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Longitudinal decline of lower extremity muscle power in healthy and mobility-limited older adults: influence of muscle mass, strength, composition, neuromuscular activation and single fiber contractile properties

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Abstract

Purpose—This longitudinal study examined the major physiological mechanisms that determine the age-related loss of lower extremity muscle power in two distinct groups of older humans. We hypothesized that after ~ 3 years of follow-up, mobility-limited older adults (mean age: 77.2 ± 4, n = 22, 12 females) would have significantly greater reductions in leg extensor muscle power compared to healthy older adults (74.1 ± 4, n = 26, 12 females).

Methods—Mid-thigh muscle size and composition were assessed using computed tomography. Neuromuscular activation was quantified using surface electromyography and vastus lateralis single muscle fibers were studied to evaluate intrinsic muscle contractile properties.

Results—At follow-up, the overall magnitude of muscle power loss was similar between groups: mobility-limited: −8.5% vs. healthy older: −8.8%, $P > 0.8$. Mobility-limited elders had significant reductions in muscle size (−3.8%, $P < 0.01$) and strength (−5.9%, $P < 0.02$), however, these parameters were preserved in healthy older ($P \geq 0.7$). Neuromuscular activation declined significantly within healthy older but not in mobility-limited participants. Within both groups, the cross sectional areas of type I and type IIA muscle fibers were preserved while substantial increases in single fiber peak force (> 30%), peak power (> 200%) and unloaded shortening velocity (>50%) were elicited at follow-up.

Conclusion—Different physiological mechanisms contribute to the loss of lower extremity muscle power in healthy older and mobility-limited older adults. Neuromuscular changes may be the critical early determinant of muscle power deficits with aging. In response to major whole

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muscle decrements, major compensatory mechanisms occur within the contractile properties of surviving single muscle fibers in an attempt to restore overall muscle power and function with advancing age.

Keywords

Aging; lower extremity muscle power; single muscle fiber; longitudinal

Introduction

The ability to successfully generate skeletal muscle power, defined as the product of dynamic muscular force and contraction velocity, is critical for activities that require human movement and locomotion (Bassey et al. 1992; Reid and Fielding 2012). Among older adults, a decline in lower extremity muscle power output with advancing years has important implications for independent physical functioning in later life. Compared to traditional measures of muscle performance such as muscle strength (the ability to generate maximal force), impairments in peak lower extremity muscle power are superior predictors of functional tasks involving mobility and ambulation (Bassey et al. 1992; Bean et al. 2002; Bean et al. 2003; Cuoco et al. 2004; Foldvari et al. 2000; Suzuki et al. 2001). Lower extremity muscle power is also a more influential determinant of falls, which accelerate other adverse outcomes in older populations, including disability and mortality (Moreland et al. 2004; Skelton et al. 2002).

Cross-sectional studies have described a multitude of physiological mechanisms that are associated with reduced muscle power output in aging humans. The well described decline in skeletal muscle size that occurs with aging, and changes in the properties of remaining muscle fibers, contribute to reduced muscle power in older adults (Brooks and Faulkner 1994; Doherty 2003). In particular, the selective atrophy and loss of type IIA muscle fibers with advancing age, which have the ability to generate four-six times more power output than type I fibers, may severely limit the successful development of dynamic muscle power during human movement (Larsson et al. 1979; Martin et al. 2000; Trappe et al. 2003). Alterations in neural function, such as the loss of motor neurons, decreased maximal motor unit firing rates and impaired neuromuscular activation inhibit muscle power output in older adults (Aagaard et al. 2010; Clark and Fielding 2012; Clark et al. 2010). Furthermore, the infiltration of adipose tissue into skeletal muscle is inversely associated with muscle performance and higher accumulation of intermuscular adipose tissue has been linked with an inability to fully activate muscles during dynamic contractions (Goodpaster et al. 2001; Yoshida et al. 2012).

However, definitive understanding of the specific physiological mechanisms that cause a decline in muscle power with advancing age is limited. The aforementioned cross sectional studies preclude definitive causal inferences about the factors causing muscle power loss and are also particularly limited by survival effect bias (Frontera et al. 2008; Goodpaster et al. 2006). This bias may lead to inaccurate estimates of the loss of muscle power over time as persons with greater muscle power may have a better chance to survive to old age and be included in cross sectional investigations. A true understanding of the nature and underlying physiological determinants of lower extremity muscle power loss in older adults can only be established using longitudinal evaluation of the same group of individuals. To date, no longitudinal investigation has examined the magnitude and major determinants of lower extremity muscle power output with advancing age. Furthermore, no study has compared the underlying mechanisms contributing to longitudinal changes of lower extremity muscle power among healthy and frail older adults. Such knowledge may be critical for identifying specific physiological factors that mediate functional loss and disability in older adults.

The purpose of this study was to comprehensively examine and quantify the longitudinal determinants of lower extremity muscle power in two distinct groups of healthy older and mobility-limited older adults. We systematically compared the changes in leg extensor muscle power and concurrent changes in lower extremity muscle size, strength, muscle quality, neuromuscular activation and the intrinsic single muscle fiber contractile properties over a three year period in both groups. By examining several physiological domains that contribute to motor performance, we sought to identify key deficits in specific physiological systems that contribute to the age-related decline in muscle power output. Because of the significant relationship between impairments in lower extremity muscle power and mobility-related tasks, we hypothesized that mobility-limited older adults would have significantly greater reductions in lower extremity muscle power compared to healthy older adults. We also sought to examine whether different physiological mechanisms would mediate the respective changes of lower extremity muscle power in healthy older and mobility-limited groups.

Methods

Study participants

A total of sixty-two older subjects (28 healthy older, 34 mobility-limited) initially completed the study protocol at baseline between 2006 – 2008. The full description of the baseline recruitment and eligibility criteria has been published previously (Reid et al. 2012). Briefly, participants were considered eligible for the healthy older group if they were community dwelling, aged 70–85 years, not taking any prescribed medications and scored ≥ 10 on the Short Physical Performance Battery test (SPPB). Older mobility-limited subjects were considered eligible if they were community-dwelling, aged 70–85 years 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 is highly predictive of subsequent disability, institutionalization, and mortality (Guralnik et al. 2000; Guralnik et al. 1995; Guralnik et al. 1994). Prior to enrollment at baseline and follow-up, 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 University Health Sciences Institutional Review Board.

Experimental Procedures

The following experimental procedures have been previously described in greater detail (Reid et al. 2012). All testing procedures were performed at baseline and repeated after 3.0 ± 0.5 years of follow-up.

Lower extremity muscle strength, power and neuromuscular activation

Participants were seated on the bilateral leg press apparatus with knees flexed to 90 degrees and hips flexed to approximately 110 degrees (Leg Press A420, Keiser Corporation, Fresno, CA). Leg extensor muscle strength was 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. Five minutes after measurement of the 1RM, assessment of leg extensor peak muscle power was performed (Callahan et al. 2007). Each participant was instructed to complete a total of five repetitions each separated by 30 seconds 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. Strength and power testing took place on two occasions, at the same time of day separated by approximately one week. From the two data collection sessions, the highest value for 1RM and peak power was recorded.

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 1cm inter-electrode distance over the muscle belly. At each study time point, muscle activation was quantified on the second data collection session during the multiple attempt peak power test performed at 70% of 1RM. Rate of activation was quantified as the mean derivative of the normalized EMG between the onset of activation (determined as resting EMG amplitude plus three standard deviations) and the onset of movement. EMG normalization involved expressing EMG amplitude relative to peak EMG acquired during maximal voluntary isometric contraction (defined by the root-mean-square average over the 100ms window with greatest activation magnitude).

Muscle size and quality

At both timepoints, a computed tomography (CT) scan of the non-dominant thigh was performed at the midpoint of the femur 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 x 512 matrix with a 25-cm field of view. From the images, the cross sectional areas (CSAs) for normal density muscle and low density muscle, subcutaneous adipose tissue, 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 (0 – 34 HU) and normal-density muscle CSA (35 – 100 HU). 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; Reid et al. 2012).

Muscle biopsy and single muscle fiber experiments

Muscle biopsies were taken from the vastus lateralis muscle at the using a 5-mm Duchenne biopsy needle and suction (Bergström 1962; Evans et al. 1982). The same biopsy site was used at follow-up as it was possible to identify the scar of the baseline biopsy in all subjects. 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 wk before use. On the day of each experiment, fiber segments were placed for 30 min in relaxing solution containing 0.5% Brij-58 (polyoxyethylene 20 cetyl ether; Sigma, St. Louis, MO) before mounting in an experimental apparatus, similar to that described previously (Larsson and Moss 1993; 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, Ontario, 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). 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 cross-sectional area was calculated from the diameter and depth, assuming an elliptical circumference. Maximum force (P_0) was adjusted for fiber cross-

sectional area after adjusting fiber area for the 20% swelling that is known to occur during skinning (Godt and Maughan 1977; Moss 1979).

Immediately preceding each activation, the fiber was immersed for 10–20 s in a solution with a reduced Ca^{2+}-EGTA buffering capacity. Maximum active force (Po) 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 (Vo) 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 wk 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). See Supplementary Methods for a representative SDS-PAGE gel of human single muscle fibers for MyHC identification.

Statistical Analysis

Data analysis was performed using SAS statistical software (Version 9.2, SAS Institute Inc., Cary, North Carolina). Data are presented as mean ± SD or adjusted mean ± SE. Statistical significance was accepted at $P \leq 0.05$. A trend for statistical significance was accepted at $P \leq 0.10$. For each parameter the change between the follow-up and baseline was used as an outcome. The association between the outcome and study group (operationalized as Healthy Older vs. Mobility-limited Older) was assessed using linear regression. Baseline value, gender, and interaction between gender and risk group was included in the model. First the interaction between gender and study group was tested. If significant, the adjusted mean change difference between the two groups was calculated for both males and females and across the two gender groups. If the interaction was not significant the adjusted mean change difference between the two groups was calculated across the two gender groups. Exploratory bivariate correlations (Pearson) were calculated within each study group to investigate potential associations between the longitudinal change in lower extremity muscle power and concurrent changes in the major physiological domains associated with muscle power.

Results

Study Participants

In 2009–2011, attempts were made to contact all of the initial 64 older study participants. Of the healthy older participants, 1 had died and 1 subject could not be located. From the mobility-limited older group, 2 were physically unable to attend the laboratory, 3 subjects elected not to participate, 2 had died and 5 subjects could not be located. Searches at the Massachusetts Department of Vital Statistics, Massachusetts Department of Motor Vehicles, Social Security Death Index, and telephone directories were used to locate individuals who were no longer living at their original address. The remaining subjects were eligible for the study and a total of 26 healthy older (92.9% of initial group, 12 females) and 22 mobility-limited participants (64.7% of initial group, 12 females) enrolled and participated in the follow-up testing. The characteristics of the study participants are displayed in Table 1.

Lower extremity muscle power, strength, muscle size and quality

Table 2 displays the longitudinal changes in muscle performance, muscle composition and quality for healthy older and mobility-limited subjects. All subjects completed the strength and power testing and CT scans were obtained at both time points from 26 healthy older 19 mobility-limited participants. Within both groups, significant and comparable losses of peak power were evident at follow-up (healthy older: −8.8% vs. −8.5% in mobility-limited). Similarly, significant decrements in contraction velocity were also apparent in both groups. 1RM strength declined significantly only among mobility-limited subjects (−5.9%). There was a trend for a significant between-group difference in the magnitude of total muscle CSA decline ($P = 0.08$). Among mobility-limited participants, a significant loss in total muscle CSA was observed (−3.8 %, $P = 0.003$) compared to a minimal reduction of −0.8% within healthy older participants ($P = 0.4$). In addition, there was also a significant group x gender interaction evident for total muscle CSA, with mobility-limited females losing significantly greater total muscle CSA compared to healthy older females (−9.6 ± 3%, $P < 0.01$). Total intermuscular adipose tissue depots were substantially increased in both groups (healthy older: 31.7 ± 15%, $P = 0.2$; mobility-limited older: 27.2 ± 17%, $P = 0.002$). Both groups lost specific muscle power (within-group changes: $P < 0.05$), although the comparative magnitude of this decrement was not different between groups ($P = 0.5$). No significant changes between or within groups were evident for bodyweight, BMI or specific 1RM strength ($P > 0.17$, data not shown).

Neuromuscular Activation

Vastus lateralis rate of neuromuscular activation data was only included if deemed of high quality after custom software analysis and secondary visual inspection of all raw data. At each time point, a significant amount of signal noise obscured reliable identification of the onset of muscle contraction, resulting in valid data from 21 healthy older and 11 mobility-limited participants at baseline or follow-up. Figure 1 displays the vastus lateralis rate of neuromuscular activation data obtained at both time points, from a final total of 14 healthy older participants (5 females) and 6 mobility-limited participants (2 females). Within-group analyses revealed that the rate of EMG rise was significantly reduced among healthy older participants (−25.6 ± 14%, $P = 0.004$). Rate of EMG rise among mobility-limited participants did not change ($P = 0.8$). A trend for a statistically significant between group difference was evident for rate of EMG rise ($P = 0.10$). No significant group x gender interaction was evident. Within this subset of participants with valid neuromuscular activation data, the magnitude of peak power loss in healthy older ($n = 14$) was −18.7 ± 5.5% ($P = 0.003$) and −20.1 ± 9.8% ($P = 0.05$) in mobility-limited participants ($n = 6$) (between group difference: $P > 0.9$).

Muscle biopsy and single muscle fiber experiments

The findings from the single muscle fiber experiments are displayed in Table 3 and Figure 2. After accounting for participants that elected not to undergo the muscle biopsy and for those who were excluded from the procedure for medical reasons, type I fiber samples were successfully obtained from 16 healthy older (5 females) and 6 mobility-limited (3 females) participants. Type IIA fiber samples were obtained at both time points from 14 healthy older (3 females) and 5 mobility-limited participants (3 females). For type I fiber properties, no significant change in type I fiber CSA were observed at follow-up. However, both groups had similar and significant within-group increases ($P \leq 0.05$) in type I fiber peak force, specific force, shortening velocity and peak power (P for between group differences: ≥ 0.13). Type I fiber specific power also increased in both groups, however this increase was only statistically significant among healthy older participants ($P < 0.0001$). For type IIA fiber properties, no significant change in fiber CSA were observed in either group. Significant within-group increases in peak force and shortening velocity were found among

the healthy older group while peak power was significantly increased among mobility-limited participants at follow-up. Both groups had similar and significant within-group increases ($P < 0.02$) of type IIA fiber specific force and specific power (P for all between group differences: ≥ 0.13). No significant group x gender interaction was evident for any single fiber variable examined. Within this subset of muscle biopsy participants, the magnitude of peak power loss in healthy older (n = 16) was −14.3 ± 7% ($P = 0.05$) and −34.5 ± 11% ($P = 0.007$) in mobility-limited older (n = 6) (between group difference: $P = 0.2$). A three dimensional plot (Figure 2) displays the overall magnitude (% change) of the longitudinal increases in peak force and shortening velocity according to fiber type and study group.

Among healthy older participants, significant correlations were observed between the decline in leg extensor power and the corresponding decline in contraction velocity ($r = 0.78$, $P < 0.001$) and the increase in intermuscular adipose tissue infiltration ($r = −0.45$, $P = 0.03$). No relationship existed between the change in muscle power and muscle size within this group ($r = 0.08$, $P = 0.7$). Among mobility-limited participants, significant relationships were evident for the decline in muscle power and corresponding declines in contraction velocity ($r = 0.84$, $P < 0.001$) and 1RM strength ($r = 0.52$, $P = 0.03$). The longitudinal change of intermuscular adipose tissue infiltration was significantly and inversely and correlated with the decline of contraction velocity among healthy older ($r = −0.43$, $P = 0.04$) (Figure 3a) and mobility-limited participants ($r = −0.52$, $P = 0.03$) (Figure 3b). No significant relationships existed between changes in subcutaneous adipose tissue and changes in muscle power or contraction velocity within healthy older or mobility-limited participants.

Discussion

The major finding of this investigation is that lower extremity muscle power deteriorates significantly over a 3-year interval in healthy and mobility-limited older groups. While the magnitude of this decline is equivalent in both groups, the underlying physiological mechanisms that determine muscle power loss differ between both groups. Specifically, our investigation has established that the loss of muscle power among healthy older adults is associated with significant declines in the rate of neuromuscular activation but minimal changes in muscle size and strength. Conversely, decrements in muscle power among mobility-limited elders are associated with significant declines in muscle size and muscle strength, but no additional declines in neuromuscular activation. In addition, we have identified that substantial compensatory adaptations occur within the contractile properties of surviving single muscle fibers among healthy older and mobility-limited elders in response to the declines in whole muscle power. Finally, for the first time, we demonstrate that significant increases of intermuscular adipose tissue infiltration into skeletal muscle with advancing age are inversely associated with the loss of muscle contractile velocity and power output in healthy older and mobility-limited adults.

Magnitude of Lower Extremity Muscle Power Loss in Older Adults

The overall decline in lower extremity muscle power in mobility-limited elders (−8.5%) was similar in healthy older subjects (−8.8%), representing annualized rates of decline of 2.9%/yr within both groups. While this finding was contrary to our primary hypothesis, there are several plausible explanations. Mobility-limited elders had significantly lower absolute levels of leg extensor muscle power at baseline compared to healthy older participants. Therefore, one possibility is that mobility-limited elders had already reached critically low levels of muscle power at baseline, beyond which compensatory mechanisms are activated in an attempt to restore muscle function and limit additional decrements in muscle power. Another possibility is that the 3-year time follow up period in this study may have been too

short to truly capture a comprehensive trajectory of muscle power changes, particularly given the variability of changes in muscle performance observed in the current study and reported in previous studies (Delmonico et al. 2009; Frontera et al. 2008; Goodpaster et al. 2008; Goodpaster et al. 2006; Hicks et al. 2012; Hughes et al. 2001).

Changes in Muscle Strength, Muscle Size and Neuromuscular Activation

Several important findings are evident from the different longitudinal changes in muscle strength, muscle size and neuromuscular activation observed across groups in this study. Despite overall decrements in muscle power, the healthy older group maintained their strength, whereas mobility-limited elders exhibited significant reductions in muscle power and strength at follow-up. The decline in neuromuscular activation, concurrent with the maintenance of muscle size and strength in the healthy older group indicate that altered neuromuscular function is the critical early determinant of muscle power loss with aging. As coexisting deficits in contraction velocity (−8.4%) were evident at follow-up within this group, an impaired rate of activation may specifically impact muscle contractile velocity leading to a longer time to reach peak force, and thus an observed decline in muscle power generation (Aagaard et al. 2010; Clark et al. 2011). It is likely that the large discrepancy between the decline in muscle power and the changes in both muscle size and muscle strength within the healthy older group is primarily accounted for by changes in neuromuscular activation and concomitantly manifested through impairments in contraction velocity. In contrast, the significant decrements in muscle size (−3.8%), strength (−5.7%) and contraction velocity (−13%) among mobility limited elders suggest that a combination of deficits are major determinants of muscle power loss within this group. Therefore, while mobility-limited elders exhibited no additional changes in neuromuscular activation, baseline impairments in neuromuscular activation were evident and it is possible that no further deficits were detectable, at least with the surface EMG methods employed in this investigation.

Single Muscle Fiber Contractile Properties

In both groups, the cross sectional areas of type I and type IIA fibers were largely preserved and emphatic increases were elicited in all single fiber contractile mechanics examined 3 years apart. A plausible explanation for these findings is that pronounced adaptations occur within the surviving single muscle fibers of both healthy and mobility-limited older adults in an attempt to restore contractile performance and compensate, albeit sub-optimally, for the major deficits in whole muscle power, size, quality and neuromuscular activation.

The magnitude of the observed myocellular contractile adaptations are directionally similar but substantially greater than reported in a previous longitudinal study by our research group. After a 9-year follow up period, Frontera et al. identified trends for increased peak force and preserved unloaded shortening velocity of type I and IIA fibers in response to significant deficits in whole muscle strength and size in a small sample (n = 9) of healthy older men and women (Frontera et al. 2008). In the current study, the substantial improvements of single fiber peak force and unloaded shortening velocity in both groups occurred during a shorter follow-up period. Taken together, these data suggest that there may be an initial early time course for pronounced myocellular contractile adaptations that, subsequently, become attenuated with advancing years in older persons. Also of particular interest in the current study is the magnitude of the single fiber peak power increases in type I (~200%) and in type IIA fibers (~200 – 300%) within both groups. These values are extraordinary when put in context with studies that have been specifically designed to improve myocellular contractile function in humans. In young and healthy older adults, maximal increases in peak power of type I and type IIA fibers have been shown to increase

by up to ~160% and ~60%, respectively, after several months of progressive resistance training (Slivka et al. 2008; Trappe et al. 2001; Trappe et al. 2000).

Overall, several factors may help explain the mechanisms responsible for the magnitude of the single fiber adaptations reported in the current investigation. We quantified the myocellular adaptations during a dynamic skeletal muscle loading period in two distinct groups of aging humans over a 3 year period. This relatively short term follow-up duration, concomitant with significant reductions in whole muscle power and other emerging and established physiological perturbations at the whole muscle level, represents a novel loading paradigm for the intrinsic properties of surviving single muscle fibers that has not been previously characterized in older adults. It is also possible that additional methodological considerations, such as differences in study populations, amount of fibers studied and potential confounding factors such as physical activity may contribute to differences between the current and previous investigations.

Adipose Tissue Infiltration within Skeletal Muscle

Both groups exhibited substantial increases of intermuscular adipose tissue and the magnitude of these increases were consistent with previous reports in healthy older and mobility limited populations (Delmonico et al. 2009; Goodpaster et al. 2008; Goodpaster et al. 2006; Marcus et al. 2012). In addition, we demonstrate significant inverse relationships between increases of intermuscular adipose tissue infiltration and corresponding losses in muscle power and contraction velocity within both groups. The mechanism linking adipose tissue infiltration to altered muscle power remains unclear. However, it is possible that adipose tissue infiltration into skeletal muscle alters muscle fiber orientation or directly inhibits central activation and neuromuscular conductivity, thus reducing the force and contractile producing capabilities of the whole muscle (Marcus et al. 2012; Yoshida et al. 2012). Another potential mechanism is the secretion by intermuscular adipose tissue of pro-inflammatory cytokines leading to inflammation that ultimately inhibits muscle force production at a systemic level (Hardin et al. 2008). Alternatively, while no changes in body weight or BMI were evident within the two groups in the current study, we speculate that the infiltration of adipose tissue into skeletal muscle could serve as a proxy for adverse lifestyle influences on muscle function related to diet and physical inactivity among older adults. In this regard, a one-year intervention of regular physical activity has been shown to attenuate increases in muscle fat infiltration and decrements in muscle performance in mobility-limited limited older adults compared to sedentary controls (Goodpaster et al. 2008).

Limitations

Major strengths of this investigation include the longitudinal study design and the use of specific eligibility criteria to characterize two distinct aging phenotypes. However, some limitations of the current investigation must be considered. The differential loss to follow-up rate between the two study groups may have influenced our overall findings. Approximately one-third of the original mobility-limited group did not return for reassessment, which may have limited our ability to fully examine the true magnitude and nature of muscle power loss and the generalizability of our findings within this group. Another limitation is that the current 3-year longitudinal analysis assumes that the age-related losses in muscle power, contributory mechanisms and subsequent mobility limitations are linear in occurrence. Consequently, the current study cannot adequately quantify any shorter term mechanisms that may be contributing to or compensating for reductions in muscle power. In addition, a number of unmeasured factors that may mediate the age-associated decline in muscle power and skeletal muscle performance were not assessed in this study. These include caloric and protein intake and the influence of inflammatory factors and protein synthesis activators. Finally, among older adults, level of physical activity has been shown to influence several

determinants of muscle power characterized in this study (Clark and Fielding 2012; D'Antona et al. 2007; Goodpaster et al. 2006). An assessment of the interaction between physical activity on the physiological domains investigated this study may have added important supplementary information to our findings.

Conclusion

In conclusion, this is the first longitudinal investigation to comprehensively characterize the major physiological determinants of the age related loss of lower extremity muscle power in healthy older and mobility-limited older adults. The overall magnitude of muscle power loss was similar between both groups; however different underlying physiological domains determine lower extremity muscle power decrements within healthy older adults and older adults with mobility limitations. Neuromuscular activation deficits precede changes in muscle size and strength, and this may be the initial mechanism that influences muscle power loss with advancing age. Despite major and emerging physiological decrements at the whole muscle level, single muscle fiber size is preserved and the contractile properties of these surviving fibers undergo substantial compensatory mechanisms in an attempt to restore whole muscle power and function in older adults with and without mobility-limitations. Additional studies are needed to elucidate the mechanisms by which intermuscular adipose tissue infiltration may directly contribute to the loss of muscle power, muscle performance and subsequent loss of mobility with advancing age.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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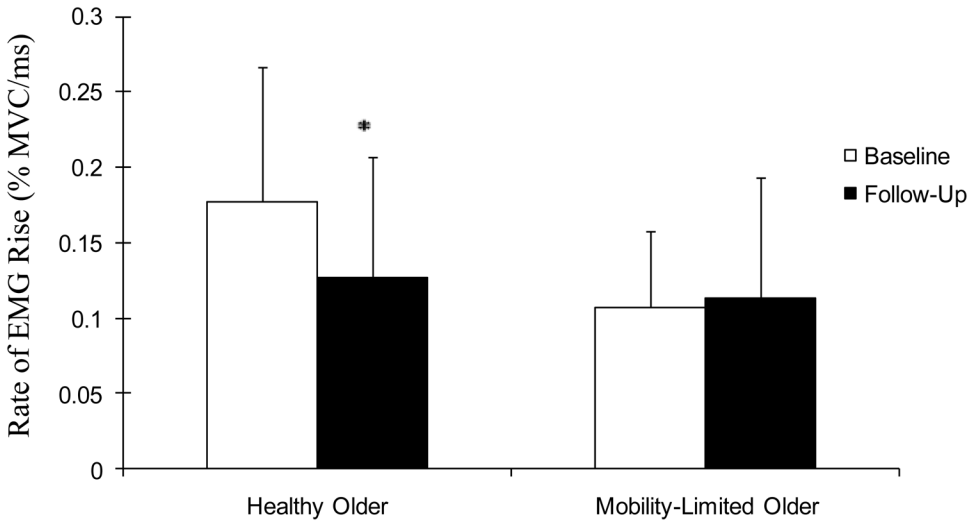

Figure 1.
Rate of vastus lateralis muscle activation. Values are mean ± SD. * within-group change: $P < 0.05$

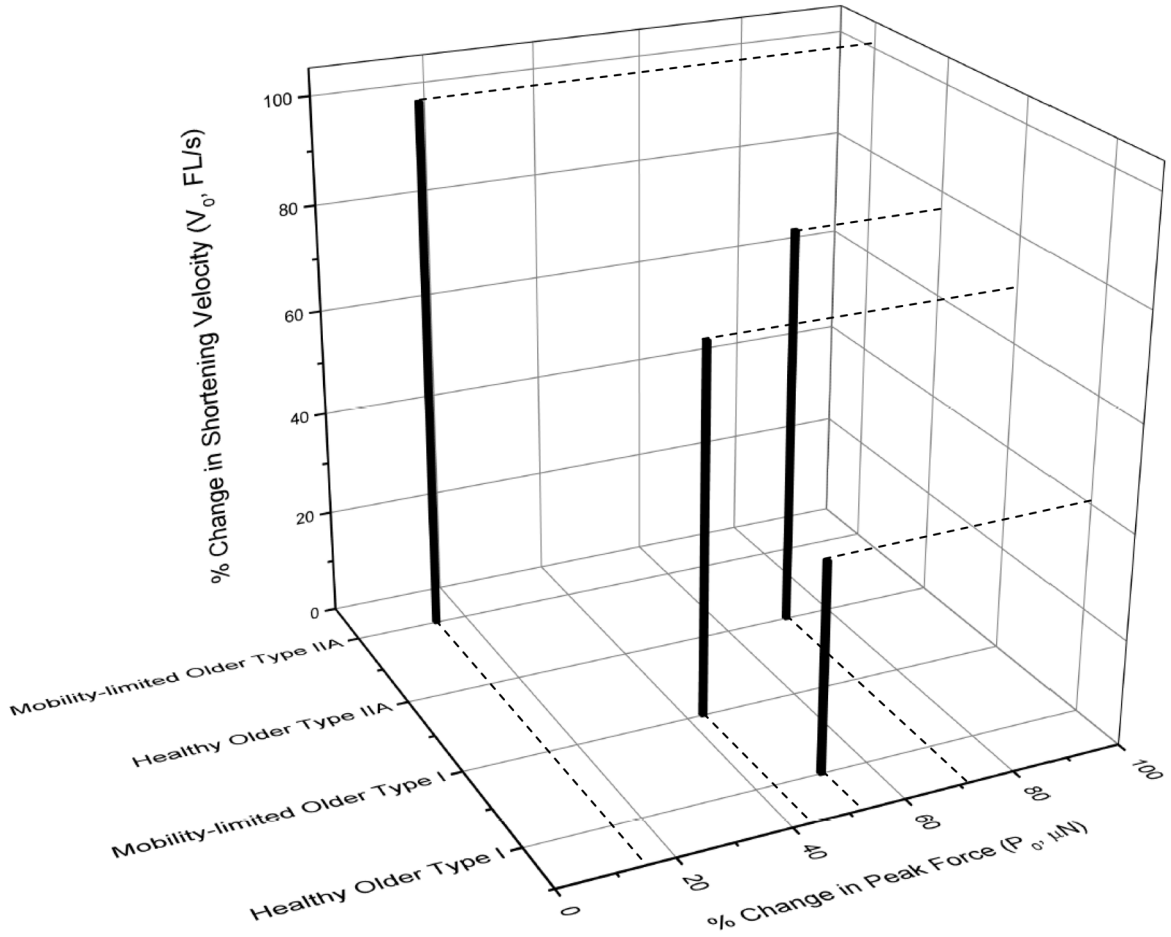

Figure 2.
Three-dimensional plot comparing the longitudinal increases in peak force vs. shortening velocity in Type 1 and Type IIA single fibers. Values are mean percentage changes

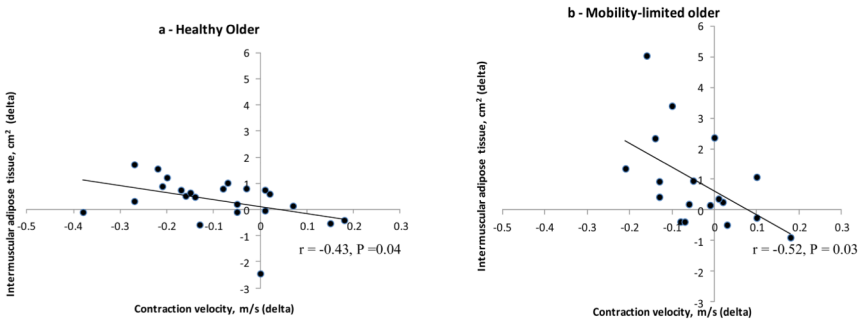

Figure 3.
Correlation between changes (delta) in contraction velocity and intermuscular adipose tissue accumulation in a) healthy older and b) mobility-limited older adults

Table 1

Baseline subject characteristics

Variable	Healthy Older (male 14, female 12)	Mobility-limited Older (male 10, female 12)	Between- group difference
Age, yr	74.1 ± 3.7	77.2 ± 4.4	0.01
BMI (kg/m^2)	24.3 ± 6	26.9 ± 3.4	0.07
Medical Diagnoses, n	-	2.2 ± 1.9	-
Number of Medications, n	-	2.8 ± 2.4	-
SPPB score	11.04 ± 0.9	7.86 ± 1.3	0.01
Duration of follow-up, yr	3.0 ± 0.7	2.9 ± 0.4	0.54

Values are mean ± SD. BMI: body mass index; SPPB: Short Physical Performance Battery

Table 2

Comparative 3 year longitudinal changes in lower extremity muscle performance, muscle composition and quality

Variable	Healthy Older			Mobility-limited Older			
	Baseline value (± SD)	Delta^ (± SE)	% Change^ (± SE)	Baseline value (± SD)	Delta^ (± SE)	% Change^ (± SE)	Between-group difference p
Peak power (W)	471.4 ± 232	−69.8 ± 22*	−8.8 ± 6.6	291 ± 116	−65.6 ± 25*	−8.5 ± 8	0.91
Contraction velocity (m/s)	0.45 ± 0.13	−0.06 ± 0.02*	−8.4 ± 5.6	0.34 ± 0.1	−0.08 ± 0.02*	−12.97 ± 6	0.42
1RM strength (N)	1277.9 ± 436	−19.6 ± 43.8	0.4 ± 3.5	1080.3 ± 343	−101.9 ± 50*	−5.9 ± 4	0.23
Total muscle CSA (cm^2) ¥	108.8 ± 27	−1.2 ± 1.4	−0.8 ± 1.7	95.13 ± 23	−5.10 ± 1.6*	−3.8 ± 2	0.08
Total intermuscular CSA (cm^2)	2.86 ± 2.31	0.30 ± 0.24	31.7 ± 15	4.39 ± 2.2	0.90 ± 0.3*	27.2 ± 17	0.11
Specific peak power, (W/cm^2)	4.09 ± 1.17	−0.41 ± 0.2*	−4.24 ± 6	2.99 ± 0.96	−0.63 ± 0.24*	−11.25 ± 7	0.49

^ Values are adjusted means ± SD or SE.

* Significant within group difference ($p < 0.05$).

¥ Group x gender interaction ($P = 0.02$)

Table 3

Single Muscle Fiber Size and Contractile Properties

	Healthy Older			Mobility-limited Older			
	Baseline	**Follow-up**	**P Value**	**Baseline**	**Follow-up**	**P Value**	**Between Group P Value**
Type I							
Number of fibers	13.6 ± 3	10.4 ± 4		14.8 ± 2	9 ± 5		
CSA, μm^2	4,787 ± 1,063	4,956 ± 1,336	0.60	4,900 ± 930	4,599 ± 646	0.39	0.32
P_0, μN	488 ± 104	705 ± 245	< 0.001	488 ± 134	689 ± 202	0.05	0.50
SF, N/cm^2	15.6 ± 3.4	21.9 ± 4.8	< 0.001	15.2 ± 4.1	22.98 ± 4.1	< 0.001	0.80
V_0, FL/s	0.63 ± 0.16	0.77 ± 0.21	< 0.001	0.61 ± 0.20	0.97 ± 0.23	< 0.001	0.13
Peak Power, μN*FL/s*	18.1 ± 7.1	47.9 ± 29.1	< 0.001	18.1 ± 7	45.2 ± 14.8	0.03	0.86
Specific Power, kN/m^2*FL/s	5.8 ± 2.4	16.3 ± 13.5	< 0.001	5.73 ± 2.2	14.9 ± 4	0.10	0.86
Type IIA							
Number of fibers	4.2 ± 3	7.4 ± 5		4.5 ± 3	4.6 ± 2		
CSA, μm^2	4,817 ± 1,339	4,881 ± 1,710	0.60	4,469 ± 1,014	3,603 ± 869	0.16	0.13
P_0, μN	437 ± 149	644 ± 248	< 0.001	386 ± 170	504 ± 211	0.56	0.39
SF, N/cm^2	13.6 ± 4.6	20.1 ± 2.9	< 0.001	12.7 ± 4.3	21.01 ± 3.4	< 0.001	0.14
V_0, FL/s	1.48 ± 0.54	2.24 ± 0.71	< 0.001	1.32 ± 0.52	2.0 ± 0.7	0.11	0.60
Peak Power, μN*FL/s*	44.3 ± 23.9	99.3 ± 58.5	0.05	35.5 ± 13.3	152.7 ± 188	0.02	0.20
Specific Power, kN/m^2*FL/s	14.1 ± 8.4	30.4 ± 10.6	< 0.001	14.5 ± 7.1	35.1 ± 21.8	0.02	0.69

Values are mean ± SD. CSA, cross sectional area; P_0, peak force; SF, specific force; V_0, shortening velocity