphically and statistically. A log transformation was used for those variables where normality did not hold. A two-way analysis of variance test was used to compare differences between the three study groups and gender groups. For each outcome, the models included gender, study group and their interaction as covariates. An analysis of whether the differences among groups were equivalent for men and women was then performed through regression models incorporating the interaction term between gender and group. A test for the interaction term provided a measure of whether men and women differed within their differences across groups. If the interaction term was significant, differences between the gender groups were estimated at each group level; otherwise an overall gender effect was estimated. Pearson correlations were used to assess the relationships between intrinsic muscle fiber properties and whole muscle parameters in males and females. Data are presented as mean ± SD and statistical significance was accepted at $P \leq 0.05$.

Results

General characteristics

A total of 93 (46 males) subjects were enrolled into the respective study groups: healthy middle-aged ($n = 31$, 14 males); healthy older ($n = 28$, 16 males); mobility-limited older ($n = 34$, 16 males). Descriptive characteristics are displayed in Table 1. Age was significantly greater among mobility-limited older participants (77.8 ± 5 years) compared to both healthy middle-aged (47.2 ± 5 years, $P < 0.001$) and healthy older participants (74 ± 4 years, $P = 0.009$). Mobility-limited individuals had significantly lower SPPB scores (7.94 ± 1.3) compared to healthy middle-aged (11.7 ± 0.5) and healthy older subjects (11.0 ± 0.9), ($P < 0.001$). No significant group × gender interaction was evident for any of the baseline general characteristics ($P \geq 0.28$). A significant overall gender effect was found for BMI, with males having consistently higher BMI values ($P = 0.01$).

Muscle power and strength

Mobility-limited older participants had significantly lower values for leg extensor peak power, contraction velocity, and 1RM strength compared to both healthy groups ($P < 0.001$) (Table 2). Healthy older adults also had significantly lower measures of peak power ($P < 0.001$), contraction velocity ($P = 0.04$) and 1RM strength ($P < 0.001$) compared to healthy middle-aged subjects. There was a significant group × gender interaction for leg extensor peak power ($P < 0.001$). The differences between males and females for peak power were 37.9% in healthy middle-aged ($P < 0.001$), 59.8% ($P < 0.001$) in healthy older and 37.5% ($P < 0.001$) in mobility-limited older participants. An overall gender difference was evident for peak power contraction velocity ($P < 0.001$). The magnitude of the respective differences between males and females for 1RM strength were 32.2% in healthy middle-aged ($P < 0.001$), 47.4% ($P < 0.001$) in healthy older and 34.1% ($P = 0.001$) in mobility-limited older participants (group × gender interaction: $P = 0.06$).

Muscle size and composition

Mid-thigh muscle size and composition values from a total of 90 study participants are reported in Table 3. Significant group effects were found for total mid-thigh CSA ($P < 0.001$), total muscle CSA ($P < 0.001$), total normal density muscle CSA ($P < 0.001$) and total intermuscular adipose tissue CSA ($P < 0.001$). Healthy middle-aged participants had significantly larger mid-thigh CSA compared to healthy older ($P < 0.001$) and mobility-limited older participants ($P < 0.001$). Mobility-limited elders had significantly lower total muscle CSA compared to healthy middle-aged subjects (−24.9%, $P < 0.001$) and healthy older participants (−13.1%, $P = 0.02$). The mobility-limited group also exhibited significantly lower normal density muscle CSA and higher deposits of intermuscular adipose tissue compared to both healthy groups ($P < 0.001$). Healthy middle-aged subjects had significantly greater levels of total muscle CSA (13.6%, $P < 0.001$) and normal density muscle CSA ($P < 0.001$) compared to healthy older participants. No significant differences in intermuscular adipose tissue CSA were found between healthy middle-aged and healthy older participants ($P = 0.78$). Overall gender effects were evident for each of the remaining measures of mid-thigh muscle composition ($P < 0.001$). Mobility-limited older males and females had equivalent differences in total muscle CSA (−24.2 vs. −25.7%, respectively) compared to healthy middle-aged males and females.

Specific muscle power and strength

Figures 1 and 2 display the muscle quality calculations. Mobility-limited older participants exhibited significantly reduced specific leg extensor peak power compared to both healthy middle-aged ($P < 0.001$) and healthy older participants ($P < 0.001$). Specific power values were similar between healthy groups ($P = 0.14$). A significant group × gender interaction was elicited for specific peak power ($P = 0.04$). The differences between males and females for specific leg extensor power were 17.3% in healthy middle-aged ($P = 0.03$), 37.8% ($P < 0.001$) in healthy older and 13.9% ($P = 0.23$) in mobility-limited older participants. Specific leg extensor strength (Fig. 2) was similar across groups ($P = 0.24$) with no group × gender effect ($P = 0.17$), although a significant overall gender difference was found ($P = 0.01$).

Rate of muscle activation

Figure 3 displays the vastus lateralis rate of neuromuscular activation data obtained from 72 participants. Mobility-limited older participants had significantly lower levels of muscle activation (activation derivative: 0.08 ± 0.1) when compared to healthy middle-aged (0.15 ± 0.1, $P = 0.05$) and healthy older (0.17 ± 0.2, $P = 0.02$) participants, corresponding to relative deficits of −47.7 and −52.9%, respectively. Rate of muscle activation was similar between both healthy groups ($P = 0.7$). No significant group × gender interaction ($P = 0.5$) or a significant overall gender effect ($P = 0.16$) was evident.

Single muscle fiber size and function

The findings from the single muscle fiber experiments are presented in Tables 4 and 5. After accounting for participants that elected not to undergo a muscle biopsy and for those who were excluded from the procedure for medical safety reasons, type I and type IIA fiber samples were successfully obtained from a total of 71 and 64 participants, respectively. Our results are generated from the average number of muscle fibers studied per participant from each study group. This contrasts with previous studies that have presented data on single fiber experiments based on the total overall number of muscle fibers evaluated from a study group (Frontera et al. 2008; Trappe et al. 2003). An average of 13.0 ± 4 type I single fibers were studied in healthy middle-aged participants, 14.2 ± 3 in healthy older adults and 13.2 ± 3 in mobility-limited elders. The average number of type IIA single fibers studied were 6.7 ± 3 in healthy middle-aged participants, 4.1 ± 4 in healthy older and 3.5 ± 2 in mobility-

limited elders. There was a significant group effect for type I fiber peak power, with healthy middle-aged participants demonstrating higher fiber peak power values compared to healthy older ($P = 0.02$) and mobility-limited older participants ($P = 0.01$). No significant group, group × gender or overall gender effects were found for the other type I fiber properties reported ($P \geq 0.1$) or for any of the type IIA fiber size or contractile properties displayed in Table 5 ($P \geq 0.1$).

Discussion

Limited understanding exists regarding the underlying mechanisms contributing to the decline in muscle power with advancing age. Previous studies have demonstrated the critical functional importance associated with the loss of muscle power with aging. However, no prior investigation has comprehensively evaluated the specific physiological domains that contribute to lower extremity muscle power. This is the first study to provide a systematic, in-depth characterization of the major physiological and gender determinants of lower extremity muscle power, not only in healthy older humans but also within a distinct population of older men and women with clinically manifest mobility limitations. Also unique to our investigation was the novel combination of physiological measurements utilized to characterize differences in whole limb muscle power and strength, muscle size, quality and attenuation, neuromuscular function, and in vitro measures of skeletal muscle contractile properties. We provide new insight into the major characteristics associated with the reduction in muscle power and loss of mobility. The main observations are: (1) mobility-limited older adults have significant deficits in lower extremity muscle power compared to healthy middle-aged and healthy older adults; (2) muscle power impairments among mobility-limited elders are associated with concomitant reductions in leg extensor muscle strength, contraction velocity, muscle size, muscle quality and rate of neuromuscular activation; (3) mobility-limited older adults demonstrate relative preservation and maintenance of intrinsic single muscle fiber size and contractile function despite the deficits observed at the whole muscle level. In addition, male mobility-limited elders exhibit greater impairments in leg extensor muscle power and specific muscle power output compared to females. Additional notable findings from our analyses include the inherent similarities in muscle quality and neuromuscular function between healthy middle-aged and healthy older participants, despite an average age difference of ~25 years.

Muscle quantity and quality

Our cross-sectional analyses using CT technology and muscle attenuation characteristics revealed that mobility-limited elders had significantly lower whole muscle and normal density muscle CSA and greater intermuscular adipose tissue deposits compared to both healthy groups. Previous findings from the Health ABC cohort have shown that the attenuation of skeletal muscle decreases with age concomitant with an increase in intermuscular fat accumulation among high-functioning older adults (Delmonico et al. 2009; Goodpaster et al. 2001). Our data extend these observations in mobility-limited older adults with significant muscle power impairments. Furthermore, the significant deficits in specific leg extensor power among the mobility-limited participants suggest that the attenuation of skeletal muscle is associated with impairments in muscle power and mobility limitations independent of the reduction in muscle CSA. This discrepancy between the reduction in muscle power and muscle size indicates that other factors, distinct from muscle atrophy, are major contributors to muscle power impairments among mobility-limited participants. Conversely, the similarities in specific leg extensor strength across all participants in the current study suggests that the preservation of muscle strength with aging has greater dependence on the maintenance of muscle mass in both healthy and mobility-limited individuals. Previous investigations have shown the strong association between the loss of

muscle mass and muscle strength with aging, however, many of the older participants studied were healthy or reported no limitations in physical functioning (Delmonico et al. 2009; Frontera et al. 1991; Goodpaster et al. 2006).

Rate of neuromuscular activation

Peak muscle power represents the integration of neural and muscular function. The present study provides evidence for the role of neuromuscular activation as a potential modulator of the age-related decline in muscle power output. As shown in Fig. 3, vastus lateralis rate of neuromuscular activation was significantly lower among mobility-limited elders compared to both healthy groups. Previous studies have shown that several underlying mechanisms can contribute to impairments in neuromuscular function: the loss of motor neurons (Lexell 1997); decreased maximal motor unit firing rates (Kamen et al. 1995); and aberrant patterns of intermuscular coordination (Hakkinen et al. 1998). It is plausible that the rate of activation impairments observed in the mobility-limited participants impact movement velocity and muscle coordination leading to a reduction or a longer time to reach peak force, and thus a decline in muscle power generation. In separate analyses performed on the current study participants, we have previously demonstrated using surface EMG on the quadriceps and hamstring musculature that mobility-limited elders have significant impairments in torque, power and agonist muscle activation during maximal isokinetic dynamometry testing (Clark et al. 2010). Similarly, we have also shown that composite measures of pre-movement time (duration between EMG onset and movement onset) and the rate of EMG rise (duration and relative amplitude of muscle activation) of the quadriceps musculature during maximal leg extensor power testing were markedly lower in mobility-limited older adults compared to both healthy groups (Clark et al. 2011). Overall, our findings indicate that impairments in neuromuscular function may be critical determinants of muscle power deficits and subsequent mobility limitations among older adults.

Single fiber contractile properties

Previous studies investigating intrinsic fiber properties of skeletal muscle with aging have been limited by small sample sizes and selection bias through the inclusion of relatively healthy and physically active older subjects (D'Antona et al. 2007; Frontera et al. 2000a, b, 2008; Trappe et al. 2003). The current study overcomes these limitations using larger and more heterogenous study groups and we also report novel information on specific force and single fiber contractile properties from mobility-limited elders. Despite the significant reductions in whole muscle performance, size and quality in mobility-limited participants, our findings suggest that the surviving muscle fibers in this population partially compensate for the major alterations at the whole muscle level through maintenance and preservation of single fiber contractile performance (force production, single fiber quality). A similar dissociation between changes in muscle performance at the whole muscle level compared to the single fiber level with aging has been reported previously in a longitudinal investigation of 12 older, healthy and physically active participants (Frontera et al. 2008). In the present study, there was also corresponding preservation of single muscle fiber size and contractile function in healthy older participants compared to healthy middle-aged participants, despite significant differences in leg extensor peak power, strength and contraction velocity but notable similarities in whole muscle quality and neuromuscular activation. Although a specific timecourse for the adaptative and compensatory mechanisms associated with surviving muscle fibers has yet to be determined, these data suggest that adaptations may occur within the surviving fibers of healthy older populations in response to emerging deficits in whole muscle performance with advancing age.

Among the contractile properties evaluated, type I fiber peak power was significantly higher in healthy middle-aged participants compared to both older groups, however these

differences were not apparent after normalization for fiber size. This observation is consistent with previous studies reporting the elimination of age-related differences in single fiber contractile performance after adjustment for fiber or cell size (Frontera et al. 2000b, 2008; Raue et al. 2009; Slivka et al. 2008; Trappe et al. 2003).

Gender

Our gender analyses revealed that males generally exhibited higher values for all parameters measured except for mid-thigh CSA. However, significant group × gender interactions were elicited for both leg extensor peak power and specific leg extensor peak power and further investigation revealed that mobility-limited male participants had greater decrements in absolute measures of peak muscle power and specific muscle power.

There may be several plausible explanations for these novel gender-specific differences. Given that mobility-limited males and females had equivalent reductions in whole muscle CSA compared with healthy middle-aged males and females, our data suggest that additional and divergent gender-specific physiologic mechanisms influence the loss of muscle power among older adults with mobility impairments. For the first time, we have demonstrated that mobility-limited females exhibit maintenance and preservation of the intrinsic quality of their single muscle fibers. Furthermore, female mobility-limited elders showed preservation of type IIA fiber CSA and notable increases in specific force and specific power of these fibers (Table 5). To our knowledge, this is the largest study to-date to quantify gender related differences and compare interrelationships between measures of whole muscle performance and the properties of single muscle fibers. Taken together, our data suggest that the attenuated deficits in muscle power among mobility-limited females may relate to the presence of enhanced gender-specific intrinsic adaptive mechanisms that are more responsive to the physiological alterations in whole muscle size and function with advancing age.

The attenuated differences in specific muscle power among mobility-limited females also further indicate that neuromuscular factors are important mechanisms contributing to the decline of muscle power among older males with mobility limitations. An additional mechanism for this gender effect not quantified in this study may include unmeasured hormonal factors and sex-specific alterations in circulating steroid hormones (Macaluso and De Vito 2004). A recent cross-sectional population based study reported that reduced levels of sex hormones were associated with impaired mobility and lower muscle performance in older men, but not in older women (Schaap et al. 2005).

Study limitations

One of the major strengths of this study was the use of specific eligibility criteria that facilitated a comparative assessment of the determinants of muscle power among three distinct populations. We also incorporated the use of robust, well-established measurement techniques in a relatively large sample of participants to accurately capture these important outcomes. The comparison of older adults to middle-aged adults (rather than young adults) also allowed for the identification of the pertinent mechanisms contributing to muscle power loss and mobility limitations across a more specific age range. However, the major limitation of this study is the cross-sectional design as it precludes definitive causal inferences about muscle power deficits and any of the physiological variables measured. In addition, the current study design assumes that the reported age-related losses in muscle power, contributory mechanisms and subsequent mobility limitations are linear in occurrence and our analyses cannot quantify any temporal changes or adequately identify any anisotropic adaptive mechanisms that may be compensating for reductions in muscle power. Furthermore, several additional factors that may contribute to the age-associated

decline and gender differences in skeletal muscle performance were not assessed in this study. These include physical activity levels, caloric and protein intake, and the influence of additional circulatory mediators such inflammatory factors and protein synthesis activators. Level of physical activity can also alter the contractile properties single muscle fibers which may have influenced our findings (D'Antona et al. 2007). It is also important to recognize that the properties of skinned muscle fibers assessed in vitro during the single muscle fiber experiments may be different from the physiological properties of living fibers in vivo. A final concern with regard to the rate of activation assessment is that the normalization procedure may lead to underestimation of activation deficits in older adults who are not fully capable of voluntarily activating the quadriceps during an isometric contraction. However, previous evidence that we have reported from these same participants indicates that all groups produced similar vastus lateralis activation during isometric contractions using the currently presented leg press task (Clark et al. 2011), as well as during an isolated knee extension task (Clark et al. 2010). This is consistent with other studies that have found little, if any, deficits in voluntary activation amplitude during isometric contractions with aging (De Serres and Enoka 1998; Kent-Braun and Ng 1999). Longitudinal analysis of the physiological mechanisms contributing to the loss of muscle power and mobility limitations in the same cohort of participants would provide more definitive evidence.

Conclusion

In conclusion, this study has provided a comprehensive analysis of the physiological determinants of lower extremity muscle power in healthy middle-aged, healthy older and mobility-limited older adults. In addition to reductions in muscle mass, the significant deficits in muscle power and subsequent loss of mobility with advancing age may be caused, in particular, by impairments in neuromuscular activation and a concomitant reduction in muscle quality. The dissociation between age related changes at the whole muscle and single fiber level indicate that the contractile properties of surviving muscle fibers are maintained in older adults with overt mobility impairments in an attempt to preserve overall muscle function. Additional longitudinal studies should examine and delineate the contributions and interrelationships between neuromuscular function, muscle quality, single fiber properties and their gender-specific associations with muscle power deficits and the subsequent loss of mobility with advancing age.

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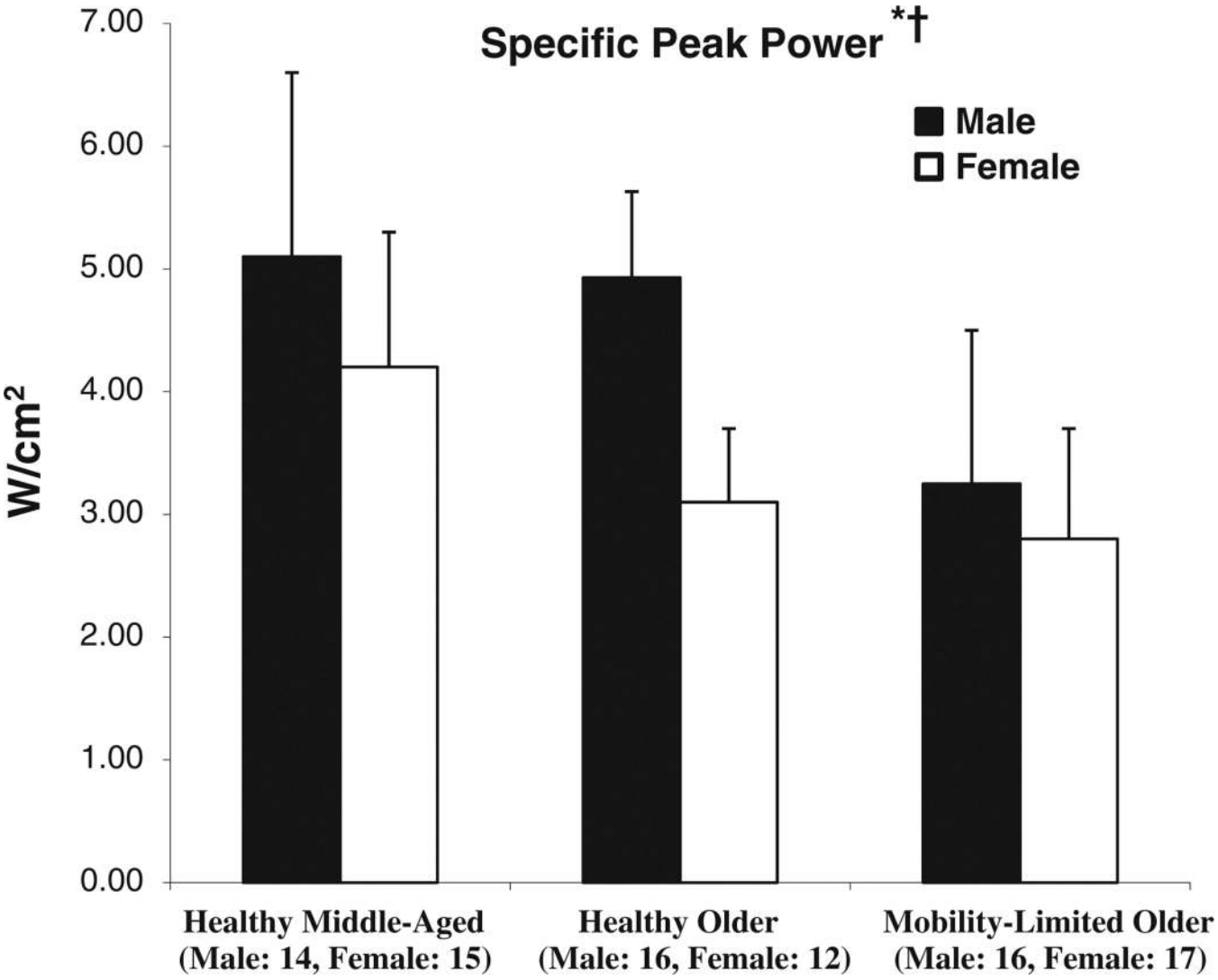

Fig. 1.
Specific peak power. Values are mean ± SD (*significant overall group differences, †significant group × gender interaction)

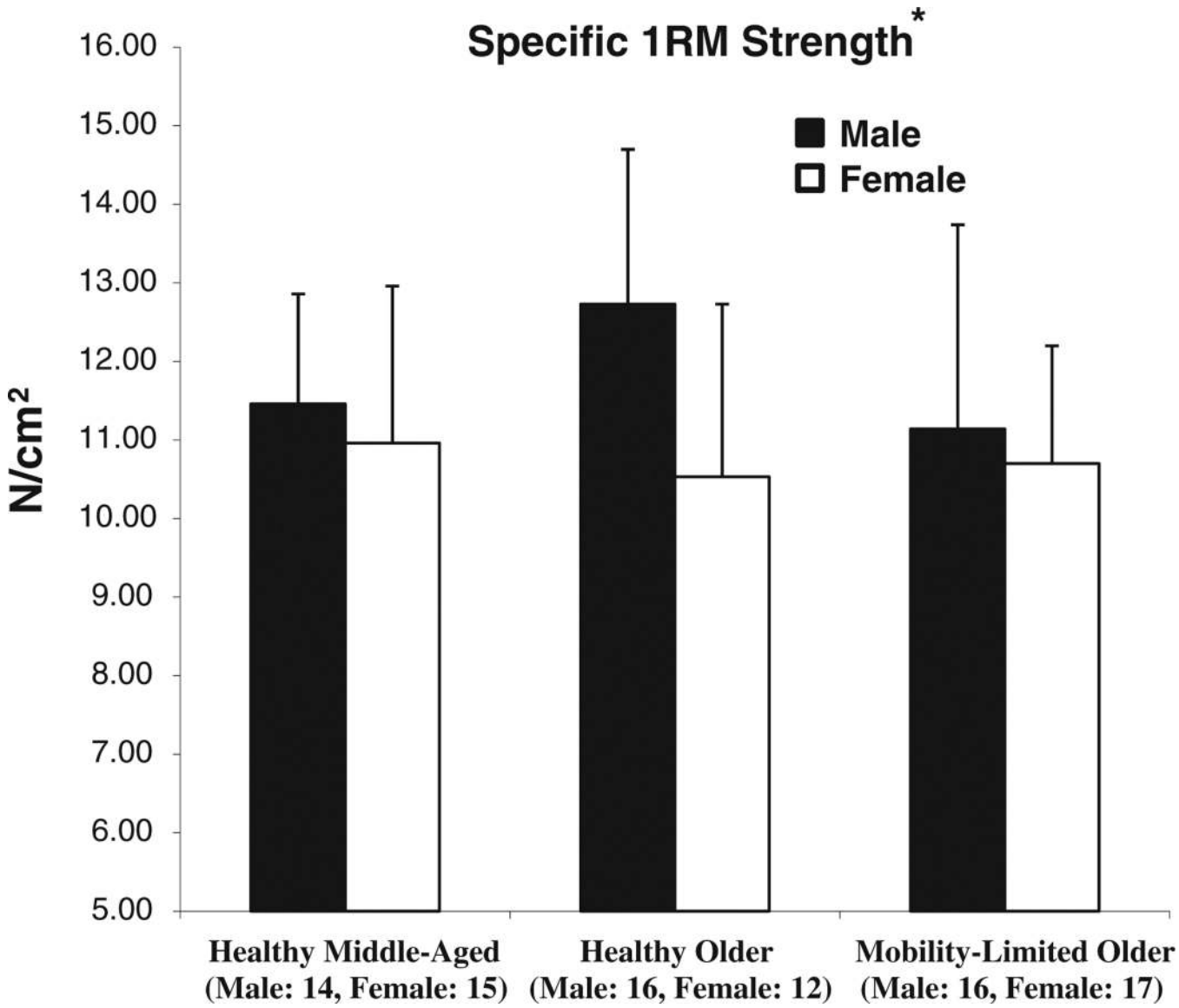

Fig. 2.
Specific 1RM strength. Values are mean ± SD (*significant overall gender difference)

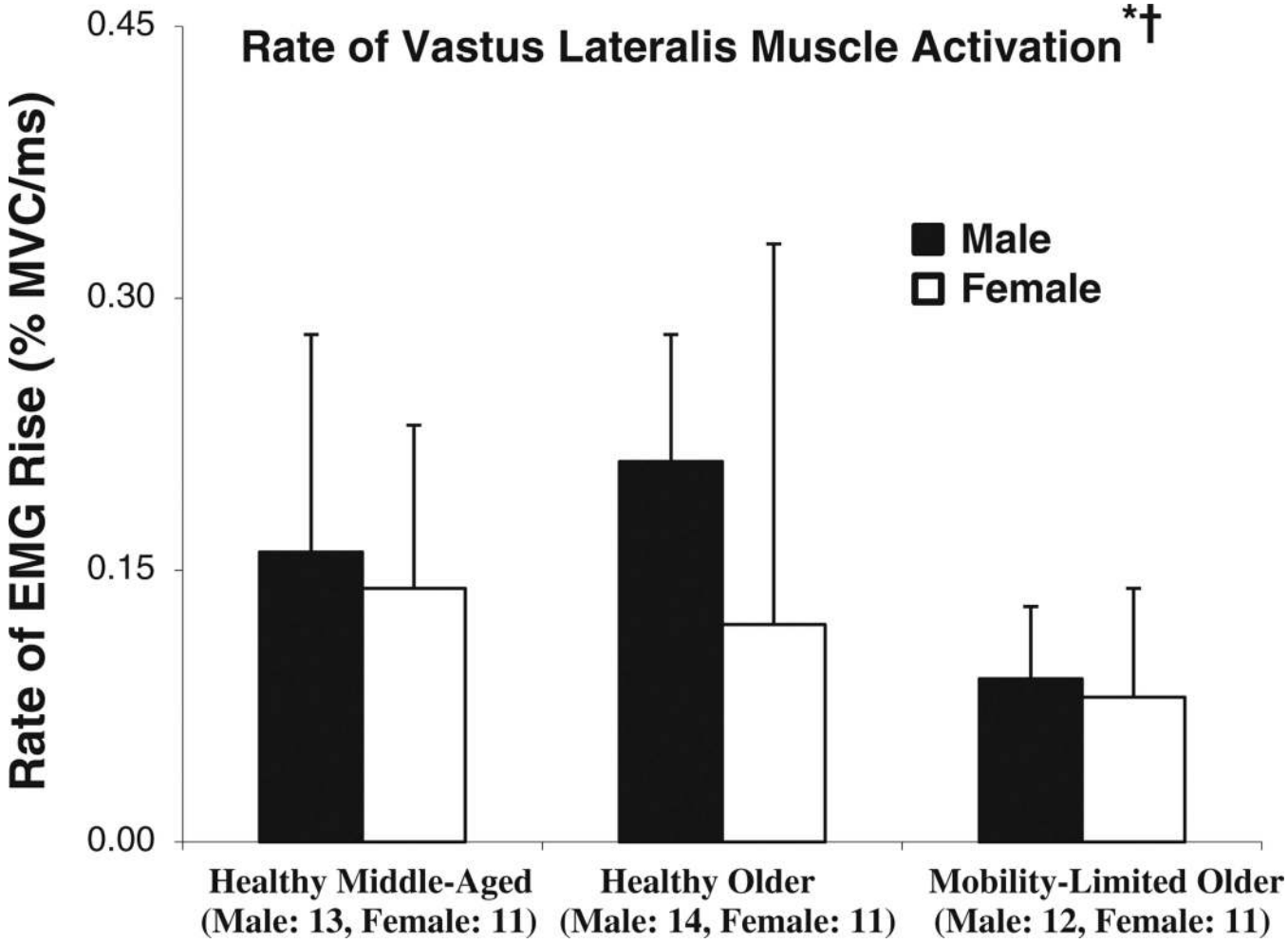

Fig. 3.
Rate of vastus lateralis muscle activation. Values are mean ± SD (*significant overall group differences, †significant overall gender difference)

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Table 1

Subject characteristics

Variable	Healthy middle-aged (male 14, female 17)		Healthy older (male 16, female 12)		Mobility-limited older (male 16, female 18)	
Age (years) *	46.5 ± 5	47.8 ± 5	73.8 ± 4	74.3 ± 4	78.9 ± 4	76.8 ± 5
BMI (kg/m^2) †	26.5 ± 3	25.1 ± 3	26.0 ± 3	22.0 ± 8	26.8 ± 3	25.9 ± 4
Medical Diagnoses ‡	–	–	–	–	2 (0–6)	2 (0–6)
Number of Medications ‡	–	–	–	–	4 (0–9)	2 (0–7)
SPPB score *	11.8 ± 0.4	11.7 ± 0.5	11.2 ± 0.8	10.8 ± 0.9	7.88 ± 1.2	8.00 ± 1.4

Values are mean ± SD

BMI body mass index, *SPPB* Short Physical Performance Battery

* Significant overall group differences,

† significant overall gender difference,

‡ median (minimum–maximum)

Table 2

Measures of leg extensor muscle power, contraction velocity and 1RM strength

	Healthy middle-aged (male 14, female 17)		Healthy older (male 16, female 12)		Mobility-limited older male 16, female 18)	
Peak power (W) *,†	724 ± 213	450 ± 124	640 ± 146	256 ± 71	365 ± 159	228 ± 77
Contraction velocity (m/s) *,‡	0.53 ± 0.2	0.47 ± 0.1	0.51 ± 0.1	0.37 ± 0.1	0.37 ± 0.1	0.32 ± 0.1
1RM strength (N) *,§	1,591 ± 265	1,078 ± 243	1,555 ± 280	818 ± 229	1,183 ± 387	780 ± 147

Values are mean ± SD

Peak power maximal average power output generated during five repetitions at 70% of the 1RM, *Contraction velocity* average velocity generated during the repetition that elicited the peak power, *1RM strength* maximum leg extensor strength measured prior to power testing

* Significant overall group differences,

† significant group × gender interaction,

‡ significant overall gender difference,

§ $P = 0.06$

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Table 3

Comparison of mid-thigh muscle area and composition using computed tomography

	Healthy middle-aged (male 14, female 15)		**Healthy older (male 16, female 12)**		**Mobility-limited older (male 16, female 17)**	
Total mid-thigh CSA (cm^2) *,†	202.8 ± 36	196.9 ± 30	175.5 ± 20	168.1 ± 41	161.1 ± 24	190.2 ± 53
Total muscle CSA (cm^2) *,‡	145.8 ± 26	107.7 ± 18	129.0 ± 15	82.5 ± 10	110.5 ± 13	79.98 ± 17
Total normal density muscle CSA (cm^2) *,‡	120.6 ± 22	88.1 ± 18	102.2 ± 15	64.6 ± 10	84.3 ± 22	57.1 ± 14
Total low density muscle CSA (cm^2) ‡	25.2 ± 9	19.6 ± 8	26.8 ± 8	17.9 ± 7	26.1 ± 9	22.8 ± 8
Total intermuscular adipose tissue CSA (cm^2) *,‡	3.07 ± 1.6	2.5 ± 1.7	3.7 ± 2.6	2.2 ± 1.6	4.6 ± 2.3	3.9 ± 1.5

Values are mean ± SD

CSA cross-sectional area

*Significant overall group differences,

‡significant overall gender difference,

$^{\dagger}P = 0.07$

Table 4

Type I single muscle fiber size and contractile properties

	Healthy middle-aged (male 12, female 11)		**Healthy older (male 16, female 7)**		**Mobility-limited older (male 12, female 13)**	
Number of fibers	11.8 ± 5	14.3 ± 4	13.6 ± 3	15.6 ± 3	12.3 ± 2	14 ± 4
CSA (μm^2)	5,334 ± 1,254	4,880 ± 993	4,999 ± 931	4,407 ± 1,174	4,989 ± 1,152	4,747 ± 887
P_0 (μN)	578 ± 137	520 ± 129	512 ± 79	453 ± 141	479 ± 142	478 ± 111
SF (N/cm^2)	16.5 ± 4.6	15.8 ± 1.4	15.4 ± 3.0	15.9 ± 4.1	14.7 ± 4.5	15.4 ± 3.6
V_0 (FL/s)	0.60 ± 0.2	0.60 ± 0.1	0.62 ± 0.13	0.65 ± 0.2	0.68 ± 0.2	0.62 ± 0.2
Peak power (μN × FL/s) *	24.6 ± 11	22.8 ± 11	19.7 ± 5.8	15.7 ± 8.9	18.1 ± 8.1	17.2 ± 4.3
Specific power (kN/m^2 × FL/s)	7.2 ± 4.0	6.5 ± 2.2	6.05 ± 2.2	5.4 ± 2.6	5.65 ± 2.0	5.74 ± 1.8

Values are mean ± SD

CSA cross-sectional area, P_0 peak force, *SF* specific force, V_0 shortening velocity, *FL* fiber length

* Significant overall group differences

Table 5

Type IIA single muscle fiber size and contractile properties

	Healthy middle-aged (male 11, female 11)		Healthy older (male 14, female 6)		Mobility-limited older (male 13, female 9)	
Number of fibers	6.8 ± 4	6.6 ± 3	4.4 ± 4	3.3 ± 2	4.4 ± 3	2.2 ± 2
CSA (μm^2)	5,354 ± 1,411	4,016 ± 1,312	4,902 ± 1,500	4,619 ± 949	4,055 ± 794	4,110 ± 1,646
P_0 (μN)	481 ± 217	411 ± 124	428 ± 151	457 ± 155	332 ± 87	391 ± 191
SF (N/cm^2)	13.94 ± 6.5	13.99 ± 2.1	13.02 ± 3.8	14.9 ± 6.3	12.7 ± 3.8	15.7 ± 8.3
V_0 (FL/s)	1.33 ± 0.22	1.29 ± 0.30	1.54 ± 0.55	1.36 ± 0.54	1.59 ± 0.64	1.24 ± 0.64
Peak power (μN × FL/s)	54.6 ± 27.8	44.4 ± 16.3	43.1 ± 21.7	47.1 ± 30.5	36.4 ± 17	36.7 ± 13
Specific power (kN/m^2 × FL/s)	17.3 ± 11.1	16.4 ± 4.8	13.2 ± 6.5	16.2 ± 12.3	16.2 ± 7.6	18.3 ± 17.5

Values are mean ± SD

CSA cross-sectional area, P_0 peak force, *SF* specific force, V_0 shortening velocity, *FL* fiber length