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Recovery From Muscle Fatigue in Young and Older Adults: Implications for Physical Function

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RECOVERY FROM MUSCLE FATIGUE IN YOUNG AND OLDER ADULTS: IMPLICATIONS FOR PHYSICAL FUNCTION

A Dissertation Presented

by

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DEDICATION

To my father, John Foulis.

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To paraphrase Yogi Berra, I'd like to thank all the people who made this day necessary. First and foremost, I'd like to thank Anne Tonson, Jessica Fay, Terri O'Brien, Jacob DeBlois, and all of the undergrads from the Muscle Physiology Lab for all of their assistance on this project. Between recruiting participants, marathon data collections, reviewing documents, and overall keeping me sane, I couldn't have done this without you guys. Thanks also to the members of the Motor Control Lab, especially Stephanie Jones, Luis Rosado, and Mike Busa for all of the help with Study 2. And to my committee, as well as all of the graduate students, faculty and staff of the Kinesiology department, thanks for all the help, whether it be intellectually, physically, or emotionally.

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ABSTRACT

RECOVERY FROM MUSCLE FATIGUE IN YOUNG AND OLDER ADULTS: IMPLICATIONS FOR PHYSICAL FUNCTION

SEPTEMBER 2013

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As adults age, skeletal muscles become smaller and weaker, which can ultimately lead to declines in physical function and disability. In general, older adults produce less isometric force and dynamic power than younger adults. The effects of this weakness are amplified following a series of muscle contractions that result in muscle fatigue. Since daily routines consist of repeated series of activity followed by rest, it is important to understand how muscle recovers from fatigue. In particular, muscle power has been shown to be related to physical function and balance. Thus, understanding the process of recovery from muscle fatigue will help in preventing declines in physical function in older adults. This dissertation consisted of two studies designed to understand how muscle recover following fatigue and the implications of that recovery on physical function. Study one examined recovery from muscle fatigue following a constrained task. Young and older adults were fatigued to a similar degree using a dynamometer, and recovery of power at 4 velocities, central activation, pre-motor signaling, neural efficiency and contractile properties were recorded over an hour. To evaluate the functional implications of the recovery, ratings of perceived exertion were collected and

the amount of fatigue following a second fatigue bout was also recorded. The second study associated changes in physical function and balance with power following an ecologically-relevant fatiguing exercise. Following a 30 minute treadmill walk, chair rise time and balance were measured during the period of recovery from this task. As a result of fatigue, we saw increased power loss at high-velocities that did not recover over the course of an hour in older adults. . This finding was concurrent with other velocity specific changes in rates of force development, muscle acceleration, and pre-motor neural signaling. Functionally, we saw an increased in perceived effort during contraction in older adults, and an increased fatigue during a second fatigue bout. While chair rise didn't differ as a group with fatigue, there was a significant relationship with loss of high-velocity power and change in chair rise time over the hour recovery period. Balance declined immediate post-fatigue but appeared to recover to a point of greater stability over an hour. This dissertation provides novel insight about alterations in the recovery process following an acute bout of muscle fatigue, and ultimately provides data that may be useful for developing strategies to prevent disability in older adults.

PREFACE

Chapters 1 through 3 include the dissertation proposal as submitted to the Graduate School in March 2012. During the IRB review process, the maximum vertical jump was removed from Study 2. Chapter 4 and 5 correspond with Study 1 and 2, respectively. In accordance with the wishes of the committee, these chapters are formatted as manuscripts to be submitted for peer-review.

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GLOSSARY

Disability- the interaction between individuals with a health condition, and personal and environmental factors

Excitation-Contraction (EC) Coupling- link between excitation of the muscle membrane and the production of force that results from the release of calcium into the cytosol and the initiation of muscle contraction

Fatigue- acute loss in force production capacity of a muscle in response to contractile activity

Fatigue Resistance- ability to maintain or minimize the decline in maximal force production during muscle contractions

Functional Reserve- strength above the minimum force needed to perform a task

Low-Frequency Fatigue- fatigue that occurs during low- but not high-frequency stimulation, likely due to changes in Ca^{++} handling

Muscle Power- Product of muscle force and velocity of contraction

Neuromuscular Efficiency (NME)- ratio of force production to surface electromyography signal

Physical Function- objective performance of everyday activities such as walking or getting up from a chair

Rating of Perceived Exertion (RPE)- A 1-10 self-reported scale indicating one's opinion of the amount of effort required for physical work

Specific Strength- voluntary force per unit-cross sectional area

Strength- Maximal force generating capacity of a muscle

Symptomatic Fatigue- self-reported sense of exhaustion or tiredness

CHAPTER 1

INTRODUCTION

The human population of the United States is getting older. Current census projections suggest that the number of individuals over 65 years of age will increase from ~35 million in 2000 to ~90 million by the year 2050 (198). During this same time period, the proportion of the population over the age of 65 is projected to increase from ~12.5% to ~20%. While this increase in the older population reflects an overall improvement in medical care, it also leads to myriad new health problems. One such issue is the decline in neuromuscular function, which can lead to physical disability.

As individuals age, they face an increased risk of disability. According to a 2005 report from the US Surgeon General, the number of individuals reporting a significant disability increases from ~11% at age 20 to 45% by age 65. This number increases to 73% by age 80 (199). In addition to the personal and societal burden of physical disability, the economic burden exceeded $300 billion during the 1990s, with that number expected to increase further. Thus, understanding the mechanisms that lead to declines in neuromuscular function and the resulting disability is of great importance.

There are a number of possible mechanisms that lead to declines in neuromuscular function. One such mechanism is the age-related loss of strength and power. With aging, there is a decrease in muscle mass, which is known as sarcopenia (70). A number of studies have shown that both isometric strength (31, 32, 115, 155) and dynamic power (32, 53, 138) decline in older adults, changes that may or may not be associated directly with the loss of muscle mass. Power, in particular, has been shown to be a strong predictor of physical function (50).

Changes in both the nervous system and within the muscle itself may contribute to these changes in force and power in old age. Neural factors may include slowed rate of neuromuscular activation (46), slowed motor unit discharge rates (107), decreased neuromuscular efficiency (158), and alterations at the cortical level (101). Within the muscle, changes such as slowed contractile properties (53, 120) and altered calcium (Ca^{++}) handling (62, 180) may lead to declines in strength and power with age. A key concept to be explored in the proposed work is the possibility that age-related muscle weakness may be of greater concern when combined with the effects of muscle fatigue, defined as acute loss in force production capacity of a muscle in response to contractile activity.

A number of studies have demonstrated greater fatigue resistance, or less of a decline in muscle force in response to repeated muscle contractions, in older compared with younger adults during an isometric contraction protocol (17, 42, 65, 99, 110, 128). It has also been shown that this fatigue resistance may be lost and even reversed during high-velocity contractions (12, 31, 32, 53, 54, 145, 163). However, the mechanisms governing the recovery from a bout of fatiguing exercise, and the impact on functional performance, are not well understood. It has been shown that power may be slower to recover in older adults than young (120, 186). Since the goal of the recovery process is to restore the neuromuscular system to homeostasis, a number of factors associated with muscle fatigue likely play a role in recovery of power. Recovery of neural factors such as altered central drive (101), slowed discharge rates (51), and altered rates of neuromuscular activation (46) may limit power production. Within the muscle, contractile properties slow during fatigue in response to alterations in pH and metabolite

concentrations. It has been reported that contractile properties may be slower to recover in older adults (120), and that contractile properties are related to recovery of power (53, 106).

Furthermore, following fatiguing exercise, low-frequency force (i.e., force during electrical stimulation at < 20 Hz) may remain depressed for several hours (27, 68) due to impaired Ca^{++} release from the sarcoplasmic reticulum (207). This low-frequency fatigue has been demonstrated in both young and old to a similar relative degree (7). Similarly Kent-Braun et al reported a slowing of contractile properties consistent with changes in calcium kinetics during fatigue, but no differences by age (116). However, given the lower absolute strength (100, 155) and slowed motor unit properties (107, 177) observed in aged individuals, it is possible that the real-world consequences of low-frequency fatigue are greater in older adults. It has been shown in young adults that, in the presence of low-frequency fatigue, a second fatiguing bout can elicit greater fatigue than the original bout (192). Thus, there may be further consequences to older adults as fatiguing exercise bouts accumulate over the course of the day.

Even in the absence of fatigue, age-related muscle weakness can lead to older adults performing functional activities at a high percentage of their maximal strength (97). As a consequence, older adults have a smaller functional reserve, or amount of strength that can be lost before task performance becomes impaired (28, 188, 212). For example, even modest decreases in strength due to muscle fatigue have been shown to reduce functional performance (91, 120, 163) and balance (16, 69, 92). Further, older women are at a greater risk of disability than older men (108, 131), perhaps due to their lower baseline muscle strength and power (81). They presumably have a lower

functional reserve (131) and may be at an even greater risk of decreased physical function and balance following fatiguing exercise bouts. As muscle force and power recover from fatigue, the decrements in physical function will likely be reversed, but the time course of this recovery has not been determined.

The impact of muscle fatigue may extend beyond the acute muscle weakness it induces. It has been suggested that older adults have greater symptomatic fatigue, or overall sense of exhaustion, than younger adults (8). Likewise, the sense of effort during submaximal muscle contractions may be increased with low-frequency fatigue, since motor unit discharge rates (MUDR) at low, sub-maximal frequencies may not be sufficient to produce the same absolute force as before exercise (19). It has been shown that neuromuscular efficiency (NME), or force divided by the rectified, integrated surface electromyography (EMG) amplitude during voluntary, submaximal contractions (158), is decreased for more than an hour following a fatigue bout (7). Since most daily activities occur at a submaximal intensity (97), and low-frequency fatigue may have a greater effect on submaximal contractions where MUDR are lower (109, 207), age-related symptomatic fatigue may develop in part because older adults require greater effort to overcome low-frequency fatigue following physical activity. Support for this novel hypothesis is provided by the observation that older adults have greater perceived exhaustion than young during submaximal fatigue bouts (5).

Overall, while many investigators have studied the acute effects of muscle fatigue in older adults, there are few data about the degree and impact of muscle weakness during recovery from fatigue. By better understanding the mechanisms of recovery following

fatigue, we may be able to develop better interventions to prevent physical disability in older adults.

Significance of Dissertation

The goal of this project is to investigate the impact of muscle fatigue on physical function and balance, and to determine how this impact may differ in young and older adults. In addition, this project will examine the role of the recovery of force and power in mediating the recovery of physical function. Study 1 will compare the recovery of neural and muscular mechanisms of force and power production following fatigue. Study 2 will measure the recovery process of power and physical function in older adults. Throughout both studies, measurements of perceived exertion will be made in an attempt to link neuromuscular and symptomatic fatigue. A summary of the proposed pathway and division of studies is provided in Figure 1.

The knee extensor (KE) muscles will be studied, as weakness in these muscles is related to risk of mobility impairment (50, 211). Given the weaker muscles of women, and their greater risk of disability (108, 131), the participants will all be female. Understanding the recovery of muscle force and power in the KE muscles may provide insight about declines in physical performance in older adults. Ultimately, the data provided by this dissertation may be useful in developing novel strategies to prevent disability in older adults.

Study 1: Mechanisms of Recovery from Neuromuscular Fatigue in Young and Older Women

The aim of Study 1 is to investigate the neural and muscular mechanisms of muscle power recovery following a fatiguing contraction protocol. To provide a matched starting point for the recovery measures, young (30-40 years) and older (65-85 years) women will complete an isokinetic contraction protocol designed to fatigue the KE muscles to a similar extent, as well as to elicit low-frequency fatigue. The fatigue protocol will be performed twice, on separate days, so that both central (i.e., neural) and peripheral (i.e., muscular) variables can be measured. Maximal isometric force, the force-velocity relationship, and recovery of peripheral factors will be measured on one day, while neural recovery will be measured on a separate visit. Muscular factors will include the 10/80Hz stimulated force ratio, as a measure of excitation-contraction coupling, and muscle contractile properties, elicited by electrical stimulation. Neural factors will include measures of NME during submaximal and maximal contractions, the rate of neuromuscular activation, and the ratio of the voluntary to stimulated rates of force development, a measure of central drive. In addition, ratings of perceived exertion (RPE) will be recorded as an index of effort, which may be associated with muscle fatigue. Measures will be made at baseline and at regular intervals for 1 hour following the fatigue bout. Following 1 hour of recovery on the peripheral measurement day, a second fatigue bout will be performed, with 10 minutes of additional recovery measures to observe any acute differences in the recovery process.

H1.1: Relative recovery of isometric force will be similar in both age groups over the course of 1 hour, but recovery of power will be slower in the older group.

H1.2: Recovery of power during high-velocity contractions will be slower than recovery of power during slow-velocity contractions.

H1.3: The 10/80 Hz ratio will decline to a similar extent in young and old during exercise, and recover at a similar rate.

H1.4: Contractile properties will slow during fatigue, and will recover more slowly in the older than the young.

H1.5: Rate of neuromuscular activation will be lower in both groups following fatigue, and slower to recover in the old.

H1.6: The ratio of voluntary to stimulated rates of force development during maximal contractions will recover more slowly in the older adults than in the young.

Exploratory Hypothesis 1.1: NME during submaximal contractions equal to 20% and 50% of baseline maximal force will be higher in both groups following fatigue, but more so in the older adults.

Exploratory Hypothesis 1.2: Perceived effort (RPE) during submaximal contractions will be increased following the fatigue protocol, and will remain elevated throughout the recovery protocol.

Exploratory Hypothesis 1.3: When the fatigue bout is repeated after 1 hour of recovery, both groups will exhibit greater fatigue than the first bout, with the older adults showing a greater increase in the amount of fatigue.

Study 2: Recovery of Physical Function from Neuromuscular Fatigue in Older Women

The aim of this study is to investigate the impact of a fatiguing task designed to simulate everyday activity on changes in balance and physical function in older women. Physical function will be measured as the time to complete 10 chair rises, and balance will be measured using measures of postural sway during quiet stance. To complete this aim, participants will perform a 30-minute walking protocol on two separate days. On one day, recovery of force and power will be measured for 1 hour, as done in Study 1. On the second day, chair rise time, balance, and maximal vertical jump force will be measured prior to, immediately following the fatigue task, and at regular intervals thereafter, for 1 hour. During measures of physical function, participants will complete measures of perceived exertion to determine whether increased effort is required to perform the task.

H2.1: Force and power will fall following the fatigue protocol.

H2.2: Power during high-velocity contractions will be slower to recover than during low-velocity contractions.

H2.3: Chair rise time, balance, and maximal vertical jump force will decline following exercise.

H2.4: Recovery of chair rise time, balance, and maximal vertical jump force will be associated with the recovery of power.

Exploratory Hypothesis: Perceived exertion (RPE) of the physical function measures will be increased following the fatigue protocol, and will remain elevated throughout recovery.

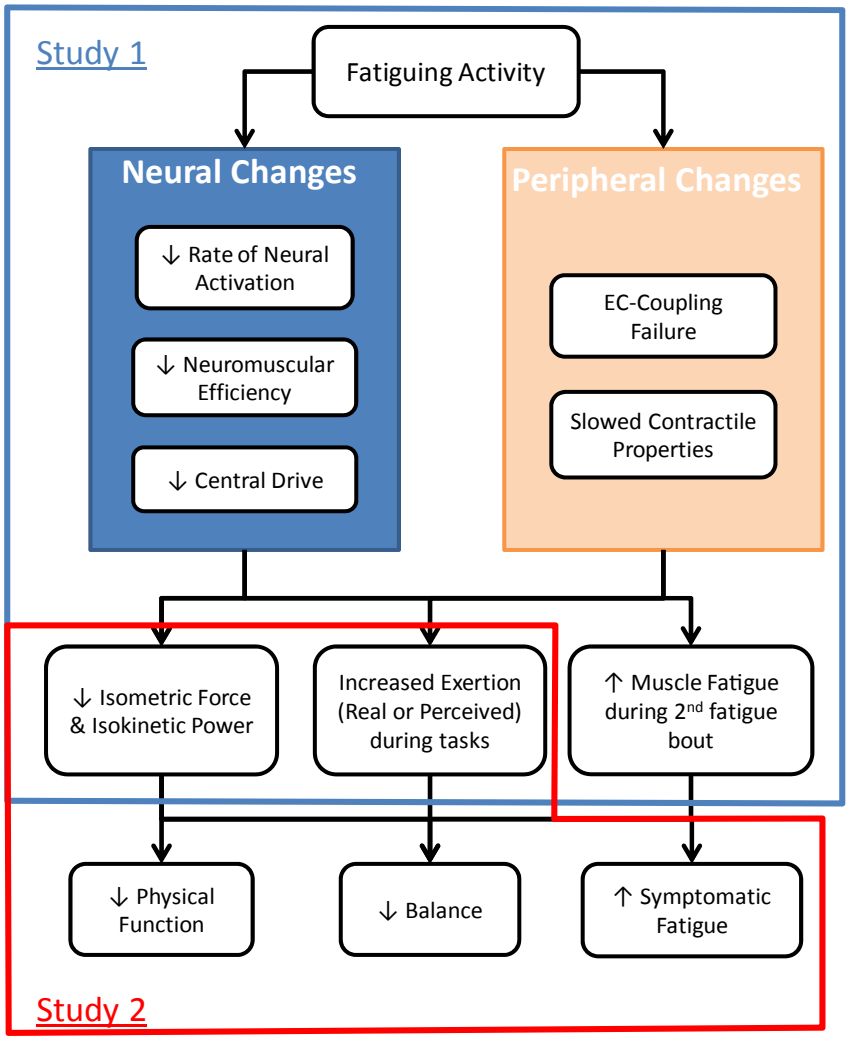

Figure 1.1: Conceptual Framework for Relationships between Fatigue, Physical Function, and Symptomatic Fatigue

CHAPTER 2

LITERATURE REVIEW

As individuals age, they become susceptible to a number of new health-related problems. Older adults are at increased risk for a variety of cardiovascular (124) and metabolic (14) diseases. In addition, a number of age-related changes occur in the nervous system and within skeletal muscles (6, 110, 111). Changes in the neuromuscular system can affect muscle force-generating capacity. Additional losses in force generation can occur during prolonged contractile activity. Ultimately, these changes may lead to declines in physical function and balance in this population.

The Aged Neuromuscular System

Muscle Size and Strength

There are a number of alterations to the neuromuscular system that occur in older adults (6, 110, 111). Changes can occur at the level of the central nervous system, such as decreased excitability or inhibition of the brain and spinal neurons. Downstream, changes in the periphery can occur at the level of the neuromuscular junction, sarcolemma, or within the contractile machinery of the muscle itself. All of these changes can ultimately affect the ability of the muscle to perform its primary function: contracting and producing force. These alterations in force-generating capacity may, in part, lead to disability. A commonly-used definition for disability is self-reported difficulty in performing everyday activities, such as walking (195).

One of the most common age-related changes reported in the literature is sarcopenia. Sarcopenia can be defined as the age-related loss in skeletal muscle mass (70).With age there is an overall decline in lean muscle mass, and an increase in the

amount of fat and non-contractile tissue (96). While the decrease in muscle mass had been noted by physicians for years, it was not until the 1990s that this phenomenon gained significant attention.

Recently, researchers have attempted to quantify and understand these declines in muscle mass. Horber et al used dual-energy x-ray absorptiometry (DEXA) to quantify appendicular lean mass in a cross-sectional study and observed a significant negative correlation between lean mass and age in 60 men (96). Notably, they observed only a trend for a decline in women. Larger scale studies, such as the Health, Aging, and Body Composition Cohort also used DEXA to study sarcopenia in over 1600 older individuals (81). At baseline, the average age of the participants was 73. Following a 3-year period, they observed an average annual decline in leg muscle mass of approximately 1%, with men losing slightly more leg mass than women. However, it is important to note that baseline leg muscle mass was 28% lower in the women, a difference that may have important consequences for physical function.

The loss of muscle mass appears to be more apparent in some muscles than in others. Kent-Braun et al (117) used magnetic resonance imaging (MRI) to separate contractile and non-contractile mass within the tibialis anterior muscle. Total cross-sectional area (CSA) of the muscle was not different in young and old, and lean muscle area was only about 12% smaller in older adults than younger. A separate study using similar techniques showed no significant change in muscle size of the dorsiflexors in 20-year old, 60-year old, or 80-year old men (146). Other muscle groups show a more profound decline in muscle size. Macaluso et al (138) showed 25% less muscle mass in the KE muscles in older compared with young women. Similarly, in the KE muscles,

Trappe et al (196)showed 27% less muscle mass in both older men and women, and Callahan & Kent-Braun (32) found a 28% decrease in size in older women. When two antagonist muscle groups were studied in the same participants, Klein et al observed a greater decline in elbow extensor muscle CSA than elbow flexor CSA in older adults (121). One of the factors that may contribute to the muscle-specific rates of decline in size may be changes in the pattern of use of muscle in old age (121). In addition, fiber type may play a role, as atrophy of the Type II muscle fibers has been shown to be greater than atrophy of Type I fibers in older adults (132).

In addition to the decline in muscle mass, there is also a decline in muscle strength in old age (81, 100, 115, 155). Voluntary isometric force has been shown to decline in a number of muscle groups. In a cross-sectional study of the adductor pollicis muscle, Narici et al (155) reported that force began to decline in adults after age 59. Kent-Braun et al (115) observed a 24% lower force in ankle dorsiflexor strength in older (aged 65-83 years) men compared with young (aged 26-44 years) men, but no difference in young and older women. McNeil et al (146) showed lower isometric force in 80-year-old men compared with 20-year-olds, but no difference in 60-year-olds. In agreement with the muscle-specific changes in muscle mass, greater muscle weakness has been observed in the KE muscles than the dorsiflexors. Macaluso (138) showed a 43% decline in muscle torque of the KE of older women (mean age 70 years) compared with younger women (mean age 23 years). Callahan et al (31) also showed a 25% decline in KE torque in healthy older women (mean age 71 years) relative to young women (mean age 26 years). In a cross-sectional study, Hunter et al (100) showed progressively lower strength of handgrip, plantar flexor, and KE muscle groups in women of increasing age. Notably,

active individuals were stronger than inactive, but activity was not able to prevent the decline of strength in any muscle group.

Muscle velocity and power also decline with age. A study by Lanza et al (129) indicated that fewer older adults were able to perform KE contractions at high velocities compared with young. Similar results were obtained by Callahan et al (32). Thus power, being the product of force and velocity, also declines with age. Lanza et al. (129) demonstrated age-related declines in the torque-velocity and power-velocity relationships in both the ankle dorsiflexors and KE muscles in a mixed population of men and women (Figure 2.1). A similar shift in the in the torque-velocity curve was observed by Callahan et al. (32) in the KE, such that older women had a lower V_{50}, the velocity that elicited 50% of peak isometric torque. Peak power and velocity continue to decline throughout old age, as it has been shown that both of these variables are lower in 80-year-olds compared to 60-year-olds (145). In a 12-year longitudinal study of older adults, a 2% yearly decline in dynamic muscle torque at $60°\cdot s^{-1}$ and a 2.5% per year decline at $240°\cdot s^{-1}$ have been reported (77). It has been suggested that this decline in power may be one of the most important determinants in the development of mobility disability in older adults (50).

Loss of muscle strength and mass may not occur in concert. While some studies have shown no impairment in specific strength (isometric strength/muscle cross-sectional area; (78, 115), other studies have suggested a disconnect between the losses in muscle size and strength (63). Macaluso (138) saw a greater difference in muscle strength than size in the KE of older adults compared with young, indicating lower isometric specific torque in this muscle group in older adults. In a large-scale, longitudinal study of older

adults, Goodpaster (81) observed a three-fold greater loss of KE muscle strength compared with lean muscle mass over a three year period. Callahan et al (32) have suggested that discrepancies between muscle size and strength may be greater at higher contraction velocities. Changes in neural and contractile properties thus may play a role in altering the relationship between size and strength.

Alterations in Neural Properties

At the neural level, modulation of muscle force is regulated primarily by two processes: recruitment and rate coding. Recruitment is the increase in the number of activated motor units (MU), from smallest to largest, as force levels increase (93). Rate-coding refers to changing the rate at which the MUs are activated, with more force being produced at greater MUDR (151).

There are a number of age-related changes in the nervous system that can have an effect on force production (6, 66), ranging from alterations at the cortical level (101) to changes in the motor neuron itself (40). It has been proposed that as individuals age, some of the faster motor neurons die off and the orphaned muscle fibers are then re-innervated by surviving, inherently slower, motor neurons (66). This process, known as MU remodeling, results in larger, slower MUs.

One of the apparent consequences of these neural changes is lower maximal MUDR (47, 107, 162, 178). Kamen et al (107) first showed that during maximal contractions of the first dorsal interosseous, older adults had slower maximal MUDR during than young. However, no difference was observed in the discharge rates during a contraction at 50% of maximal voluntary contraction (MVC) force. Connelly (47) later showed lower discharge rates across a range of submaximal and maximal intensities in

the tibialis anterior muscle in older adults. A similar trend also has been observed in a number of other muscle groups (162, 178). However, not all studies report differences in MUDR by age group. Roos (176) found no difference in MUDR across a range of intensities between young and old in the KE, and Foulis et al (74) showed similar maximal MUDR in the tibialis anterior in young and old. It is possible that physical activity patterns play an important role in moderating changes in MUDR with age, as a number of studies have shown an increase in MUDR even with short-term training (40). It is also possible that the response is muscle-group specific (52).

The importance of slowed MUDR may be minimized, though, by an overall slowing of muscle contractile properties (177). The force-frequency relationship has been shown to shift to the left in older adults (4, 155, 158, 194), allowing force to plateau at a lower activation frequency. However, this altered relationship may not hold true for all muscle groups (52); therefore, it may not completely mitigate the importance of slowed discharge rates. Additionally, slowed discharge rates may be important in the loss of power, especially during high-velocity contractions. Harwood et al (87) found increased discharge rates in higher-velocity contractions of the anconeus muscle than slower.

Changes in other neural properties may alter the ability of the nervous system to produce force. Christie et al (40) showed a longer duration of the after-hyperpolarization period of the motor neuron in older compared with young women. This change slows the ability of the motor neuron to produce additional action potentials, and thus is a potential mechanism for slowing discharge rates in older adults. Decreases in the rate of neuromuscular activation have been reported in older adults with mobility impairment,

which may be a possible mechanism for lower power production (46, 172). Changes also occur at higher centers of the nervous system (6). Decrements in central activation in older adults have been reported (190), although most studies report no impairment during isometric contractions (7, 31, 43, 116, 119, 122). Motor cortex excitability may also be reduced (161). Additionally, a number of studies (121, 138) have shown an increase in antagonist coactivation, which may limit agonist force production.

There is some evidence to suggest that older adults require greater neuromuscular effort during submaximal contractions. Ng et al (158) found that older adults had a lower ratio of voluntary force production per unit surface EMG, termed elsewhere as NME. It is possible that a higher EMG in older adults at the same relative force level as young adults may indicate a need for greater neuromuscular drive in order to achieve a given submaximal force level. Since most daily activities occur at submaximal intensities, this result could have important implications for the amount of effort required for physical function and balance tasks in older adults.

Alterations in Physical Function, Balance, and Symptomatic Fatigue

Muscle weakness due to age-related alterations in the neuromuscular system leads to declines in physical function, such as the ability to perform important everyday tasks such as walking or getting up from a chair. For example, weakness of the KE and ankle dorsiflexor muscles has been associated with impairments in gait and balance, as well an increased frequency of falls compared to stronger individuals (211).

Several investigators have proposed the concept that a minimum level of muscular strength is necessary to perform a variety of functional tasks (28, 188, 212). Above this minimum, people operate in a "functional reserve," and increased strength

does not affect performance of a functional task. However, when strength falls below this threshold, physical function declines, and eventually a point is reached where functional tasks can no longer be performed. Some investigators have tested this concept of a strength threshold for physical function. Rantanen et al (170) found that older women with an isometric KE torque below 2.3 $Nm \cdot kg^{-1}$ body mass showed slowing of gait speed compared with those above this level. Ploutz-Snyder et al (164) found longer chair rise time, slower gait speed, and longer stair ascent and descent times in older men and women who exhibited KE strength below 3.0 $Nm \cdot kg^{-1}$ of body mass. Recent work by Foulis et al (*submitted*) suggested that these functional reserve thresholds may also be associated with the intensity of daily physical activity, and that 10 minutes of daily moderate-to-vigorous physical activity (MVPA) may be sufficient to maintain physical function in older adults.

Using surface EMG, Petrella (163) showed that older adults required relatively greater muscle activation than young in order to perform a sit-to-stand task from a chair. Furthermore, Hortobayagi (97) has shown that older adults may operate closer to their functional reserve threshold than younger adults during functional tasks. By measuring peak KE torque during leg press exercise and 3 functional tasks, they determined that older adults perform chair rise, stair ascent, and stair descent tasks at 80%, 78%, and 88% of their maximal strength, respectively. Thus, a transient decline in peak force by 12% would lead to temporary impairment in physical function, and any long-term decline could lead to permanent functional deterioration and disability. Due to their low baseline strength, it is likely that older women work at an even greater percent of their maximal strength than men, and thus have a smaller functional reserve (108, 131). This may, in

part, explain the greater incidence of physical disability in women. Neural impairments may also contribute to the declines in physical function. Clark et al (46) observed a lower rate of neuromuscular activation in older adults with mobility impairments compared with healthy older adults. In addition, the rate of activation correlated with performance on a physical function battery.

Similar to mobility function, the ability to maintain balance and prevent falls is associated with leg muscle strength. Wolfson (211) demonstrated that increasing knee and ankle muscle strength results in improvements in function and balance. Campbell (33) used a multiple regression model to determine that leg strength was a significant predictor of falls in older adults. It has been suggested that lateral sway may be a potent predictor of falls (139), and that sway may be higher in people with muscle weakness (69).

Muscle Fatigue

Isometric Force and Dynamic Power

Muscle fatigue can be defined as the loss in the maximal force generating capacity of a muscle in response to exercise (79). As early as 1954 (148), it had been shown that peak muscle isometric force production is reduced following a series of muscle contractions. Many follow-up studies have confirmed this observation of decreased isometric force production in response to contractions (110). Dynamic torque and power are also reduced with muscle fatigue (105). Callahan et al (31) showed a decline in dynamic torque at $120°\cdot sec^{-1}$ following a dynamic fatigue protocol in the KE. Similar results were observed by Dalton (54) in the plantar flexors. Following a fatigue protocol, Jones et al (106) demonstrated that there is a downward and leftward shift of the

force-velocity curve, and an overall depression of the power-velocity curve. In addition, dynamic power loss during the protocol was greater than isometric torque, suggesting a primary impairment in velocity production with fatigue.

Mechanisms of Muscle Fatigue

As described by Bigland-Ritchie (18) and later adapted by Kent-Braun (111), fatigue can occur at any site along the pathway of force production (Figure 2.2). Thus, the source of muscle fatigue is multifactorial. Major sites of fatigue are within the muscle itself, through inhibition of the cross-bridges by metabolites or impairments in excitation-contraction (EC) coupling. Alterations in neural activation, such as slowing of MUDR and decreased neuromuscular excitability, may also contribute to fatigue.

Metabolic inhibition of contractile force has also been shown. Early studies implicated lactate production as a key source of fatigue (73). In response to fatiguing exercise, muscle increases its dependence on glycolysis, resulting in the production of lactic acid, which can then dissociate into lactate and proton (H^+). However, Chase and Kushmerick showed that lactate, per se, had no direct effect on muscle force production (36). Instead, it was the decline in pH (increased [H^+]) that led to lower force production. A number of studies, both in vitro and in vivo, have confirmed these results, thus implicating changes in muscle intracellular pH in the development of muscle fatigue (48, 57, 71, 112, 114, 116, 149).

The mechanism by which H^+ alters force production appears to be through its interaction with Ca^{++}. In vitro experiments have shown that changes in pH alter the pCa-force relationship (71). Fabiato suggested that lower pH can decrease the release of Ca^{++} from the sarcoplasmic reticulum (SR). In addition, it was suggested that H^+ can compete

with Ca^{++} for the troponin binding site and thereby inhibit force production (71). Under physiological conditions, though, pH does not drop low enough to affect Ca^{++} release, and $[Ca^{++}]$ is far greater than $[H^+]$, even at the lowest pH observed in fatigued muscle (2). Therefore, these mechanisms likely do not explain the effects of pH on muscle fatigue. Recently, Debold et al. suggested that low pH may increase the time that myosin is bound to actin, due to a slowing of ADP release from myosin (59). It is also believed that the interaction of high $[H^+]$ with inorganic phosphate (Pi) may be important in the development of muscle fatigue (160).

The buildup of Pi is another metabolic consequence of muscle contraction. To maintain constant ATP levels, phosphocreatine is broken down via the ATP-PCr pathway into its two constituents: creatine and Pi (2). During high-intensity muscle contractions, Pi concentrations can increase by an order of magnitude (57). Two forms of Pi exist, HPO_4^{2-} and $H_2PO_4^-$, with the diprotonated form increasing in concentration as the muscle becomes more acidic (160, 208). A number of studies have implicated Pi as a cause of muscle fatigue (48, 57, 116, 149, 179, 208). The mechanism by which Pi leads to muscle fatigue is likely two-fold. First, the release of Pi from myosin is a key step of the cross-bridge cycle (197). High [Pi] is thought to prevent the transition of the myosin from the weakly to strongly bound state (72). In addition, there is likely an interaction between Pi and Ca^{++} (191). It is believed that Pi can alter the release of Ca^{++} from the SR, and there is also evidence that Pi can bind to Ca^{++} and precipitate in the SR (3). This hypothesis is supported by a depression in the pCa-force relationship with increased Pi in skinned muscle fibers (60), particularly at $[Ca^{++}]$ similar to those observed in muscle fatigue (61).

Thus, it appears that, within the muscle, both a decrease in pH and an increase of Pi are sources of fatigue.

An important step in force production upstream of the accumulation of metabolites is the conversion of the electrical signal from the nervous system to a mechanical output (force) during a process known as EC coupling (67). In response to depolarization of the sarcolemma, the dihydropyridine receptors (DHPR) signal the ryanodine receptors (RyR) on the SR. This leads to a conformational change, allowing Ca^{++} release into the cytosol, where it binds to troponin and permits cross-bridge cycling. During fatiguing muscle contractions, there is evidence of a breakdown in EC coupling. This evidence originates from in vitro models. Using isolated frog muscles, twitch torque was shown to decline following a stimulated fatigue protocol, despite no change in the action potential amplitude (82). When caffeine was used to maximally stimulate the release of Ca^{++} from the SR, twitch force returned to the unfatigued level, showing a disconnect between the excitation signal and Ca^{++} release. Human studies in vivo have shown that, following stimulated and voluntary fatigue protocols, force from a twitch and low-frequency (20 Hz) tetanus decline to a much greater extent than force from a high-frequency (100 Hz) stimulus (68). Because force production was impaired only at low frequencies of stimulation, and there were differences in the rates of metabolic and 20Hz force recovery, EC coupling failure was implicated as a source of fatigue, particularly long-lasting fatigue. A number of subsequent studies have found similar results in vitro (207) and with human muscle in vivo (7, 11, 30, 167, 171, 181), under a variety of conditions.

The mechanism of EC coupling failure is not well understood, although calcium appears to play a key role (27). Early evidence pointed to a reduction in cytoplasmic [Ca^{++}] in response to muscle activation (82). This was first directly measured by Westerblad et al. using isolated mouse fibers (207). Rates of Ca^{++} release, uptake, and Ca^{++}-ATP pump activity are all reduced with fatigue (133), possibly because the presence of high levels of calcium during prior contractions activates other Ca^{++}-sensitive proteins, which have an inhibitory effect on future Ca^{++} release from the SR (38). Impaired Ca^{++} release does not appear to be of metabolic origin (68). The reason high-frequency (50-100Hz) force is unaffected while low-frequency (10-20Hz) force is depressed is that high-frequency stimulation releases Ca^{++} at a rate along the upper plateau of the pCa-force relationship, while low-frequency stimulation is on the steep portion of the slope (207). Thus, an inhibition of Ca^{++} release has a greater effect on low-frequency muscle activation. The exact pathway of this inhibition is not known (125).

At the neural level, declines in MUDR have been reported in a number of studies of muscle fatigue (20, 22, 41, 51, 141, 167, 178). Marsden et al. provide one of the earliest records of this phenomenon by reporting a profound decline in the discharge rates of a single nerve fiber during an MVC (141). Bigland-Ritchie et al. later used micro-electrodes inserted in the muscle to show a decline in mean MUDR during a sustained MVC (20). In a follow-up study, both force and MUDR were shown to remain depressed following a fatiguing exercise bout when a cuff was applied to make the muscle ischemic (22). Thus, the mechanism of the declines in MUDR appears to be due to a reflex affected by the intramuscular conditions. When blood flow was restored, recovery occurred normally. These data lead to the conclusion that there must be afferent

feedback, based on the metabolic condition of the muscle, which initiates a reflex that slows MUDRs. It appears that the group III and IV afferent sensory neurons provide a reflex stimulus to increase MUDR, and this stimulus is damped during fatigue. The stimulus that leads to the reflex inhibition is not yet known. Some investigators have proposed the "muscle wisdom hypothesis" which suggests that MUDR is modulated in conjunction with contractile properties in order to optimize force production (142). However, Bigland-Ritchie demonstrated in unfatigued muscle that when contraction speed (21) and muscle length (23) are manipulated, MUDR do not appear to be affected. Other results have supported the muscle wisdom hypothesis, by showing a matching decline in relaxation time following muscle stimulation and MUDR during a fatiguing task (123). Since group IV afferents are sensitive to changes in pH (55), changes in pH may lead to declines in MUDR (80), although this has not been directly tested.

Consequences of Muscle Fatigue

The combined neural and muscular changes that occur in the fatigued state may lead to alterations in neuromuscular efficiency. Bigland-Ritichie first noted that, in response to a sustained submaximal contraction, there was an increase in surface EMG (19). It was hypothesized that additional MUs were recruited in order to overcome low-frequency fatigue. This interpretation was further supported by Miller (150), who observed a decreased neuromuscular efficiency (force/EMG signal) during contractions at 60% of MVC following a four-minute contraction bout. Similarly, Allman and Rice (7) observed an increase in EMG during submaximal contractions following a fatigue bout.

In response to fatigue of the leg muscles, there are acute declines in physical function and balance even in healthy younger individuals. Petrella reported a decline in sit-to-stand transition time in response to a fatiguing bout of chair rises (163). A number of studies have shown that balance measures of center of pressure velocity and surface area during quiet stance are both increased following fatiguing leg contractions (37, 49, 204). These changes suggest a decrease in postural control and balance. Furthermore, the postural response to a balance perturbation is also impaired following fatigue (56), possibly indicating an increased risk of falls.

Recovery from Muscle Fatigue

While much data exist on the acute effects of fatiguing exercise, less is known about the neuromuscular recovery from fatigue and its functional consequences. In the absence of muscle damage, most studies report a rapid recovery of maximal force during which force returns to 80-90% of initial, although it often does not fully return to baseline within 10 minutes (12, 128, 150, 167). However, some studies have shown complete recovery of force within 10 minutes (106). Miller (150) showed near-complete recovery of maximal isometric force within 20 minutes following a 4 minute maximal contraction of the adductor pollicis. This was matched by the time course of the recovery of pH and PCr, suggesting a metabolic basis for the recovery of maximal isometric force. Klein (120) also showed complete recovery of maximal isometric force of the triceps surae 60 minutes following fatiguing exercise.

Dynamic power may take longer to recover than isometric force. While no direct comparison was made, data from Jones et al (106) suggests that power and velocity remain depressed following 6 minutes of recovery from KE muscle fatigue. In particular,

this may be due to impairments in velocity. Other studies have shown that power may remained depressed for over 30 minutes, possibly due to uncoupling of excitation-contraction (167).

Perhaps due to its long-duration nature, the recovery of EC coupling is much more widely studied than other recovery measures. Many of these studies show depression of force for hours to over a day (7, 11, 68). Since the effects of EC coupling failure are most apparent during low-frequency stimulation, a decrease in the ratio of low-frequency to a high-frequency stimulated tetanic force is often used to assess the presence of low-frequency fatigue. While high-frequency (50 or 100 Hz) force generally recovers within an hour, Edwards et al (68) showed that depression of 20-Hz stimulated force can last for over a day. Similarly, data from Allman and Rice (7) showed a depression of the 10Hz-50Hz stimulated ratio for over an hour following a 5 minute intermittent isometric fatigue protocol. Concurrent with their depressed power, Power et al (167) noted a depressed 10-50Hz ratio during 30 minutes of recovery following an eccentric fatigue protocol, possibly indicating a link between low frequency fatigue and power loss.

Most of the neural changes with fatigue recover relatively quickly. M-wave amplitude in response to a single twitch is often used as a measure of peripheral excitability. It has been shown to recover within 10 minutes following voluntary intermittent (7) and sustained (150) fatigue protocols. Motor unit discharge rates also recover relatively quickly. During a submaximal fatigue task designed to elicit fatigue to 50% MVC, maximal MUDR were shown to recover as quickly as 1 minute following the task in young adults (51). Bigland-Ritchie (22) showed a complete recovery of MUDR

within three minutes of non-occluded recovery following a 20-second maximal sustained hold. Discharge rates did not recover when blood flow was occluded. Since pH changes may have a relatively rapid early phase of recovery , slowed discharge rates with fatigue may be in response to feedback from the Group IV afferents, which are sensitive to changes in pH.

Neuromuscular efficiency appears to have a prolonged recovery, similar to that of low-frequency fatigue. Miller (150) observed that neuromuscular efficiency remained depressed for over 20 minutes of recorded recovery, despite a complete recovery of maximal force and PCr. Since the recovery of neuromuscular efficiency matched the response of the potentiated twitch, the decreased neuromuscular efficiency was attributed to an increased activation of the muscle in order to release sufficient Ca^{++} as a consequence of low-frequency fatigue. Allman and Rice (7) demonstrated that EMG during contractions at 60% of baseline MVC can be elevated for over an hour following a fatigue protocol.

While the acute effects of muscle fatigue on function and balance tasks have been studied, the recovery of these tasks following a fatigue bout is not known. Prior research has shown that there is a greater amount of fatigue during a subsequent low-frequency (20Hz) fatigue protocol imposed 15 minutes following an initial fatigue bout (192). Due to the effects of EC uncoupling, the muscle may have been more sensitive to further perturbations, particularly in the low-frequency range. Assuming that low-frequency stimulation might serve as an analog to submaximal discharge rates during balance and functional tasks, it is possible that there are long-term implications of muscle fatigue on

balance and physical function during the recovery period. One such implication could be the need for greater activation in order to perform these tasks.

Aging and Muscle Fatigue

Fatigue Resistance in Older Adults

It is well documented that adults lose a considerable amount of muscle mass (78, 81, 96, 117) and strength (45, 78, 110, 173) in old age. However, there are a number of other age-related alterations to the neuromuscular system (110, 111). Given the number of alterations in the aging neuromuscular system, it is not surprising that there are alterations in muscle fatigue in older adults. While most of these changes may appear deleterious on a superficial level, many of these changes actually result in greater fatigue resistance in older adults under a variety of conditions (42, 111).

Isometric fatigue is generally reported to be less in older adults than in young (42). Ditor and Hicks (65) showed a decrease in fatigability of the adductor pollicis following a three-minute intermittent fatigue protocol. Kent-Braun and colleagues have shown fatigue resistance in older adults in the tibialis anterior muscle under a variety of conditions including incremental tasks (116), and intermittent MVCs with (43, 128, 182) and without (43, 127) blood flow. Fatigue resistance is also maintained during isometric conditions when fatigue is measured as endurance time (99, 155). However, isometric fatigue resistance is not universal even within the same participants. Bemben (17) reported age-related fatigue resistance in the thumb adductors and ankle plantar flexors, but not the ankle dorsiflexors or finger flexors.

While isometric fatigue is generally less, older adults most often have been shown to have similar or greater fatigue under dynamic conditions. Callahan et al observed

fatigue resistance to 4 minutes of isometric contractions of the KE muscles, but no difference in fatigue following a 4 minute dynamic protocol in the same individuals (31). In a follow-up study, Callahan and Kent-Braun (32) determined that relative dynamic fatigue resistance could be manipulated by altering contraction velocity. Specifically, older adults fatigued less than young during isometric contractions, more than young during high-velocity contractions, and similar to young adults during contractions matched for relative position on the force-velocity relationship. The dependence of age-related muscle fatigue resistance on contractile velocity has also been reported by other researchers (53, 54). These studies are in agreement with data from Petrella (163), who showed that velocity decreased faster in older than young during a dynamic fatigue test with a constant resistance of 40% MVC. The relative degree of velocity-dependent fatigue may be greater as age increases, as McNeil (145) showed greater power loss in 80 year old men compared to 60 year old and young (22-33 year old) men. Increased fatigue during dynamic contractions does not appear to influence the isometric response. Following a dynamic fatiguing task which induced greater power loss in old than young, isometric force was better preserved in the old compared to the young (54).

Mechanisms of Alterations Muscle Fatigue in Older Adults

The mechanisms of age-related alterations in muscle fatigue are just as multifactorial as the causes of fatigue itself. Muscle metabolism has been shown to be altered in older adults, likely leading to changes in muscle fatigue. At the end of an incremental fatigue test, it has been shown that older adults have a higher pH, lower [P_i], and lower [$H_2PO_4^-$] (116). This is likely due to alterations in energy production. Lanza et al. showed that older adults depend more on oxidative phosphorylation and less on

glycolysis to produce ATP during a 60s MVC compared to a younger, activity-matched group (126). This preference was not due to impaired glycolytic metabolism, as demonstrated during ischemic contractions (127). The reduced dependence on glycolysis in older adults leads to less H^+ accumulation. In addition, total ATP cost during 6 MVCs was lower in older adults, despite no differences in muscle strength, suggesting older adults are more economical at producing force than younger adults. Tevald et al. supported this result by showing the ATP cost of contraction to be lower in older adults during stimulated twitches and tetani when compared to young (194). Even though the slope of the fatigue-[$H_2PO_4^-$] relationship has been shown to be the same between young and old (116), suggesting that the metabolites have a similar effect on muscle fatigue, the decreased cost of contraction results in a decreased demand for ATP production and decreased buildup of these fatigue-inducing metabolites.

It is unclear whether EC coupling is altered in older adults. Renganathan et al. have shown that muscles in older rats have a lower ratio of DHPR to RyR, suggesting that Ca^{++} release may be less responsive to neural activation (174). Furthermore, the amount (62) and rate (180) of Ca^{++} released from the SR in isolated muscle fibers is also lower in aged animals. These results would suggest that older adults may be more susceptible to low-frequency fatigue than young. When this hypothesis was tested in humans, no difference in low-frequency fatigue was observed (7, 43, 182). However, Power et al (166) did observe a greater decline in the 10/50 Hz tetanic ratio in older women during, and several minutes following, a fatiguing bout. Thus, the limited literature on the subject would suggest that despite differences in Ca^{++} handling in resting

muscle, it is unclear whether alterations in EC coupling exist, and whether they may affect muscle fatigue in older adults.

Changes at the neural level may also contribute to the decreased isometric fatigue observed in older adults. In conjunction with the slowing of contractile properties, which results in a leftward shift in the force-frequency relationship (4, 155, 158, 194), older adults use lower MUDR to achieve same relative forces as young (4). This may lead to the decreased metabolic cost of contraction and reduced fatigue (194). The results of studies of aging on the fatigue-induced declines in MUDR are inconclusive. Rubinstein et al showed that, despite lower baseline strength and MUDR, there was better maintenance of force and maximal MUDR in older adults following a fatiguing test (178). However, no age-related differences in the decline of MUDR were observed following sustained contractions at both 75% MVC (51) and 50% MVC (41). Thus the potential impact of age-related alterations in MUDR on power are not known at this time.

Consequences of Muscle Fatigue in Older Adults

Due to lower baseline isometric strength and dynamic power in older adults, it is likely that the acute consequences of muscle fatigue are greater in older adults than in young. This is despite greater fatigue resistance of the old. Allman and Rice (7) showed similar declines in the 10-50 Hz tetanic force ratio following a fatigue test, suggesting similar amounts of low-frequency fatigue in young and older individuals. They also showed similar increases in surface EMG during contractions at 60% of baseline force. While this may suggest that EC uncoupling has a similar effect on young and older adults, it is difficult to directly assess from surface EMG whether or not young and older adults are using the same neural strategies to overcome low-frequency fatigue (39). In

addition, it is important to note that Ng (158) showed baseline differences in neuromuscular efficiency only during low intensity (10-20% MVC) contractions, and not at 60% MVC.

There are also age-related alterations in the acute functional consequences of muscle fatigue (92). This is not unexpected, as muscle power has been shown to be predictive of disability (50). Maximal vertical jump height is diminished to a greater extent in older adults than in young for more than an hour following muscle fatigue (120), suggesting that other mobility tasks demanding power may also be affected. Helbostad (91) showed that, following a fatigue test involving repeated chair rises to exhaustion, several gait characteristics including step width, step length variability, and mediolateral trunk acceleration amplitude were all negatively affected. Velocity of a sit-to-stand transition also declined following a fatigue task (163). While there was not a significant age-by-fatigue interaction in this study, there was an effect of age, such that older adults had lower velocities at both baseline and the fatigued condition.

Balance is also affected acutely by a bout of muscle fatigue in older adults (92). Although there was no young group for comparison, following dynamic fatigue of the ankle and knee muscles, Bellew et al found decreased balance performance on three functional balance tasks: modified Functional Reach Test, Lower-Extremity Reach Test, and Single-Limb Stance Time Test (16). Egerton showed that young, healthy older, and balance-impaired older all had similar increases in mediolateral center of pressure displacement, a key predictor of balance, following fatiguing leg exercise(69). While the change in postural control between groups was the same, baseline performance was impaired in the healthy older relative to the young, and moreso in the balance-impaired

older. These results suggest that fatigue could be enough to the increase risk of falls in older adults, particularly those in the beginning stages of mobility impairment.

Alterations in the Recovery from Muscle Fatigue in Older Adults

There are mixed results in terms of differences in the recovery of muscle fatigue in young and older adults. Lanza et al (128) showed no age-by-time interaction during the recovery of isometric torque or dynamic power in the ankle dorsiflexors following fatigue. Similarly, there were no effects of age during recovery of isometric force of the plantar flexors (51), dorsiflexors (116) or KE (120).

In contrast, there may be greater effects of age on the recovery of power following fatigue. Power (166) showed that relative power loss following fatigue is greater in old than in young following 10 minutes of recovery. Schwendner et al reported that older women with a history of falls had a slower recovery of power during the first few minutes following KE fatigue compared with young women (186). In a study by Klein et al, maximal jump height, a measure dependent on muscle power, was lower in older, but not younger, adults for an hour after a fatiguing muscle task (120). Since maximal isometric force had completely recovered, it is likely that this prolonged depression of power was due to impairment in muscle velocity production. A number of studies have linked contractile properties to power production (32, 53, 106), and it has been shown that contractile properties may fatigue to a greater extent (53) and be slower to recover in older adults (120), although this is not always the case (116).

The process of recovery of EC coupling failure is not clear. Powers (166) showed an initially lower 10-50 Hz stimulated ratio in older adults post fatigue, but by two minutes of recovery, there was no age-related difference for the remaining 30 minutes of

data collection. Allman and Rice (7) showed no differences in the recovery of low frequency fatigue for 60 minutes following fatigue.

On the neural side, there are no reported differences by age in the recovery of the M-wave amplitude, suggesting no effect of age on the recovery of peripheral excitability (43, 116). There have been some reports of slowing in supraspinal fatigue in older adults. Hunter et al (101) showed an increase in motor-evoked potential area in older adults over the first 10 minutes of recovery, despite a similar decline in this variable in young and old at the end of a fatiguing submaximal hold. These results suggest an age-related alteration in the recovery of cortical excitability. In the only known study measuring MUDR during recovery from fatigue, it appears that there is a slowed recovery of MUDRs in older adults (51). However, this is confounded by the fact that the fatigue test was to task failure, and older adults took longer to reach task failure.

There are few data on the long-term functional consequences of the recovery from fatigue in aging adults. Allman and Rice (7) showed no difference in young and old in the recovery of increased surface EMG during submaximal contractions following fatigue. There currently are no studies tracking age-related alterations in physical function or balance through a recovery period. However, given the possibility of a slower recovery of muscle power and velocity, it seems likely that functional performance and balance would be affected. Since older adults already perform many functional tasks at greater than 80% of their muscular capacity (97), even a 20% reduction in force or power will lead to some functional impairment. In addition, it is not known whether an initial fatiguing exercise bout can have an effect on fatigue resistance during subsequent exercise bouts. Baudry et al (12) reported a protocol of 5 intermittent

bouts of 30 concentric contractions, with 1 minute of rest between each bout. They showed a greater increase in fatigue in older adults compared to young after the first bout.

Symptomatic Fatigue in Older Adults

Symptomatic fatigue can be defined as a subjective measure of overall tiredness or exhaustion and is a common complaint of older adults (8). Symptomatic fatigue may be an early symptom of a disease process (8). In particular, fatigue during daily activities has been correlated with the risk of disability (9) and even mortality (10). Often, the exact source of symptomatic fatigue can not be identified (1). Recently, muscle strength has been shown to be a modifier of the relationship between mobility-related symptomatic fatigue and physical function, in the form of walking speed (140).

Because of the relationship between strength and symptomatic fatigue, it is possible that there is a further connection between symptomatic and muscle fatigue. Based on the work of Manty et al, an acute decline in muscle force and power likely contributes to symptomatic fatigue (140). If older adults lose power at a greater rate than young and are slower to recover it (120, 166), the accumulation of activities over the course of the day may lead to a greater accumulation of symptomatic fatigue.

Older adults likely are working at a greater relative workload during many daily tasks (97). Although most tasks normally do not require maximal effort, the presence of EC uncoupling may necessitate increased neural activation in order to overcome the effects of EC coupling failure and produce submaximal levels of force (19, 109). Relative to young adults, weaker muscles and slower baseline MUDRs may require older adults to increase their neural input by a greater degree in order to produce sufficient force to perform functional tasks. This hypothesis is supported by data from Allman and

Rice (5), who reported greater ratings of perceived exertion in older adults compared to young during an intermittent submaximal fatigue task. However, there were no neural measures during this study, so this hypothesis has not yet been directly tested.

Summary

Despite extensive research on muscle fatigue in older adults, there remains a number of gaps in the literature. There is little information about the recovery of power, a key factor in physical function (50). While Jones et al have provided some data in young adults regarding the acute change in the force-velocity relationship following fatigue (106), the acute effects in older adults, as well as the recovery of this relationship, are not yet known.

It is also clear that there are changes in neuromuscular efficiency in response to both age (159) and fatigue (7, 19, 150). The decline in neuromuscular efficiency in response to fatigue may last more than an hour (7). The functional consequences of age-related changes in neuromuscular efficiency are not known.

There are also many questions remaining regarding EC coupling failure in older adults. Evidence exists both supporting (62, 166, 180) and refuting (7, 43, 116) greater EC coupling failure in the aging population. Even if there is not greater failure in older adults, the functional consequence of low-frequency fatigue in performing everyday tasks has not been fully explored. Given that older adults are generally weaker at baseline (78, 100, 155), are performing tasks closer to their maximal effort (97), and have less of a functional reserve (28), they may have to work harder to overcome low-frequency fatigue (109), possibly leading to greater effort and symptomatic fatigue (8). Additionally, it is possible that accumulation of low-frequency fatiguing bouts over the course of the day

may attenuate fatigue resistance, leading to a progressive increase in their symptomatic fatigue.

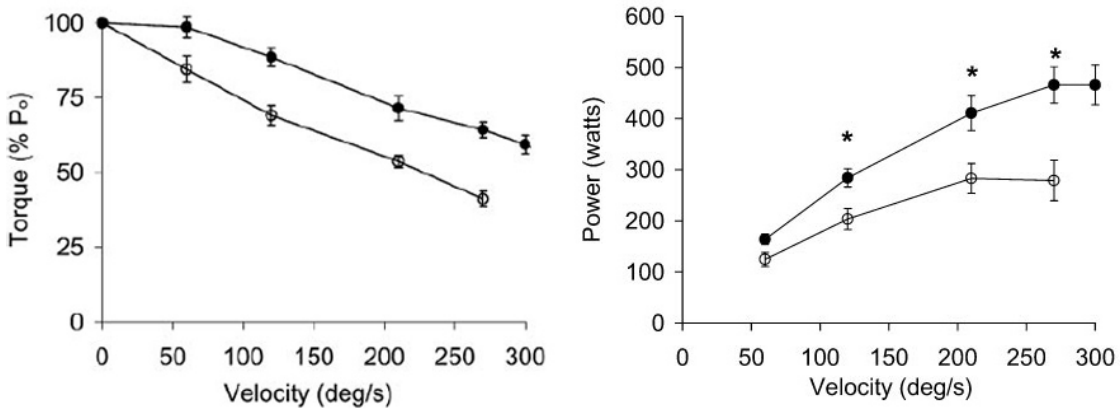

Figure 2.1: Torque-Velocity (left) and Torque-Power (right) Relationship in the KE of Young and Older Adults. Young are shown in filled circles, older are shown in open circles.

Adapted from Lanza 2003 (129)

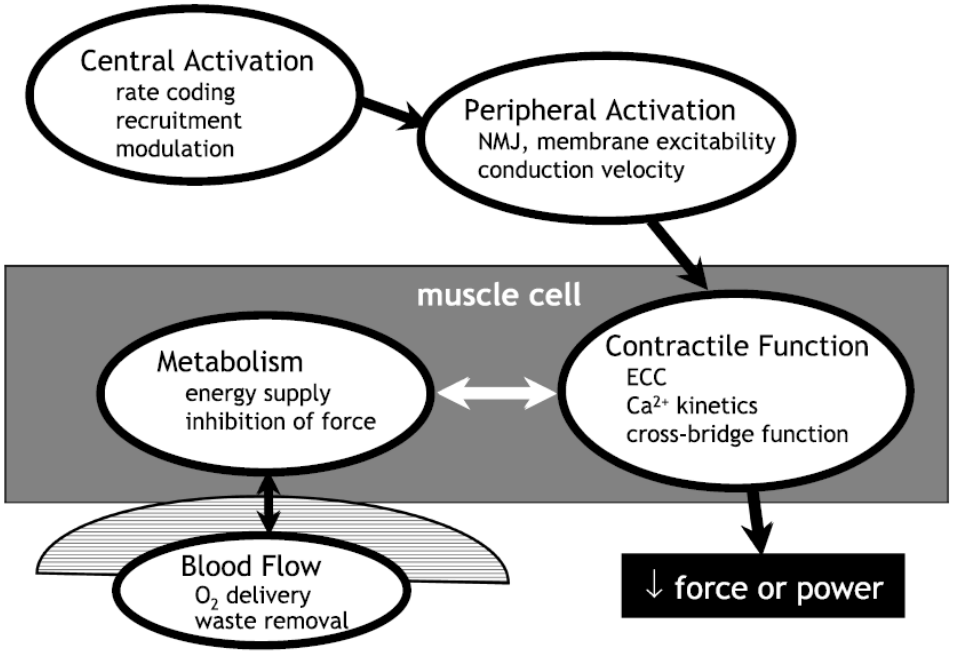

Figure 2.2: Pathway of Force Production. Alterations at any level can lead to muscle fatigue.

From Kent-Braun 2009 (111)

CHAPTER 3

PROPOSED METHODS

Participants

For study 1, the subject population will consist of 12 young (30-40 years old) and 12 older (65-85 year old) women recruited from Amherst and surrounding communities using flyers, website posts, and mailings. Because of their lower strength which can lead to a greater risk of disability (108, 131), the participants will all be female. Sample sizes are based on the ability to detect a clinically relevant 10% difference in muscle power, with 80% power and a within-group standard deviation of 10% (Callahan, unpublished data). Groups will be matched for physical activity, and all participants will be sedentary to recreationally active, defined as not exceeding the current physical activity recommendations of 75 minutes of vigorous, or 150 minutes of moderate physical activity per week, (156, 200). Volunteers who participate in cycling, rowing and swimming will be excluded due to our inability to capture these activities using accelerometry. In addition, no participants may have taken part in a strength training program in the past year, and their training status will be constant for at least the previous 6 months.

All participants will be relatively healthy, non-smokers and free of any limb injury that could affect physical performance. No participants will have a history of metabolic disease, neurological disease, pulmonary disease, stroke, myocardial infarction, or heart revascularization surgery. Women with other medical conditions may be included in the study as long as they have been clinically stable for at least 1 year and their disease would not have any effect on the outcome measures or participant safety.

Individuals on beta-blockers will be excluded from the study due to the possible effects of these drugs on exercise capacity. Physician's consent will be obtained for all older women prior to their participation in the study. Before enrollment, all participants will read and sign an informed consent document as approved by the University of Massachusetts, Amherst human subjects review board, and in accordance with the Helsinki Declaration. All subject information will be coded in accordance with HIPPA standards, ensuring subject confidentiality. Participants will receive $50 compensation for completion of each study.

For Study 2, a total of 24 older women will be studied, which will provide 80% power to detect a 6% change in muscle power from baseline based on a 10% standard deviation. When possible, members of the older cohort from Study 1 will be included in Study 2. Additional replacement participants will be recruited as necessary to attain a group size of 24. All criteria for the study population will remain the same.

Summary of Protocols

Study 1

Study 1 will require 3 (young group) or 4 (older group) visits to the Muscle Physiology Lab at the University of Massachusetts, Amherst, plus 1 visit to the Amherst Community Health Center for an MRI. To ensure complete recovery between visits, while minimizing any effects due to long-term changes, the time between visits will be at least 4 days, but no more than 2 weeks. Participants will be asked to refrain from exercising for 24 hours and consuming caffeine for 8 hours prior to each visit, due to their influences on muscle function and fatigue.

Visit 1.1 (Paperwork Visit) is required only for the older women. This additional visit for the older group is needed in order to fill out a letter to their personal physician prior to participating in the study. During this visit, participants will fill out an informed consent, as well as health and fatigue questionnaires. Participants will also complete the Short Physical Performance Battery (SPPB,(83, 84)), which measures physical function using chair rise time, balance time, and gait speed. In addition, blood pressure and anthropometrics will be recorded during this visit.

Since the young do not have to complete Visit 1.1, they will begin Visit 1.2 (Habituation) with the same paperwork, blood pressure and anthropometric measurements that the older women completed on the first visit. All participants will then warm up with 5 minutes of light cycling (Schwinn, Nautilus, Inc., Vancouver, Washington) followed by stretches of the KE and flexor muscle groups. They will then be positioned on a Biodex dynamometer (Biodex Medical Systems, Shirley, NY), with all settings recorded so that the participant is in the same position for all visits. Participants will be familiarized with the stimulated and voluntary force measures, and the torque-velocity measurements will be made. Following these measures, participants will be familiarized with the fatigue task. At the end of Visit 2, participants will receive an accelerometer (Actigraph, LLC Pensacola, FL) and activity log, and instructed in their use. Accelerometer data will be used to calculate the participant's physical activity level, in order to ensure that there is no difference across groups.

So that there is no effect of the order of the two fatigue visits, Visits 1.3 and 1.4 will be blocked and sequentially assigned across study groups. Thus, each group will have an equal number of individuals who complete each visit first. Visit 1.3 (Recovery

of Power and Force) will consist of a warm-up, baseline strength measures, a unilateral fatigue protocol, and recovery measures of strength and 10 and 80 Hz stimulation. Primary outcome measures will include isometric force, power at 3 velocities, the 10/80 Hz ratio and stimulated and voluntary contractile properties, to measure central and peripheral recovery. Recovery measures will be made 0, 2, 5, 10, 30, 45 and 60 minutes post-exercise. Following 1 hour of recovery, participants will repeat the fatigue protocol and measures of force and power again will be recorded.

Visit 4 (Neural Recovery) also will consist of a warm-up, baseline strength measures, a unilateral fatigue protocol, and recovery measures. The recovery measures for this visit will consist of MUDR and NME measures at 20%, 50%, and 100% of MVIC, along with measures of perceived exertion during each contraction. Recovery measures will again be made 0, 2, 5, 10, 30, 45 and 60 minutes post-exercise. A final visit (Visit 1.5) to Amherst Community Health Center for magnetic resonance imaging (MRI) of the thigh will be scheduled either prior to Visit 3 or 4, or on a separate occasion, depending on scheduling. A summary of procedures for each visit is provided in Figure 3.1.

Study 2

Study 2 will require 4 visits to the Muscle Physiology Lab at the University of Massachusetts, Amherst using the same guidelines on the spacing of visits and blocking of Visits 2.3 and 2.4 as used for Visits 1.3 and 1.4 in Study 1. Visit 2.1 (Paperwork) will be the same as the first visit in Study 1, and will be waived for any participants of that study. Visit 2.2 will begin with the same stretching and baseline strength measures as in Visit 1.2. Participants will then perform contractions at a range of velocities to produce a

full force-velocity relationship. The visit will end with an introduction to the treadmill protocol and the 3 measures of physical function.

Visit 2.3 (Recovery of Power and Force) will consist of a warm-up, baseline strength measures, a 30-minute walking protocol designed to induce muscle fatigue, and 1 hour of recovery measures of isometric strength and power. Visit 2.4 (Functional Recovery) will consist of a warm-up, baseline strength and physical function measures, the same walking protocol, and 1 hour of functional measures during recovery. These functional measure will be time to complete 10 chair rises, balance during quiet stance, and maximal vertical jump force. A summary of procedures for each visit in Study 2 is provided in Figure 3.2.

Force Measurement- Dynamometry

KE isometric torque and dynamic power will be measured during Visits 1.2, 1.3, and 1.4 for Study 1 and Visits 2.2 and 2.3 for Study 2. Measurements will be made using a Biodex System 3 dynamometer, as has been done previously in our lab (31, 32, 129). Participants will be seated with the hips at 90° and a resting knee angle of 100° extension. Torque, velocity and position signals from the Biodex will be output to a customized Matlab (Mathworks, Natick, MA) program, where it will be saved for future analysis. All data will be recorded at 1000 Hz for voluntary contractions and 2500 Hz for stimulated contractions.

Participants will perform maximal voluntary isometric contractions (MVIC), each sustained for approximately ~3-4 s. Verbal encouragement will be provided by the investigator and visual feedback will be provided by way of a lighted box. Participants will perform 3 MVICs, with 2 minutes of rest between contractions. If 2 peak values are

not within 10% of each other, an additional MVIC will be obtained. Peak torque (Nm) and the maximal rate of voluntary torque development (see Stimulated Measures) will be calculated from these contractions.

Maximal voluntary dynamic torque (MVDC, Nm) and power (W) will be measured over a 70° range of motion (100°-170° of extension), for 10 velocities. Participants will be instructed to kick out as quickly and as hard as they can, relax as soon as they reach the end of their range of motion, and allow the lever arm to passively return the leg to resting position. At each test velocity, participants will complete 2 series of 3 rapid contractions, with each series separated by 2 minutes of rest.

Following determination of peak isometric force, the baseline force-velocity relationship will be assessed during the second visit. As done previously (32), peak MVDC will be measured at 10 velocities from 30-300°· s^{-1} at 30°· s^{-1} intervals. Data will be expressed relative to MVIC, and fit to a second-order polynomial so that the velocity at which 50% (V_{50}) and 75% (V_{75}) of MVIC is generated can be calculated (Figure 3.3). The V_{50} will be used to characterize the participants based on their force-velocity relationship. The V_{75} variable will be the velocity used for each individual for the fatigue test on Visit 3, as it has been shown to elicit similar fatigue in young and older adults (32).

Muscle Stimulation

During Visits 1.2 and 1.3 of Study 1, muscle stimulation will be done over the motor point of the quadriceps muscles in order to determine muscle properties independent of input from the central nervous system. One 7.6 x 12.7 cm self-adhesive electrode (FastStart; Vision Quest Industries, Irvine, California) will be placed over the

quadriceps, distal to the inguinal crease, and the other will be placed just superior to the patella. Using a constant-current stimulator (DS7A; Digitimer, Hertfordshire, UK), stimulations will be induced at a current for which a 500 ms, 80 Hz train elicits 50% of MVIC force. The pulse duration will be 200 μs.

Muscle contractile properties will be measured using the 80Hz isometric tetanic train (31, 32). Peak torque, maximal rates of force development and relaxation, and half-relaxation time will be calculated from the tetanus, as measures of peripheral function. The rate of force development during a MVIC will also be normalized to the stimulated rate of force development. Any decrease in that ratio will be indicative of central drive failure (118). To assess EC coupling, peak force during a 10-Hz, 0.5s stimulated isometric tetanic train will also be determined, and the ratio of 10/80 Hz calculated. Any decrement of the 10/80Hz ratio will be indicative of EC failure (68, 206).

Electromyography- Surface Electrodes

Surface electromyography (EMG) will be recorded during Visit 1.4 of Study 1. Surface EMG will be collected using a bipolar electrode placed over the vastus lateralis muscle. The electrode is a paired Ag/AgCl electrode (Therapeutics Unlimited, Iowa City, IA), 8-mm in diameter with a separation of 2 cm. Signals will be amplified by a Theraputics amplifier (gain = 2,000), high-pass filtered (cutoff = 20Hz), and recorded at 2500 Hz. Surface EMG signals during 5-s isometric contractions at 20 and 50% of baseline MVIC torque will be used to calculate NME ($N \cdot mV^{-1}$). EMG data during a 0.5 s window corresponding to a plateau in force at target will be rectified and integrated. The ratio of contractile torque (Nm) to rectified EMG signal (mV) will be calculated. In addition, lag in neuromuscular activation (ms) and rate of neuromuscular activation (%

maximal EMG·ms^{-1}) will also be measured (46, 172). As illustrated in Figure 3.4, the lag in neuromuscular activation is defined as the delay between the time at which EMG amplitude exceeds 3 SD of the resting amplitude and the time of initiation of force development. Rate of neuromuscular activation is calculated as the derivative of the EMG signal, normalized to the maximal EMG signal from an MVIC, during that time period.

Physical Function and Balance- Chair Rise and Force Plate

Physical function and balance will be measured during Visit 2.4 of Study 2. Physical function will be assessed using a series of 10 consecutive chair rises, as older adults perform that task at a high percentage of their maximal strength (97), and chair rise performance is affected by fatigue (163) in young and older adults. Chair rise time (s) will be recorded as the time required to completely stand up and sit back down in a chair (seat height = 45 cm) 10 times, without the use of the arms. Time will start by cue of the investigator and stop when the participant is seated in the chair for the 10th time.

Balance will be assessed in the Motor Control Lab at the University of Massachusetts during quiet stance using 2 side-by-side force plates (AMTI, Newton, MA). As is standard procedure for balance measures (44, 201), participants will place one foot on each plate parallel to each other and shoulder width apart. Data will be recorded at 100 Hz using Qualisys track manager (Qualysis Medical AB, Gothenburg, Sweden). Postural sway and time to contact of the stability boundary will be calculated separately in the anterior-posterior and medial-lateral directions, as done previously by Van Emmerik et al (201).

As an additional measure of dynamic function (120), participants will also complete a maximal vertical jump on the force platforms. Participants will be instructed to jump as high as they can 3 times in a row with 5 seconds of rest between each jump. Maximal ground reaction forces will be recorded for each jump. Peak ground reaction force normalized to body mass (N/kg) will be reported.

Fatigue Test and Recovery

Study 1

For study 1, the fatigue test will consist of 4 minutes of MVDCs over the 70° range of motion at each participant's V_{75} velocity (32). Participants will be cued for all contractions by an auditory signal. To maintain a constant 30% duty cycle for all participants, the timing of the contractions will be individualized for each participant, depending on their force-velocity characteristics. Thus, the number of contractions will also vary by participant. Fatigue will be calculated as:

[(average peak power from the final 10s of contractions) / (baseline peak power) x 100]

Immediately after the protocol, and for one hour following, recovery measures will be collected. During Visit 1.3 (Recovery of Power and Force), recovery measures of maximal isometric force and power will be made 0, 2, 5, 10, 30, 45 and 60 minutes post-exercise. To determine the effect of velocity on the recovery of power, peak power will be assessed at a slow velocity ($30°\cdot s^{-1}$), a velocity relative to each participant's own force-velocity curve (V_{75}) , and a fast velocity ($270°\cdot s^{-1}$), which is the fastest velocity all older participants could attain in a prior study (129). Stimulated 10Hz and 80Hz measures will also be recorded at 0, 10, 30, 45 and 60 minutes post-exercise, to provide measures of central and peripheral function. Following 1 hour of recovery, participants will repeat the

same fatigue protocol, in order to determine the effects of a second fatiguing bout on force and power. Recovery measures of maximal isometric force and power will again be made 0, 2, 5, and 10 minutes post-exercise.

The fatigue protocol for Visit 1.4 (Neural recovery) will be the same as in Visit 1.3. Following the fatigue protocol, the rate of neural activation, RPE, and NME at 20%, 50%, and 100% MVIC will be determined. These measures will be repeated at 2, 5, 10, 30, 45 and 60 minutes post exercise.

Study 2

For Study 2, the fatigue test will consist of a 30-minute walking task on a treadmill. Walking speed will be set at 3 mph. At minutes 7,17, & 27, the treadmill grade will be increased to 5% for 2 minutes in order to simulate situations that require increased effort. Immediately upon completion of the walking protocol, the participant will be transported by wheelchair to either the Muscle Physiology Lab (Visit 2.3) or the Motor Control Lab (Visit 2.4), for measures of the recovery of power or physical function, respectively.

At visit 2.3 (Recovery of Power and Force), participants will be seated on the Biodex, which will be set up in the correct position prior to the walking protocol. Measures of isometric force and power at $30°\cdot s^{-1}$, V_{75}, and $270°\cdot s^{-1}$ will be recorded 2, 5, 10, 30, 45 and 60 minutes post-exercise. At Visit 2.4 (Functional Recovery), participants will be transported to the force platform, where they will immediately complete the balance test, chair rise task, and maximum vertical jump, in that order. These measures will be repeated at 5, 10, 30, 45 and 60 minutes post exercise.

Muscle Size- MRI

To ensure maximal activation of the muscle in all participants, specific strength will be calculated as peak isometric torque (Nm) / maximal muscle cross-sectional area (cm^2). To measure muscle size, T1-weighted axial MRIs will be acquired along the length of the thigh, using a phased-array coil. Images will be acquired at the Amherst Community Health Center, on a 1.5T GE system. Image acquisition parameters will be as follows: echo time = 11 ms, matrix = 256, field of view = 300 x 300 mm, slice thickness = 6 mm, with no gaps.

A custom-written MATLAB program (32) will be used to separate and quantify the maximum fat-free muscle cross-sectional area (mCSA, cm^2) for the KE muscles. Because it has been shown that differences between young and older participants in muscle contractile tissue can be obscured by the increase in intramuscular fat that also is present in older adults (175), this technique is an important step in calculating true contractile muscle size, and it has been used by our lab and others to successfully measure mCSA (90, 117, 146, 183). The investigator will begin by visually inspecting the images until it appears that the quadriceps muscles are nearing peak CSA. At that point, a circular region around the muscle of interest will be selected. The software will produce a histogram showing the signal intensity of the pixels within this region, which typically consists of three distinct peaks. The peak with the lowest intensity contains primarily bone and connective tissue, the center peak is the muscle region, and the highest-intensity peak contains mostly fat. The investigator will select the left and right boundaries of the muscle peak to assign thresholds for each region. The muscle will then

be outlined, carefully avoiding inclusion of any subcutaneous fat, and the software will compute the mCSA and percent fat area (%fCSA).

This process will be repeated for each of the neighboring slices, until the maximal mCSA is obtained. A minimum of 10 slices will be analyzed, and each slice will be analyzed twice and averaged in order to minimize any error in threshold selection and muscle outlining. Additionally, only one investigator will perform all analyses, thus eliminating any inter-investigator error. The mean of the mCSA of the three largest consecutive slices will be recorded.

Habitual Physical Activity Level- Accelerometry

To characterize habitual physical activity, Actigraph GT1M uniaxial accelerometers will be used to measure each participant's physical activity level. Accelerometers will be worn at the hip, and data will be recorded using 60-s epochs for 7-10 days, which has been shown to be sufficient to predict overall, light, and MVPA levels (86, 143). Participants will also be given a diary to record daily activities, sleep schedule, illness, and activities they considered to be outside their normal habits. A custom-written MATLAB program (Foulis, *submitted*) will be used to calculate total activity counts, as well as minutes spent in various activity levels, using established thresholds for Actigraph accelerometers (144, 144).

Statistical Analyses

All analyses will be performed using SAS software (SAS Institute, Cary, NC). Significance will be established at the $p \leq 0.05$ level. Exact p-values, 95% confidence intervals for differences in means between groups, as well as mean ± SD will be provided.

Study 1

Subject characteristics and baseline values will first be tested for normality. If the data are not normally distributed, a non-parametric analysis will be used to compare across groups. When data are normally distributed, Levene's test will be used to test for equal variance across groups. Unpaired t-tests will be used to compare values across groups, with appropriate weighting of the variance if deemed appropriate by the outcome of the Levene's test.

All hypotheses for Study 1, except for Exploratory Hypothesis 1.3, will be tested over time and across groups by two-factor (age, time) repeated measures ANOVAs, using the MIXED procedure, using separate ANOVAs for each measure. When significant age-by-time interactions are observed, data will be compared at each time point and adjusted for multiple comparisons, in order to determine at which time points group differences occurred. Exploratory Hypothesis 1.3 will be tested with a three way (age, time, repetition) ANOVA to test across repetitions of the fatigue protocols.

Study 2

Subject characteristics and baseline values will be tested as in Study 1. Hypotheses 2.1, 2.2, 2.3, and the exploratory hypothesis will be tested over time with repeated measures (time) ANOVAs using the MIXED procedure. Separate ANOVAs will be used for each variable. In addition, linear regressions will be used to explore relationships between the recovery of power and physical function (H2.4).

Visit 1.1: Paperwork *(Older only)*

- Informed Consent
- Health & Safety Questionnaires
- Fatigue Questionnaires
- Letter to Physician
- Anthropometrics & BP
- Short Physical Performance Battery (SPPB)

Visit 1.2: Habituation/Familiarization *(and paperwork for Young)*

- Warmup/Stretching
- Baseline MVIC
- Stimulation: 10Hz Tetanus, 80 Hz Tetanus
- Torque-Velocity Measures
- Familiarization with KE Fatigue Protocol
- Provide Physical Activity Monitor and Instructions

Visit 1.3: Recovery of Power and Force

- 5 Minute Warm-up on Stationary Bike, Stretching
- Baseline Measures
    - MVIC
    - Tetanic Stimulation: 10Hz, 80 Hz
    - MVDC: $30°\cdot s^{-1}$, V_{75}, $270°\cdot s^{-1}$
- 4-Minute Biodex Isovelocity (V_{75}) Fatigue Protocol
- Recovery Measures at 0, 2, 5, 10, 30, 45 and 60 min:
    - MVIC, MVDC ($30°\cdot s^{-1}$, V_{75}, $270°\cdot s^{-1}$), 10Hz & 80 Hz Tetani
- Repeat 4-Minute Biodex Isovelocity Fatigue Protocol
- Recovery Measures 0, 2, 5, and10 min
    - MVIC, MVDC

Visit 1.4: Neural Recovery

- 5-Minute Warm-up on Stationary Bike & Stretching
- Baseline Measures
    - MVIC (with RPE)
    - Submax RPE: 20% & 50% MVIC
    - MVDC: V_{75}
- 4-Minute Biodex Isovelocity (V_{75}) Fatigue Protocol
- Recovery Measures at 0, 2, 5, 10, 30, 45 and 60 min:
    - MVIC, 20% MVIC 50% MVIC (with RPE)

Visit 1.5: MRI

- Imaging of the KE Muscles

Figure 3.1: Summary of Procedures for Study 1.

Visit 2.1: Paperwork

- Informed Consent
- Health & Safety Questionnaires
- Fatigue Questionnaires
- Letter to Physician
- Anthropometrics & BP
- Short Physical Performance Battery (SPPB)

Visit 2.2: Habituation/Familiarization

- Warmup/Stretching
- Baseline MVIC
- Torque-Velocity Measures
- Familiarization with Treadmill Walking Protocol
- Familiarization with the Functional Measures
- Provide Physical Activity Monitor and Instructions

Visit 2.3: Power Recovery

- 5 Minute Warmup on Stationary Bike & Stretching
- Baseline Measures
    - MVIC
    - MVDC: $30°\cdot s^{-1}$, V_{75}, $270°\cdot s^{-1}$
- 30-Minute Treadmill Walking Fatigue Protocol
- Recovery Measures at 0, 2, 5, 10, 30, 45 and 60 min:
    - MVIC
    - MVDC ($30°\cdot s^{-1}$, V_{75}, $270°\cdot s^{-1}$)

Visit 2.4: Functional Recovery

- 5 Minute Warmup on Stationary Bike & Stretching
- Baseline Measures
    - Physical Function: 10x Chair Rise, Balance Maximum Vertical Jump Force
    - MVIC
    - MVDC: $30°\cdot s^{-1}$, V_{75}, $270°\cdot s^{-1}$
- 10-Minute Treadmill Walking Fatigue Protocol
- Recovery Measures at 0, 5, 10, 30, 45 and 60 min:
    - 10x Chair Rise
    - Balance
    - Maximum Vertical Jump

Figure 3.2: Summary of Procedures for Study 2.

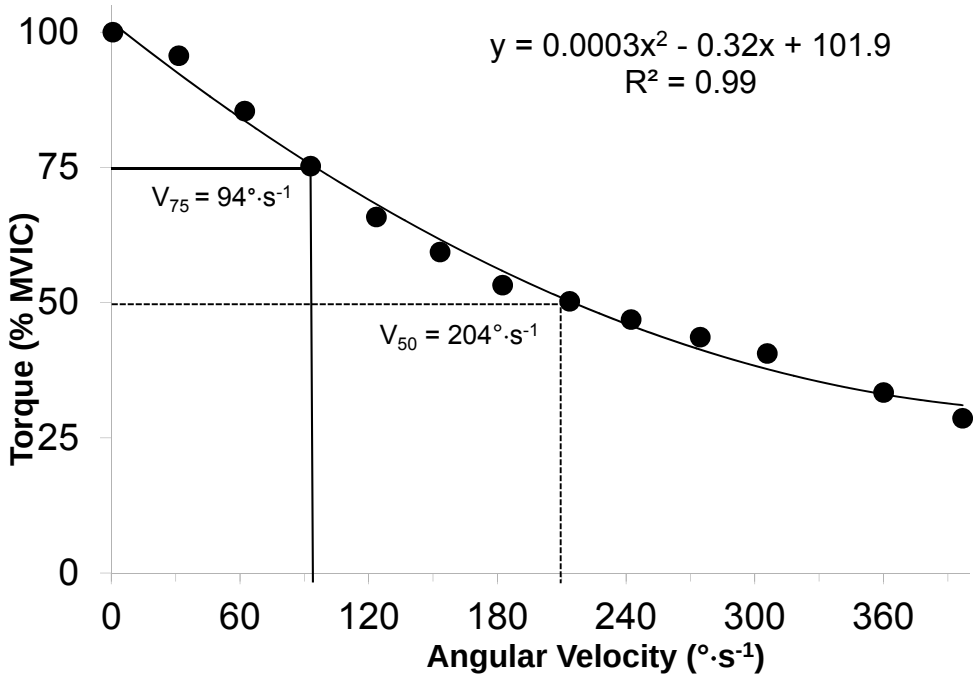

Figure 3.3: Example of Torque-Velocity Data from One Older Woman. Data are normalized to peak force and fit by a second order polynomial, so that the velocity at which 50% (V_{50}) and 75% (V_{75}) of maximal isometric force can be calculated. Callahan, Unpublished Data

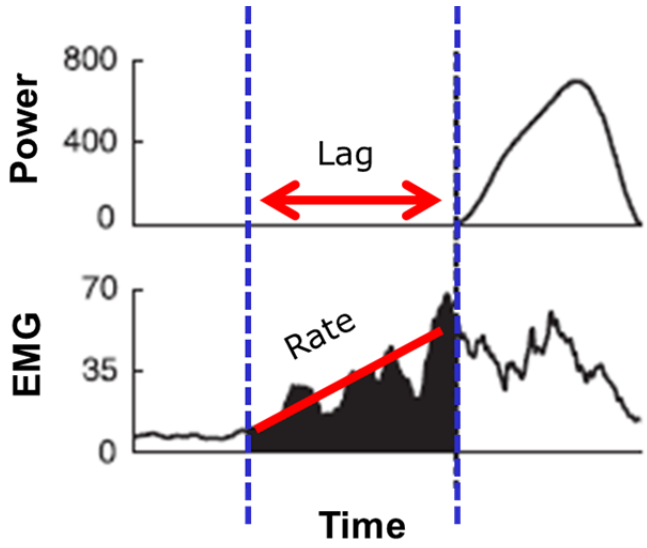

Figure 3.4: Example of the Measurement of the Rate of Neuromuscular Activation. The lag in neuromuscular activation is determined as the time between the onset of the EMG signal and the initiation of force or power. The rate of neuromuscular activation is then calculated as the derivative of the EMG signal during the lag period.

Adapted from Clark 2011 (46)

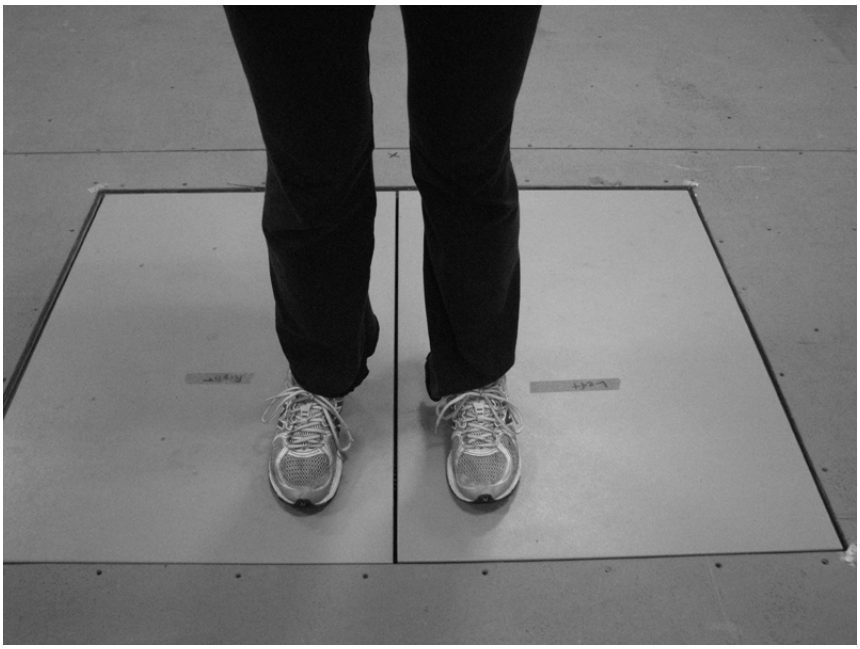

Figure 3.5: Example of Foot Position on the Dual Force Platform Setup. The participant's feet are positioned shoulder width apart, with one foot each platform.

CHAPTER 4

MECHANISMS OF RECOVERY FROM NEUROMUSCULAR FATIGUE IN YOUNG AND OLDER WOMEN

Abstract

Changes in the neuromuscular system due to both old age and muscle fatigue can limit the ability to produce power. While it has been shown that different aspects of the neuromuscular system may recover from fatiguing exercise at different rates, the effects age-related changes on this recovery process are not known. We tested the hypotheses that fatiguing contractions would induce greater loss and slower recovery of power during high-velocity contractions in older compared with young women, and that these decrements would be accompanied by impairments in contraction velocity, neural activation and contractile function in the older group. Eleven young (25-37 years) and 12 healthy older (66-81) women completed 4-min of maximal dynamic knee extension contractions designed to elicit similar fatigue (fall of power) in both age groups. Power at 4 velocities, central activation, pre-motor signaling, neural efficiency, contractile properties and ratings of perceived exertion were measured before, immediately following and after 60 min of recovery from the contraction protocol. Isometric torque and low-velocity power fatigued and recovered similarly in young and older women ($p>0.58$). High-velocity power declined more in older (38%) than young (13%, $p<0.01$); in the older group this did not recover in 60 minutes ($p<0.01$). Excitation-contraction coupling was impaired in both groups following and 60 minutes the fatigue bout ($p<0.01$), and tended to be more impaired in the older ($p=0.07$). In response to fatigue, the EMG:Torque ratio responded similarly in young and old during isometric contractions at 20% and 100% of maximal torque, but only the young had an increased ratio with fatigue at 50% of max. Older adults also had an increase in perceived exertion during maximal isometric contractions following fatigue that did not return to baseline

over the hour. This slower recovery of high-velocity power in older adults could lead to impairments in the ability to perform functional tasks following an exercise bout.

Introduction

There are a number of detrimental changes in the neuromuscular system which occur in old age (65+ years) that increase the risk of impairments in physical function. One such change is the age-related loss of muscle strength and power. A number of studies have shown that both isometric torque (100, 155) and power, the product of torque and velocity, are lower in older adults (32, 53, 138) and in women (108, 131). Thus, older women are at particular risk for disability, as low muscle power has been shown to be a good predictor of impaired physical function (50).

In response to exercise, there is a transient decrease in the ability to produce torque, a response that is termed muscle fatigue. As a result, age-related muscle weakness in older adults may be of greater concern when combined with the effects of muscle fatigue (113). While a number of studies have demonstrated greater fatigue resistance in older compared with younger adults during isometric contraction protocols in a variety of muscle groups (42, 110), it has also been shown that this fatigue resistance may be lost and even reversed as contraction velocity increases (32, 53). These results strongly suggest that there may velocity-dependent mechanisms contributing to muscle fatigue in older adults.

In younger adults, it has been shown there are different rates of recovery of several neuromuscular processes that cause muscle fatigue (150). Following fatiguing isometric contractions, it has been reported that torque, contractile function, and the ratio of surface electromyography (EMG):torque recover in a similar manner in both young and older adults (7). However, many of these factors are already lower at baseline in older adults compared with young (46, 53, 62, 101, 120, 158, 180), possibly leading to

greater effects of these changes on torque production, even if there are no age-related changes with fatigue. Given the existing evidence of age-related changes in neuromuscular function and the velocity-dependence in the amount of fatigue in older adults (31, 32, 53), it is possible that there are differences in the recovery of power compared to isometric torque following a fatiguing exercise bout. When a single velocity or resistance is used, studies have shown that power may be slower to recover in older adults than young (120, 186). Many neuromuscular processes altered by fatigue may contribute to reduced power throughout the recovery process, such as altered central drive (101), slowed motor unit discharge rates (51), and reduced neuromuscular activation (46). The recovery of these factors during dynamic contractions of fatigued muscles have not been thoroughly investigated. Within the muscle itself, it has been reported that contractile properties, such as rate of torque relaxation, may be slower to recover in older adults (120). While slowing of contractile properties may allow for maintained isometric torque via a shift in the torque-velocity relationship, these changes may inhibit the production of power, particularly at high-velocities (53, 106). Furthermore, following fatiguing exercise, it has been shown that low-frequency torque (i.e., torque during electrical stimulation at < 20 Hz) can be depressed for several hours in young and older adults (68) due to impaired excitation-contraction coupling (207). However, several investigators have found no age-related differences in the degree of low-frequency fatigue (7, 116). Given the numerous other neuromuscular changes observed in aged individuals, it is possible that the influence excitation-contraction coupling failure on torque and power production is greater in older adults, even in the absence of an age-related difference.

Functionally, reduced power during recovery may have a large impact on everyday life. It has been reported in young adults that, when excitation-contraction coupling failure occurs, a second fatiguing bout can elicit greater fatigue than the original bout (192), If this were the case in older adults, it is possible that increased effort is required to perform everyday activities as fatigue accumulates due to several bouts of physical activity over the course of the day. Since many older adults already perform everyday activities at a high percentage of their maximal strength when unfatigued (97), any increased neuromuscular effort in response to fatigue could lead to increased perceived effort of activities throughout the day.

Overall, while many investigators have studied the acute effects of muscle fatigue in older adults, there are few data about the degree and impact of muscle weakness during recovery from fatigue, particularly in response to dynamic contractions. Since any persistent decline in maximal power in the knee extensors could have a profound influence on the physical function in older adults (13, 50), the aim of this study was to provide unique insight into the changes in torque and power following muscle fatigue and throughout 60 min of recovery. To explain any possible alterations in recovery in the older group, we quantified the changes contraction velocity, rate of isometric torque production, central and pre-motor activation, neural efficiency, and contractile properties. We hypothesized that older adults would have a slower recovery of high-speed power due to alterations in the recovery of these neuromuscular processes required for power production. Finally, we tested the hypothesis that age-related impairments in the recovery of muscle power would lead to functional consequences: increases in both perceived exertion during contractions and fatigue during a second exercise bout.

Methods

Participants

Measures of neuromuscular function were collected in 11 young (age 25-37 years) and 12 older (age 66-81 years) women before and following muscle fatigue. All participants were relatively healthy, non-smokers and free of any limb injury that could affect physical performance during our testing. No participants had a history of metabolic, neurological, or cardiopulmonary disease. With the exception of one participant on a low dose beta-blocker (atenolol), no participant was on any medication with potential side effects on neuromuscular function. Physician's consent was obtained for all older women prior to their participation in the study. Prior to enrollment, all participants read and signed an informed consent document as approved by the University of Massachusetts, Amherst human subjects review board.

Self-reported physical activity levels for all participants were below the ACSM recommendations of 75 minutes of vigorous, or 150 minutes of moderate physical activity per week (156). To quantify habitual physical activity, participants wore Actigraph GT1M (Pensacola, FL) uniaxial accelerometers at the hip for 7-10 days. Total activity counts, as well as minutes spent in moderate-vigorous activity (MVPA), were calculated using established thresholds for Actigraph accelerometers (76).

Descriptive characteristics of anthropomorphic measurements and functional ability were collected on all participants. Functional status was quantified using the Short Physical Performance Battery (SPPB, (83, 84)). As a global measure of central motor function, participants completed a foot-tap test (115), during which they were instructed to tap their foot by hinging at the ankle as fast as they could for 10 s. This was done one

foot at a time, with each foot repeated twice, and the fastest number of taps recorded. Participants also completed a 400m walk consisting of 10 loops of a 40m course at the fastest pace they thought they could maintain for the full course.

Torque and Power Measurement

Knee extensor torque and power were measured using a Biodex System 3 (Biodex Medical Systems, Shirley, NY) dynamometer, as previously described (32). Briefly, participants were seated with the hips at 90° and a resting knee angle of 100° extension. Torque, velocity, and position signals from the Biodex were output to a customized Matlab (Mathworks, Natick, MA) program, where it was recorded at 2500 Hz.

During the participant's baseline testing visit, peak isometric torque (Nm), power (W), and the torque-velocity curve were measured. Maximal voluntary isometric contraction torque (MVIC) was recorded during 3-4 s contractions of the knee extensors. Verbal encouragement was provided by the investigator and visual feedback was provided by way of a lighted box. Participants performed 3 MVICs until the peak torque of two were within 10%, with 2 minutes of rest between contractions. Peak torque (Nm) and the maximal rate of voluntary torque development (% peak torque$\cdot ms^{-1}$) were calculated from these contractions.

Peak power was measured during dynamic contractions over a 70° range of motion (100°-170° of extension). At each velocity, participants completed a series of 3 rapid contractions cued by the investigator. Each series was separated by 1 minute of rest. Minimum time-to-target velocity (ms), i.e. the time from the beginning of torque development until the time at which the participant reached target velocity, was recorded for each set. The torque-velocity curve was calculated by assessing peak torque for 10

velocities from 30-300°· s^{-1} at 30°· s^{-1} intervals (32). Torque-velocity data were also expressed relative to MVIC and fit to a second-order polynomial so that the individual's velocity at which 75% of MVIC (V_{75}) was generated could be calculated. The V_{75} was used to match all individuals for their same position on the torque-velocity curve, in order to provide a common relative torque level for the fatiguing contractions and recovery measures.

Muscle Size

To normalize the torque data to muscle size, fat-free muscle cross-sectional area (mCSA) was determined from T_1-weighted axial magnetic resonance images (MRI), acquired along the length of the thigh using a phased-array coil and a 1.5 tesla Siemens MRI system. Image acquisition parameters were: echo time = 11 ms, matrix = 256, field of view = 300 x 300 mm, slice thickness = 4 mm, with no gaps. A custom-written MATLAB program was used quantify the maximum mCSA (cm^2) and fat area (% total CSA) for the knee extensor muscles, by using the signal intensity of the pixels to distinguish the different tissues (32, 115). Mean mCSA of the three largest consecutive slices was used to calculate specific torque ($Nm \cdot cm^{-2}$) and specific power ($W \cdot cm^{-2}$).

Muscle Stimulation

Contractile properties, central motor drive, and low-frequency fatigue were assessed using stimulated isometric contractions of the quadriceps muscles. One 7.6 x 12.7 cm self-adhesive electrode (FastStart; Vision Quest Industries, Irvine, California) was placed over the quadriceps, distal to the inguinal crease, and the other was placed just superior to the patella. Stimulations were induced using a constant-current stimulator

(DS7A; Digitimer, Hertfordshire, UK). Target current was set so that a 500 ms, 80 Hz train elicited ~50% of MVIC torque.

Muscle contractile properties, including maximal rates of force development and relaxation (RFD and RFR, respectively; %peak·ms^{-1}), and half-relaxation time ($T_{1/2}$, ms), were calculated from the 80 Hz tetanus (31, 32). The RFD during the MVIC was normalized to the RFD during the tetanus; a decrease in this voluntary:stimulated RFD ratio suggests a reduction in central motor drive (118). Low-frequency fatigue was quantified by changes in peak torque during a 10-Hz, 500 ms train relative to that of the 80 Hz stimulus. Any decrement of the 10:80 Hz ratio is indicative of low-frequency fatigue, which likely reflects excitation-contraction coupling failure (68, 206).

Surface Electromyography

Surface electromyography (EMG) was collected using a bipolar paired Ag/AgCl electrode (Therapeutics Unlimited, Iowa City, IA) placed over the vastus lateralis muscle. Signals were recorded at 2500 Hz, amplified (gain = 2,000), and high-pass filtered (cutoff = 20Hz). Two measures of the rate of neuromuscular activation of the muscle were determined at all velocities. The delay between the time at which EMG amplitude exceeded 3 standard deviations of the resting amplitude and the time of initiation of torque development (pre-motor time, ms) was calculated (15). In addition, the average EMG (%max) during the pre-motor period was also determined.

The EMG:Torque ratio (mV·Nm^{-1}) was used as a measure of neuromuscular efficiency. Due to the complications of assessing the EMG:Torque ratio during dynamic contractions, it was instead assessed during isometric contractions at 20%, 50%, and 100% of baseline MVIC. Surface EMG signals were calculated during a 500ms window

corresponding to a plateau in torque. All EMG data were normalized to the maximal EMG signal obtained during the baseline MVIC during a similar 500 ms window. Any increase in the EMG:Torque ratio represented a decrease in neuromuscular efficiency.

Fatigue Test and Recovery

Participants were asked to refrain from exercising for 24 hours and from consuming caffeine for 8 hours prior to each visit, due to their influences on muscle function and fatigue. The fatigue test consisted of 4 minutes of maximal dynamic contractions over the 70° range of motion at each participant's V_{75} velocity (32). Participants were cued for all contractions by an auditory signal. To maintain a constant 30% duty cycle for all participants, the timing of the contractions and rest periods were individualized for each participant, depending on their V_{75}. Fatigue was calculated as:

$$\frac{\text{Average peak power from the final 3 contractions}}{\text{Average peak power from baseline and the first 3 contractions}} \times 100\%$$

Recovery measures were collected immediately following the final contraction, and 2, 5, 10, 30, 45, and 60 minutes following the fatigue test. The fatigue test was repeated on two different days so that two separate sets of recovery measures could be collected. The order of these two visits was randomized for each participant. On one of the days, recovery measures were collected during an MVIC ($0°\cdot s^{-1}$), at a velocity relative to each participant's own torque-velocity curve (V_{75}), and at a slow ($30°\cdot s^{-1}$) and fast ($270°\cdot s^{-1}$) absolute speed. The speed of $270°\cdot s^{-1}$ was selected based on a prior study from our lab which indicated it was the fastest speed all participants could achieve (129). The order of the slow and fast contractions was randomized across subjects. At each contraction, peak specific torque (isometric) or power (dynamic), maximum rate of torque development (isometric) and time-to-target velocity (dynamic), pre-motor time,

and pre motor EMG were determined. Immediately following the voluntary recovery contractions except after the 2 and 45 minutes post-fatigue time-points (omitted to minimized the number of stimulations, and therefore maximize subject comfort), stimulated 10Hz and 80Hz measures were also recorded to provide measures of central and peripheral function. Again, the order of the stimulated contractions was randomized. In order to determine the effects of a second fatiguing bout following 1 hour of recovery, participants repeated the same fatigue protocol 2 minutes after the 60 minute recovery measure. Measures of maximal isometric torque and power at all 4 velocities were measured again immediately following this second 4-minute fatigue bout.

During the other testing visit, the recovery measures, performed at the same recovery times, consisted of the EMG:Torque ratio and ratings of perceived exertion (RPE, 1-10, (24)). Due to the complications of assessing the EMG:Torque ratio during dynamic contractions, isometric contractions of 20%, 50%, and 100% MVIC were used to capture the changes in muscle efficiency and perceived effort with changing contraction intensity.

Statistical Analyses

All analyses were performed using SAS software (SAS Institute, Cary, NC), with significance established at $p \leq 0.05$. Mean ± SE are provided. Descriptive and baseline characteristics were compared across age groups using unpaired t-tests. Group x time repeated-measures ANOVA was used to evaluate the hypotheses relating to the recovery (relative to baseline) of power and the neuromuscular mechanisms. Each velocity or contraction intensity was tested independently. Results of the rmANOVA were used to determine whether there was a difference by group in the recovery. T-tests were then

used to compare the baseline to 0-minute recovery time point (0R) in order to determine the effects of fatiguing contractions. Likewise, data at baseline and following 60 minutes of recovery (60R) were compared to evaluate the completeness of recovery. To minimize the effects of multiple comparisons, only changes at these two time-points were tested. Both pairwise comparisons were assessed independently for each group unless there was no group effect and group x time interaction, in which case, data were collapsed by group. Differences in specific torque and specific power following the second fatigue bout were evaluated using group x bout rmANOVA.

Results

Group Characteristics

Group characteristics are shown in Table 4.1. Young and older did not differ in height, body mass, BMI, or total PA counts ($p \geq 0.09$). However, MVPA was lower in the older group than in the young group ($p=0.01$). All of the young women scored 12 on the SPPB, while 9 of the older women scored 12 and 3 scored 11. Foot tap speed and 400m walk time were slower in the older women compared with the young($p \leq 0.03$).

Baseline Characteristics

Older adults had lower mCSA, and greater fat area than the young group ($p<0.01$ for both). There was no difference in V_{75} (young: 62.3±7.0, older: 62.9±5.7, $p=0.94$), as calculated from polynomial fits of the individual torque-velocity curves (Appendix G). The older women were weaker than young across all velocities (Figure 4.1), although, when normalized to mCSA, baseline specific isometric torque and power were similar across groups ($p \geq 0.18$).

Among the neuromuscular properties (Table 4.2), there were no group differences in voluntary or voluntary:stimulated RFD. Time-to-target velocity at $30°\cdot s^{-1}$ and at V_{75} were also similar across groups (Table 4.3). In contrast, the older women were slower to attain the target velocity at $270°\cdot s^{-1}$, signifying slower knee extension acceleration. Pre-motor time was longer in the older at $30°\cdot s^{-1}$ and $270°\cdot s^{-1}$, but not at isometric or V_{75}, indicating no consistent patterns. Pre-motor EMG was similar across groups at all velocities. The EMG:Torque ratio (Table 4.2) was greater in the older at 20% (young: 0.56±0.04, older: 0.76 ± 0.07; p=0.04), possibly due to larger motor units or greater coactivation in the older. This ratio was similar across groups at 50% (young: 0.53±0.03, older: 0.59 ± 0.04; p=0.39) and 100% (Young: 0.56±0.02, older: 0.58 ± 0.02; p=0.59) MVIC.

Muscle stimulation data (Table 4.2) were available for all of the younger women and 9 of the older adults. Baseline tetanic 80Hz torque was not different between young and older (young: 50.9±2.0%, older: 47.9 ± 2.0%, p=0.32), and was close to our target of 50% MVIC. For the contractile properties, 80Hz RFD was faster in the older than the young (Table 2). In contrast, RFR and $T_{1/2}$ were slower in the older, indicating slower contractile properties in older adults. The baseline 10:80 Hz ratio was greater in the older adults than young, consistent with their slower muscle relaxation properties.

Ratings of perceived exertion were similar at 20% MVIC (young: 1.1±0.2, older: 1.0 ± 0.2; p=0.87), and tended to be lower in the older at 50% (young: 3.9±0.5, older: 2.5 ± 0.5, p=0.06) and 100% (young: 7.4±1.1, older: 4.9 ± 0.9, p=0.06) MVIC.

Torque and Power Recovery

Muscle fatigue in response to the protocol did not differ across groups and testing days (young: 80 ± 5%, 83 ± 6%; older: 71 ± 3%; 78± 3%; on testing day 1 and 2, respectively; $p \geq 0.12$). Specific torque and power decreased in both groups at isometric, $30°\cdot s^{-1}$, and V_{75} at the end of the fatigue bout ($p < 0.01$, Figure 4.2). At $270°\cdot s^{-1}$, peak specific power tended to be lower than baseline at 0R ($p = 0.07$), and was significantly lower in the older ($p < 0.01$). Young and older had similar power decrements at isometric, $30°\cdot s^{-1}$, and V_{75} velocities ($p \geq 0.61$); however, there was a significantly greater power decrement in the older compared to the young at $270°\cdot s^{-1}$ ($p = 0.02$).

At 60R, isometric torque remained depressed from baseline ($p < 0.01$) however, this was similar in young and older adults ($p = 0.71$). Power at $30°\cdot s^{-1}$, and V_{75} in both young and older recovered to baseline ($p \geq 0.17$), with no difference by group ($p \geq 0.58$). Power at $270°\cdot s^{-1}$ recovered in the young ($p = 0.27$), but not the older ($p < 0.01$). There was a significantly greater decrement in power at this velocity in the older than young ($p < 0.01$).

Neuromuscular Mechanisms of Recovery

Voluntary RFD (Figure 4.3) increased following the exercise in the older group ($p = 0.01$), but not in the young ($p = 0.47$). It tended to be different across groups ($p = 0.07$). By 60R, it recovered to baseline in both groups ($p \geq 0.37$). When normalized to the 80Hz stimulated RFD, the voluntary:stimulated RFD response differed by group, such that it was elevated from baseline in the older at 0R ($p = 0.02$), but not the young ($p = 0.77$); however there was no difference across groups ($p = 0.22$). It returned to baseline in the older by 60R ($p = 0.38$), suggesting a transient increase in central motor drive in the older

following the fatigue bout. The young remained unchanged from baseline and similar to the young ($p \geq 0.51$)

In both groups, time-to-target (Figure 4.4) at $30°\cdot s^{-1}$ not differ from baseline at 0R ($p=0.15$). Time-to-target was longer at 0R for both groups at V_{75} or $270°\cdot s^{-1}$ ($p \leq 0.03$) indicating slower acceleration, however there were no group differences ($p=0.23$). By 60R, time-to-target was similar to baseline at all velocities ($p \geq 0.11$) with no differences across groups ($p \geq 0.31$).

Under isometric condition, pre-motor time (Figure 4.5, left) was elevated relative to baseline in both groups at 0R ($p=0.20$), with no difference across groups ($p=0.65$). At $30°\cdot s^{-1}$ and V_{75}, this time did not change at 0R ($p \geq 0.25$) in either group ($p \geq 0.13$). At $270°\cdot s^{-1}$, neither group was significantly different from baseline at 0R ($p \geq 0.24$); however, the older had less slowing of pre motor times than the young ($p=0.05$). Following 60 minute of recovery, isometric pre-motor time tended to remain elevated ($p=0.07$), in both groups to a similar extent ($p=0.74$). At $30°\cdot s^{-1}$ and V_{75}, it remained unchanged ($p \geq 0.14$) in both groups. During contractions at $270°\cdot s^{-1}$, both groups were still similar to baseline ($p \geq 0.88$); however, the older continued to have less slowing of pre motor times than the young.

Isometric pre-motor EMG (Figure 4.5, right) was unchanged at 0R in the young ($p=0.86$), but was significantly increased in the older ($p=0.01$). It trended to be greater in the young than older ($p=0.09$). At $30°\cdot s^{-1}$, V_{75}, and $270°\cdot s^{-1}$, there were no differences from baseline in either group ($p \geq 0.13$), nor were there differences across groups ($p=0.55$). By 60R, isometric, V_{75}, and $270°\cdot s^{-1}$, pre-motor EMG responses were all similar to baseline ($p \geq 0.32$), with no differences across groups ($p \geq 0.29$). However, at $30°\cdot s^{-1}$, the

young had a reduction in pre-motor EMG compared to baseline ($p<0.01$), while the older remained similar to baseline ($p=0.69$). This resulted in a greater relative reduction in the pre-motor EMG in the younger than the older ($p=0.01$).

At 0R, during contractions at 20 % MVIC, there was no difference in the EMG:Torque ratio from baseline ($p=0.25$, Figure 4.6) or across groups ($p=0.28$), indicating no change in neuromuscular efficiency. At 50% MVIC, the ratio increased in the young at 0R ($p<0.01$) while the older remained unchanged ($p=0.21$), leading to a greater increase in the young compared to older ($p=0.01$). At 100% MVIC, both groups increased their ratio similarly at 0R ($p<0.01$), with both groups increased to a similar extent ($p=0.99$). By 60R, EMG:Torque ratio returned to baseline at all contraction intensities ($p\geq0.17$), with no differences across groups ($p\geq0.58$).

Of the contractile property measures (Figure 4.7), stimulated RFD did not change immediately post-exercise ($p=0.20$), but was elevated similarly in both groups at 60R ($p=0.01$). Stimulated RFR was lower in both groups at 0R ($p<0.01$) but recovered by 60R ($p\geq0.27$). Consistent with the RFR, half relaxation time was increased in both groups immediately at 0R ($p<0.01$), but no difference was found from baseline by 60R ($p=0.77$). All of the contraction properties responded similarly across groups both immediately following the fatigue bout and following 60 minutes of recovery ($p=0.11$).

The 10:80 Hz ratio (Figure 4.7, Bottom) was reduced at both time-points following the fatigue in both groups ($p<0.01$), indicating the presence of low frequency fatigue. There was a trend for it to be lower at all time-points in the older group ($p=0.07$). (Changes in peak tetanic torque at 10 Hz and 80 Hz can be found in Appendix G).

Functional Implications

At 20% and 50% MVIC, ratings of perceived exertion (Figure 4.8) were increased at 0R ($p<0.01$) and responded similarly in both groups ($p\geq0.20$). During contractions at 100% MVIC, RPE in the young did not increase significantly from baseline ($p=0.23$). In the older it increased following fatigue ($p<0.01$), and tended to be to a greater extent than in than in the young ($p=0.10$). This age-related different indicated greater perceived effort by the older during maximal contractions. By 60R, RPE was and recovered to baseline at 20% and 50% MVIC in both group ($p\geq0.41$). At 100% MVIC, RPE remained elevated both relative to baseline ($p=0.05$), and relative to the young ($p=0.04$).

When the fatigue protocol was repeated after 60 min of recovery, specific torque and power were lower across all velocities at the end of the second fatigue bout compared with the end of the first ($p\leq0.03$, figure in Appendix G). There was no age-related difference in the change in the amount of fatigue following the second bout ($p=0.33$).

Discussion

In the present study, we observed the hypothesized decrease in power, regardless of age, following the fatiguing knee extension exercise. Our novel finding was a velocity-specific response in the recovery of torque and power which was altered in old age. Power during slow speed contractions (Isometric, $30°\cdot s^{-1}$, V_{75}) recovered similarly in young and older adults; however, as we hypothesized, older adults experienced greater loss of power during high-speed ($270°\cdot s^{-1}$) contractions, and did not recover over the course of 60 min. Throughout the recovery period there were several differences in the recovery of neuromuscular properties across velocities, contraction intensities and age groups. Functionally, we observed the hypothesized increase in perceived exertion at all

contraction intensities, in both age groups. However, while perceived exertion during submaximal contractions decreased back to baseline in both groups within 60 min, RPE during maximal contraction remained elevated in the older group throughout the entire recovery period. In addition, fatigue during a second 4-minute fatigue bout was greater than the first; however, contrary to our hypothesis this did not differ across groups.

Torque and Power

When normalized to muscle mass, baseline torque and power was similar across all velocities. Thus, at baseline, there was no impairment in the ability to produce power in older adults. While baseline power did not differ, baseline time-to-target velocity at $270°\cdot s^{-1}$ was lower in the older adults, indicating an impairment in velocity production, even prior to the exercise bout. This is in agreement with findings that older adults tend to have difficulty reaching high contraction velocities (129, 169).

By design, we achieved the same degree of fatigue in young and older adults at V_{75}. Indeed, prior work by our lab has shown that matching young and older adults for their same relative velocity during a fatigue protocol results in similar fatigue across groups (32). This standardization of fatigue protocol is important in studies of dynamic fatigue since changes in the torque-velocity curve with aging (169) may result in biasing fatigue if an absolute velocity is chosen. While studies have measured differences in muscle responses at a single velocity following fatigue protocols (32, 53), we are not aware of any prior aging studies which measured the changes across multiple velocities following a single-velocity fatigue bout. Interestingly, our approach of measuring recovery of power across multiple velocities also revealed similar declines across age groups in isometric torque and $30°\cdot s^{-1}$ power following the fatigue bout, possibly due to

the fact that those velocities are relatively similar to the V_{75}. However, at $270°\cdot s^{-1}$, we observed a greater decline in power in the older adults compared to the young. These results would suggest that following a fatiguing exercise bout, the ability of the muscle to generate velocity is affected to a greater degree than the ability to generate torque in older adults. While the change in time-to-target velocity during the high-velocity contractions did not differ in young and old following fatigue, the older adults did have a lower baseline time-to-target, which may have contributed to these differences. Relative to the younger women, the older women also had a lower change in pre-motor time with no change in EMG at $270°\cdot s^{-1}$ following the fatigue bout. This may be due to greater musculotendon stiffness, as muscle stiffness has been shown to be related to power, but not isometric torque in older adults (102).

In agreement with previous results by our lab and others (7, 128, 150), we observed an incomplete recovery of isometric torque in both groups following 60 minutes. However, in the tibialis anterior muscle, Lanza et al (128) showed incomplete recovery in young, but not older adults after 10 minutes of recovery following a dynamic fatigue both. Nevertheless, in the Lanza study, there was greater fatigue in the young group compared to the older, which could account for differences in recovery. Our deficits in MVIC following a dynamic fatigue protocol are in agreement with to that of Allman and Rice (7), who observed deficits in MVIC of 6% in the young and 9% in the older after 1 hour of recovery from an isometric elbow flexor fatigue bout which elicited similar fatigue in young and older adults.

At $30°\cdot s^{-1}$ and V_{75}, recovery was similar across groups and complete by 60 min post-exercise. The similar response to the two velocities is not surprising considering the

average V_{75} (~62°·s^{-1}) was similar to 30°·s^{-1}. However, there was a differential recovery across groups at 270°·s^{-1}, such that deficits in power were greater in the older adults than the young across all time-points, and, contrary to the young, the older did not fully recover to baseline following 60 min. The complete recovery of power in the young, but not the older, is contrary to what Lanza et al (128) observed in the dorsiflexors following dynamic fatigue at 90°·s^{-1}. Their observation of complete recovery in the old but not the younger after 10 minutes of recovery may again be affected by the greater fatigue they observed in the young, or their use of the same absolute velocity during the fatigue protocol in young and older adults. Following eccentric contractions of the dorsiflexors, Power et al (166) observed both incomplete recovery and a greater isotonic power loss in older compared to young for their full 30 minutes of recovery measures. Their low resistance (20% MVIC) is comparable to our high speed (270°·s^{-1}) contraction, as based on the torque-velocity curve in our older women, torque produced at 270°·s^{-1} was approximately 33% of MVIC. Notably, these authors also reported incomplete recovery in the young; however, this may be due in part to their use of eccentric contractions, which can induce muscle damage which can inhibit force production.

The differential fatigue and recovery of isometric torque and high-velocity power is not surprising, as the development of force and velocity has been shown to be differentially regulated, even at the muscle fiber level (59, 60). Specifically increased inorganic phosphate has been shown to decrease maximal isometric tension while not significantly affecting maximal shortening velocity in isolated muscle fibers (60). Changes in intracellular pH, however, affect maximal velocity production to a greater degree than force production (59). When applied to an intact human, these changes, in

addition to possible alterations in neural input and Ca^{++} handling, could lead to a dissociation between decrements in isometric torque and dynamic power production.

Neuromuscular Mechanisms of Recovery

Under isometric conditions, we observed no change in the voluntary:stimulated RFD ratio in response to fatiguing exercise in the young; however in the older adults, we observed an increase immediately post-fatigue, followed by a decrease back to baseline by 60 min. As we observed no change in stimulated RFD, the increase in the ratio was due to the increase in voluntary RFD. This would suggest transient improved central drive following exercise in the older adults. We are not aware of any data to suggest an increase in this drive following a fatiguing exercise bout. The increase in this ratio, in conjunction with the temporary increase in isometric pre-motor EMG post-fatigue could indicate an increased initial neural burst to the muscle in older adults, which may allow for faster initial motor unit discharges and a more ballistic contraction (64) to try to maximize force production. This transient increase in neural signaling in the older adults may be a compensation mechanism in the muscle to try and partially overcome the other neuromuscular changes which are depressing force production. However, if this explanation is correct, the increase in neural signaling did not translate into a faster dynamic contraction, as time-to-target velocities either stayed the same or increased in the older adults with fatigue. Future studies may want to include cortical excitability and indwelling EMG measures in order to determine the precise nature of these neural changes.

At baseline, we observed a greater EMG:Torque ratio in the older at 20% MVIC, but no difference across groups at 50% or 100% MVIC. This response is in agreement

with the findings of Ng and Kent-Braun (158), who only found a difference in this ratio at low torque levels and attributed it to either the larger motor units in older adults or increased antagonist co-activation. Immediately following the fatigue protocol, we observed no change in the ratio in either group at 20% MVIC, an increase only in the young at 50% MVIC, and an increase in both groups at 100% MVIC. No prior study has measured changes in this ratio following exercise in young and older adults across a range of intensities. This differential response by age group across intensities indicates a difference in neural strategy of modulating torque production following the fatigue protocol. It is possible that younger individuals depend more on agonist activation to achieve 50% torque post-fatigue, while the older may depend more on decreasing antagonist co-activation. However, we did not record any measures of antagonist activity in the present study. Allman and Rice (7) found that EMG at 60% MVIC increased by 19% in the young and 13% in the old in the dorsiflexors, with no difference by group. Their findings, combined with ours, could indicate a threshold level for increased activity in the older between 50-60%, such that there is a change in neural strategy within this range. Finally, we observed a relatively rapid recovery of the EMG:Torque ratio in the young at 50% MVIC and both groups at 100% MVIC. Other groups have observed slower recovery of this ratio in both young (150) and older (7) adults following fatiguing exercise. The reason for these differences in recovery speed is unclear, but it may be due to the muscle group or the dynamic nature of this fatigue protocol. While the presence of this change in neural strategy during submaximal isometric contractions may seem trivial for the development of power, there is prior evidence to suggest an incomplete ability to activate the muscle during dynamic contractions in young adults (157). Thus,

submaximal central activation during maximal dynamic contractions may be similar to that of submaximal isometric contractions, providing a link between our intensity-specific and velocity-specific measures.

Our protocol induced a number of changes in contractile properties, with few differences across groups. The increase in RFD at the end of the recovery period may support the possibility of a stiffer muscle, which might contribute to lower power. However, the lack of a difference in the change in RFD across groups would seem to suggest this effect is not the primary cause of difference in the recovery of high-velocity power. In agreement with previous studies (7, 128), stimulated rates of force relaxation and half-relaxation time had transient increases with fatigue and returned to baseline shortly thereafter. While these changes may not be the primary sources of long-term changes in power with recovery observed in this study, the slowing of muscle may limit power production during the initial portions of recovery, particularly at higher velocities.

Low-frequency fatigue, as measured by the 10:80 Hz ratio, was present in both groups following fatigue, and did not recover in either group over the course of 60 min. This is consistent with findings from other researchers (7, 166), who have shown no recovery in this ratio in the hour following fatiguing exercise. Furthermore, low-frequency fatigue has been suggested to be linked to long-term depression of muscle power (166) and decreased torque production in response to a second fatigue bout (192), as was the case in our study. In addition, we did observe a trend ($p=0.07$) for greater low-frequency fatigue in the older group. This would indicate greater excitation-contraction coupling failure in the older compared to the young. It has been suggested that older adults may have impaired calcium handling (62, 180). While many studies

have shown similar responses of fatigue on excitation-contraction coupling in young and older adults (7, 116, 165), this is the first study we are aware of to suggest a greater in older adults. Further investigation into this trend is needed.

Mechanisms of Differences in Recovery in Young and Older Adults

We observed several differences in the recovery of young and older adults which could contribute to the differences in the recovery of high velocity power. We observed a trend for differences in EC coupling across groups at both 0R and 60R. Thus, this is an obvious candidate for the differential recovery. It is also possible that there are different causes of the reduction in power at 0R and 60R. We observed age related changes in the EMG:Torque ratio and pre-motor signaling during isometric contractions following the exercise bout, which could perhaps indicate age-related changes in neural signaling may limit power in the early phases of recovery from fatigue. It also possible that some of the variables which showed deficits at baseline in older compared to young, and decreased similarly in young and older following the fatigue bout played a role. If there is a non-linear relationship between the changes in these variables and the changes in power, it is possible the older fell below some critical threshold where these mechanisms became limiting factors in power production. Thus changes in contractile properties or time-to-contact (i.e. muscle acceleration) may have contributed to the loss in power if the older fell below this critical threshold.

Functional Implications

In response to the fatigue protocol, we saw no group differences in ratings of perceived exertion at 20% or 50% MVIC; differences were apparent at 100% MVIC. Following the exercise, RPE during maximal contractions was elevated only in the older

group and remained elevated for the full 60 min of recovery. This result suggests to us that older adults may exhibit greater symptomatic fatigue in response to exercise. Furthermore, it is possible that older adults change their physical activity patterns following a fatiguing exercise bout due to this increase perceived exertion. This is particularly notable since many everyday tasks, such as getting up from a chair or walking up the stairs, are performed at a relatively high level of their maximal strength (97). Our observation of increased fatigue with a second fatigue bout could further augment this symptomatic fatigue. Thus, our results indicate that repeated bouts of activity may lead to an accumulation of symptomatic fatigue throughout the day, providing a novel link between symptomatic and muscle fatigue. Future studies may want to directly assess intra-day changes in symptomatic fatigue in response to accumulation of activities of daily living as well as exercise.

The observation that high-velocity contractions may not recover in older adults following a fatiguing exercise bout could have important implications for physical function. Baseline muscle power has been correlated with physical performance and gait speed in older adults. While a direct correlation of the effects of changes in power due to fatigue on physical function have not been tested, a number of studies have shown concurrent declines in physical function in response to fatigue (92, 163). In particular, Klein et al (120) showed that maximal jump height in older adults, a measure highly dependent on knee extensor power, was depressed an hour after exercise. Since older adults already perform many of their everyday activities close to their functional reserve threshold (28, 97), the level of strength required to perform a task unimpaired, even a short-term decline in strength could have important implications for physical function.

Our results indicate that velocity may be affected more than just torque production following fatiguing exercise in older adults. Thus, interventions in older adults to prevent disability may want to focus more on preventing the impairments in producing high-velocity contractions following exercise, rather than solely focusing on maximizing torque production. High-speed power training has been shown to increase peak power and velocity of dynamic contractions in older adults (184); however, the impact of this training on fatigue and recovery are not known.

Conclusions

This study provides the first detailed analysis of the age-related differences in neuromuscular response during and following 60 minutes of recovery from fatiguing dynamic exercise. We have shown differences in the fatigue and recovery of high-velocity power production, excitation-contraction coupling, neural modulation of isometric torque, and perceived effort in older adults. While we have provided novel insight into the possible mechanisms of slowed recovery of power in older adults, future studies should use more direct methods to assess the precise physiological processes which may limit this recovery.

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Table 4.1: Group Characteristics

Variable	Young (n=11)	Older (n=12)
Age (years)	30.3 (1.3)	70.7 (1.4)
95% CI	*36.0 – 43.7*	
p-value	*<0.01*	
Height (m)	1.65 (0.02)	1.64 (0.02)
95% CI	*-0.06 – 0.06*	
p-value	*0.97*	
Body Mass (kg)	64.3 (2.5)	72.1 (4.3)
95% CI	*-3.0 – 18.7*	
p-value	*0.15*	
BMI ($kg \cdot m^{-2}$)	23.7 (0.7)	26.7 (1.5)
95% CI	*-0.6 – 6.6*	
p-value	*0.09*	
Physical Activity ($counts \cdot day^{-1} \cdot 1000^{-1}$)	268 (24)	218 (22)
95% CI	*-109 – 27*	
p-value	*0.23*	
MVPA ($min \cdot day^{-1}$)	36.8 (4.5)	19.9 (3.4)
95% CI	*-26.1 - -3.4*	
p-value	*0.01*	
400m Speed ($m \cdot s^{-1}$)	1.70 (0.05)	1.35 (0.04)
95% CI	*-0.50 - -0.24*	
p-value	*<0.01*	
mCSA (cm^2)	51.9 (2.3)	38.6 (1.3)
95% CI	*-18.8 - -7.9*	
p-value	*<0.01*	
Intramuscular Fat (% total CSA)	6.36 (1.04)	14.08 (1.37)
95% CI	*4.10 – 11.35*	
p-value	*<0.01*	

BMI: Body Mass Index; MVPA: Moderate-vigorous physical activity; mCSA: maximal knee extensor ean muscle cross-sectional area. Data are mean (SE), as well as 95% CI, and p-values for the difference across groups.

Table 4.2: Baseline Isometric Measures

Variable	Young	Older
Vol RFD ($\%\cdot ms^{-1}$)	0.77 (0.23)	0.78 (0.23)
95% CI	*-0.42 – 0.56*	
p-value	*0.76*	
Vol:Stim RFD	0.53 (0.05)	0.47 (0.06)
95% CI	*-0.26 – 0.08*	
p-value	*0.26*	
Stim RFD ($\%\cdot ms^{-1}$)	1.47 (0.06)	1.87 (0.10)
95% CI	*0.16 - 0.65*	
p-value	*<0.01*	
Stim RFR ($\%\cdot ms^{-1}$)	-1.18 (0.04)	-0.88 (0.06)
95% CI	*0.16- 0.45*	
p-value	*<0.01*	
$T_{1/2}$ (ms)	112.4 (4.6)	138.1 (5.6)
95% CI	*7.1 – 27.0*	
p-value	*<0.01*	
10:80 Hz	0.46 (0.02)	0.56 (0.01)
95% CI	*0.04 – 0.14*	
p-value	*<0.01*	

V_{75}: Velocity at which 75% of MVIC was generated; RFD: Rate of Force Development; RFR: Rate of Force Relaxation; $T_{1/2}$: 80 Hz Half-relax Time; Data are mean (SE), as well as 95% CI, and p-values for the difference across groups.

Table 4.3: Baseline Dynamic Measures

	Isometric		$30°\cdot s^{-1}$		V_{75}		$270°\cdot s^{-1}$	
Variable	**Young**	**Older**	**Young**	**Older**	**Young**	**Older**	**Young**	**Older**
Time-to-Target (ms)	--	--	77.7 (4.4)	77.6 (8.2)	92.1 (4.6)	110.6 (10.7)	165.6 (9.5)	213.3 (16.0)
95% CI			*-19.9 – 19.7*		*-6.4 – 43.4*		*8.8 - 86.4*	
p-value			*0.99*		*0.14*		*0.02*	
Pre-Motor Time (ms)	48.3 (9.1)	51.6 (7.2)	57.8 (7.5)	110 (18.0)	58.6 (8.1)	65.3 (7.3)	50.2 (4.1)	94.0 (14.0)
95% CI	*-20.7 – 27.3*		*10.2 – 94.1*		*-16.0 – 29.3*		*12.1 – 77.3*	
p-value	*0.77*		*0.02*		*0.55*		*0.01*	
Pre-Motor EMG (%)	9.59 (1.75)	11.64 (1.99)	13.24 (3.11)	20.95 (3.34)	13.49 (2.53)	19.02 (2.81)	13.41 (3.50)	19.28 (2.55)
95% CI	*-3.1 – 7.6*		*-1.8 – 17.2*		*-1.4 – 14.2*		*-3.0 – 14.8*	
p-value	*0.39*		*0.11*		*0.10*		*0.18*	

V_{75}: Velocity at which 75% of MVIC was generate; Data are mean (SE), as well as 95% CI, and p-values for the difference across groups.

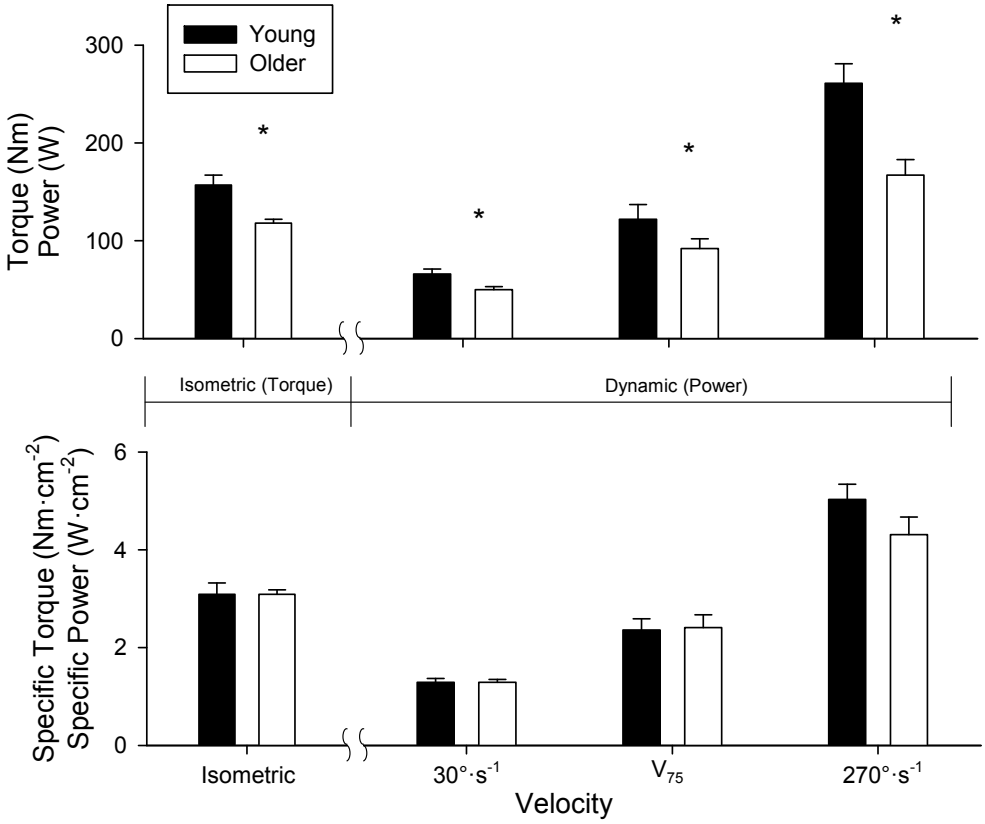

Figure 4.1: Baseline Torque and Power. Absolute torque and power were lower in older women at all velocities ($p<0.01$), but did not differ across groups when normalized to muscle cross-sectional area ($p\geq0.18$). Data are mean+SE. * indicates $p\leq0.05$ across groups for that velocity. V_{75}: Velocity at which 75% of maximal isometric torque was generated.

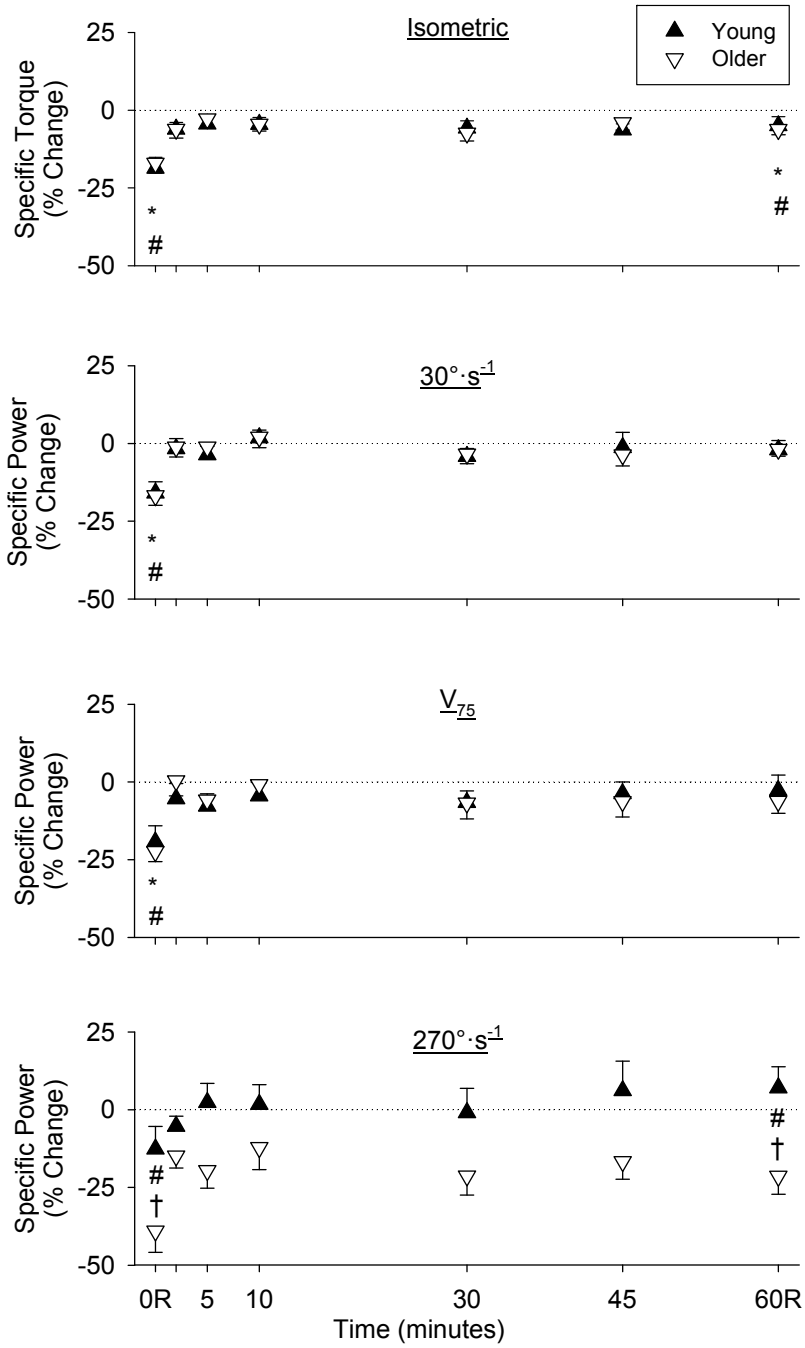

Figure 4.2: Fatigue and Recovery of Specific Torque and Specific Power. Isometric torque declined in both groups with fatigue and did not return to baseline following 60 minutes of recovery. Power at $30°\cdot s^{-1}$ and V_{75} declined with fatigue and recovered by 60R in both groups. At $270°\cdot s^{-1}$, power declined only in the older group and remained depressed after 60 minutes of recovery. Data are mean and SE. At 0 and 60 min of recovery: * indicates young different from baseline; #older different from baseline;

†young different from older ($p<0.05$). V_{75}: Velocity at which 75% of maximal isometric torque was generated.

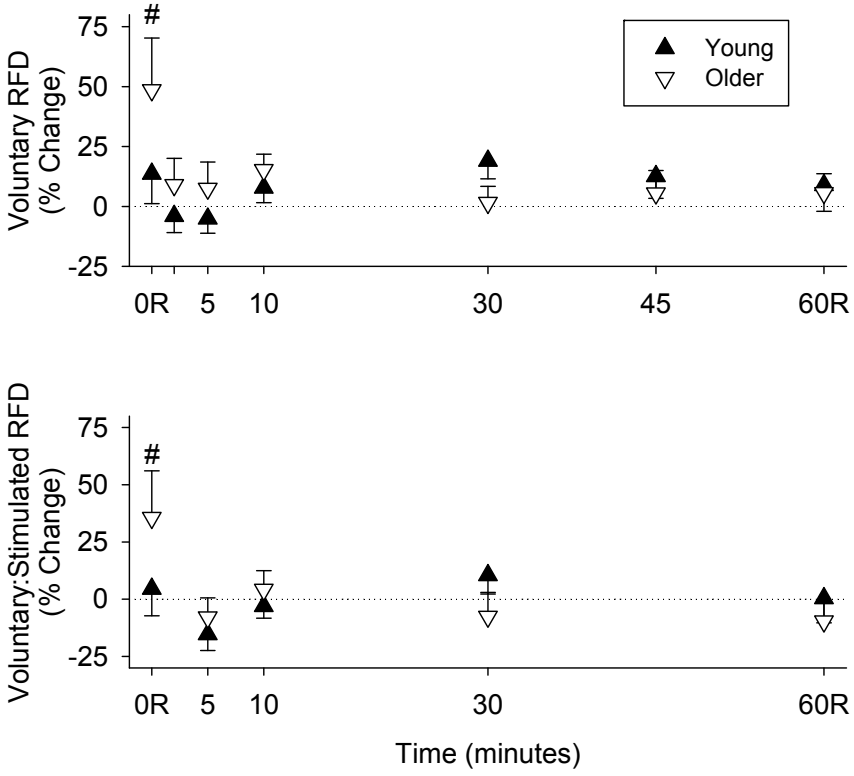

Figure 4.3: Fatigue and Recovery of Voluntary RFD and Voluntary:Stimulated RFD ratio. Both voluntary isometric RFD (top) and the voluntary:stimulated RFD ratio (bottom) increased only in the older group, but returned to baseline with 60 minutes of recovery. Data are mean and SE. At 0 and 60 min of recovery: # indicates older different from baseline ($p<0.05$).

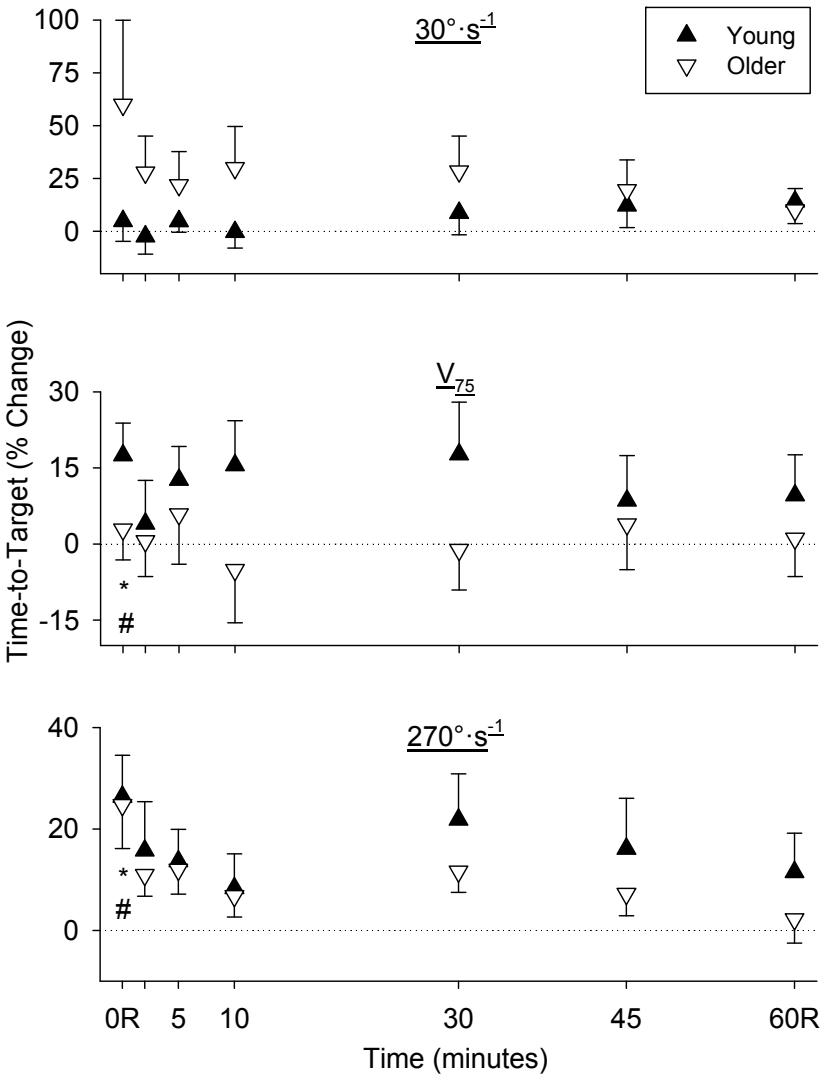

Figure 4.4 Fatigue and Recovery of Time-to-Target Velocity. Time-to-target did not change in either group at $30°\cdot s^{-1}$. At V_{75} and $270°\cdot s^{-1}$ it increased in both groups to a similar degree at the end of the fatigue bout, but recovered to baseline after 60 minutes. Data are mean and SE. At 0 and 60 min of recovery: * indicates young different from baseline; # older different from baseline. V_{75}: Velocity at which 75% of maximal isometric torque was generated.

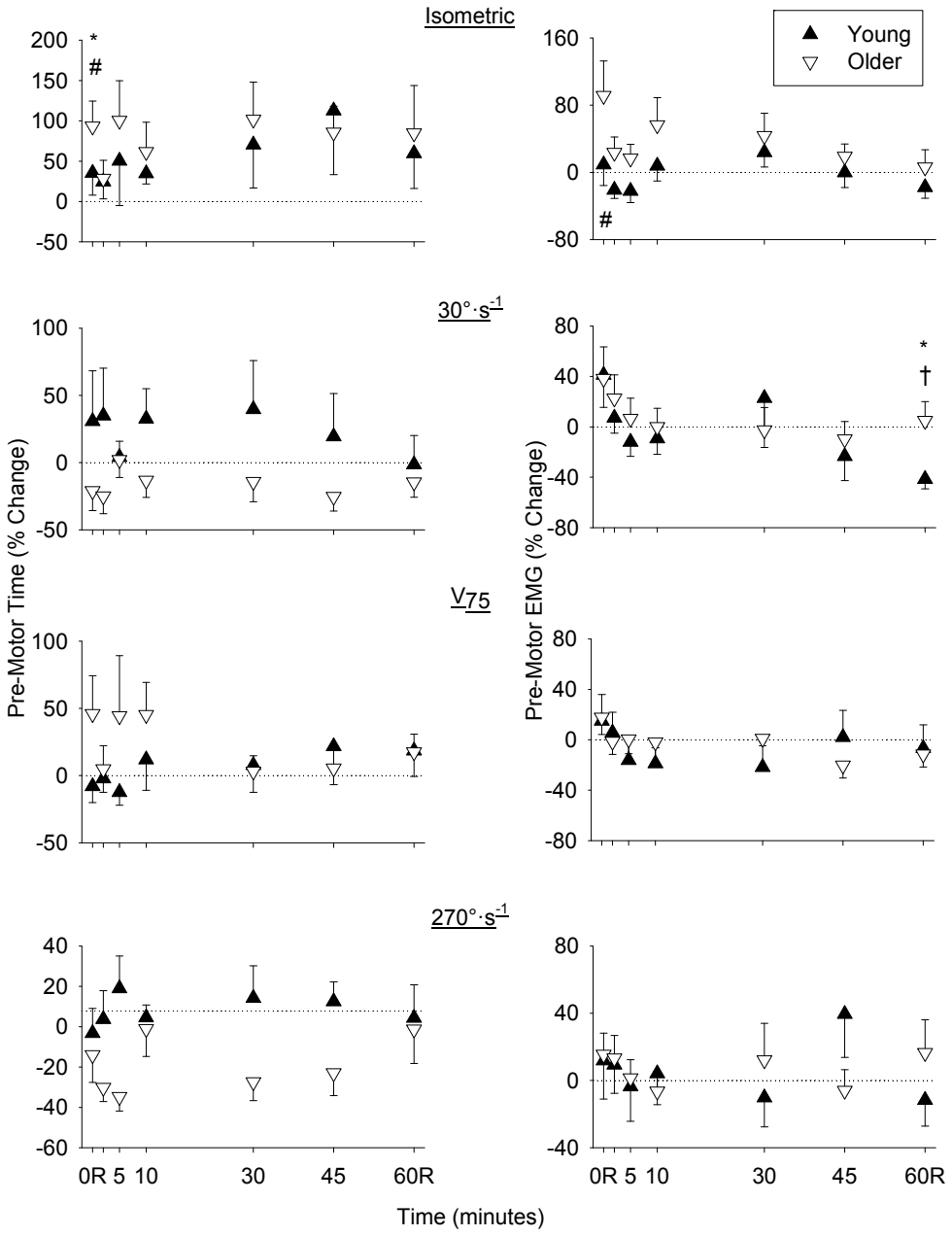

Figure 4.5: Fatigue and Recovery of Pre-Motor Time (*left*) and Average Pre-Motor EMG (*right*).

During isometric contractions, pre-motor times increased following fatigue in both groups to a similar extent, but recovered to baseline by 60 minutes. At 270°·s^{-1}, older had a lower premotor time throughout the 60 minutes of recovery (group p=0.05); however, neither group significantly differed from baseline. Pre-motor EMG increased in the older under isometric conditions only immediate following fatigue. At 30°·s^{-1}, pre-motor EMG did not differ post-fatigue, but in the younger, it was significantly lower than both the older and baseline following 60 minutes of recovery. Data are mean and SE. At 0 and 60 min of recovery: * indicates young different from baseline; # older different from

baseline; † young different from older ($p<0.05$). V_{75}: Velocity at which 75% of maximal isometric torque was generated.

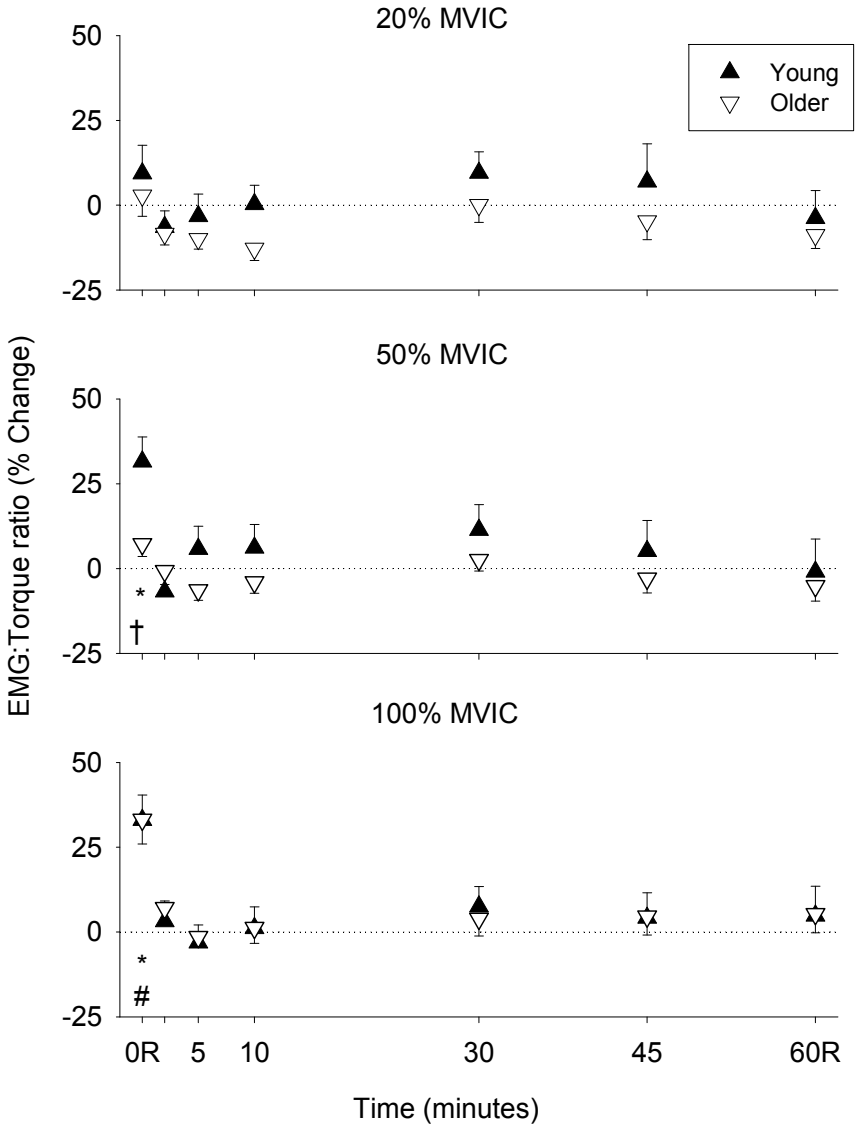

Figure 4.6: Fatigue and Recovery of EMG:Torque Ratio. Post-fatigue, the EMG:Torque ratio did not change in either group at 20% maximum voluntary isometric contraction torque (MVIC), increased only in the young at 50% MVIC, and increased in both groups at 100% MVIC. The ratio returned to baseline following 60 minutes of recovery. Data are mean and SE. At 0 and 60 min of recovery: * indicates young different from baseline; # older different from baseline; †Young different from older ($p<0.05$).

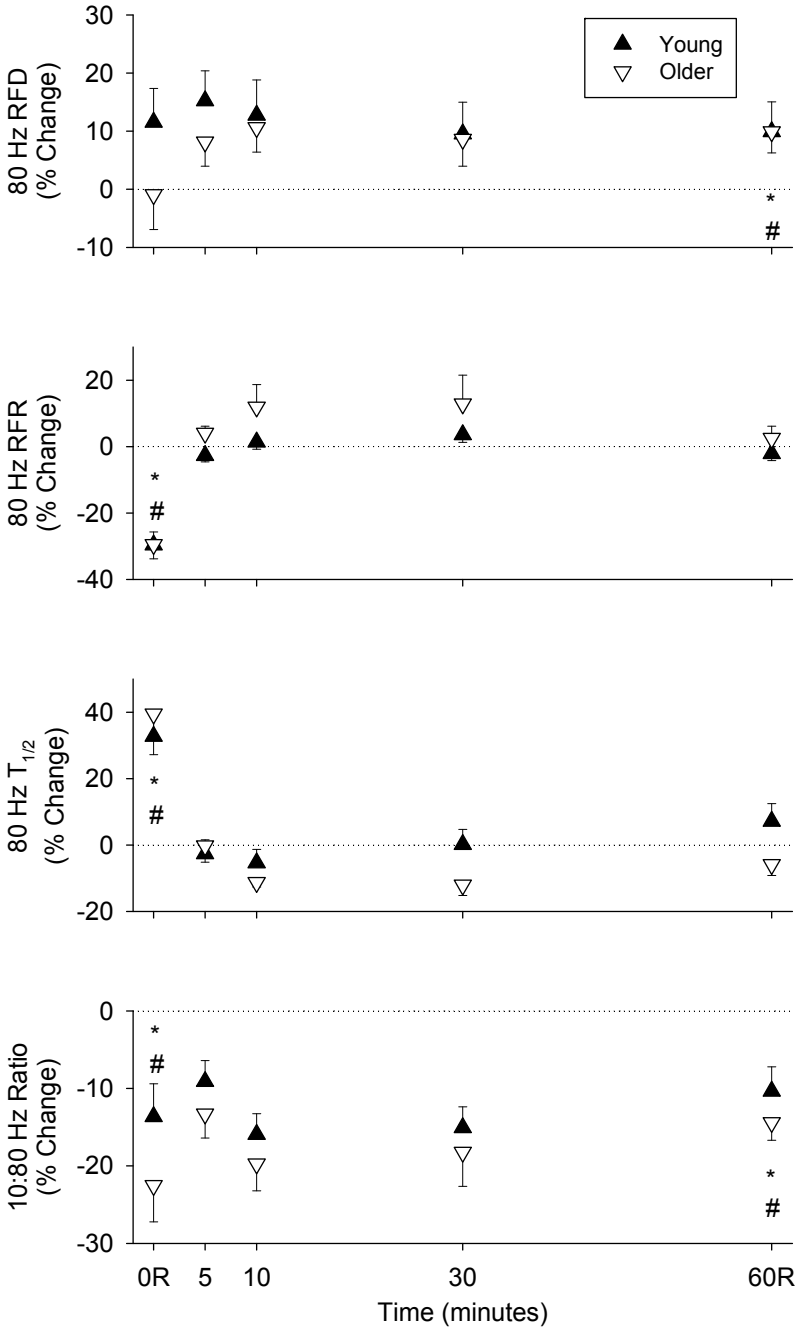

Figure 4.7: Fatigue and Recovery of Stimulated Measures. Maximum 80 Hz RFD did not change with fatigue, but was elevated in both groups similarly following 60 minutes of recovery. RFR and $T_{1/2}$ slowed similarly in both groups with fatigue and recovered to baseline by 60 minutes. The 10:80 Hz ratio was depressed at both 0R and 60R in both groups. Across all time points, it was a trend for the ratio to be lower in the older than young (group p=0.07). Data are mean and SE. At 0 and 60 min of recovery: * indicates young different from baseline; # older different from baseline ($p<0.05$).

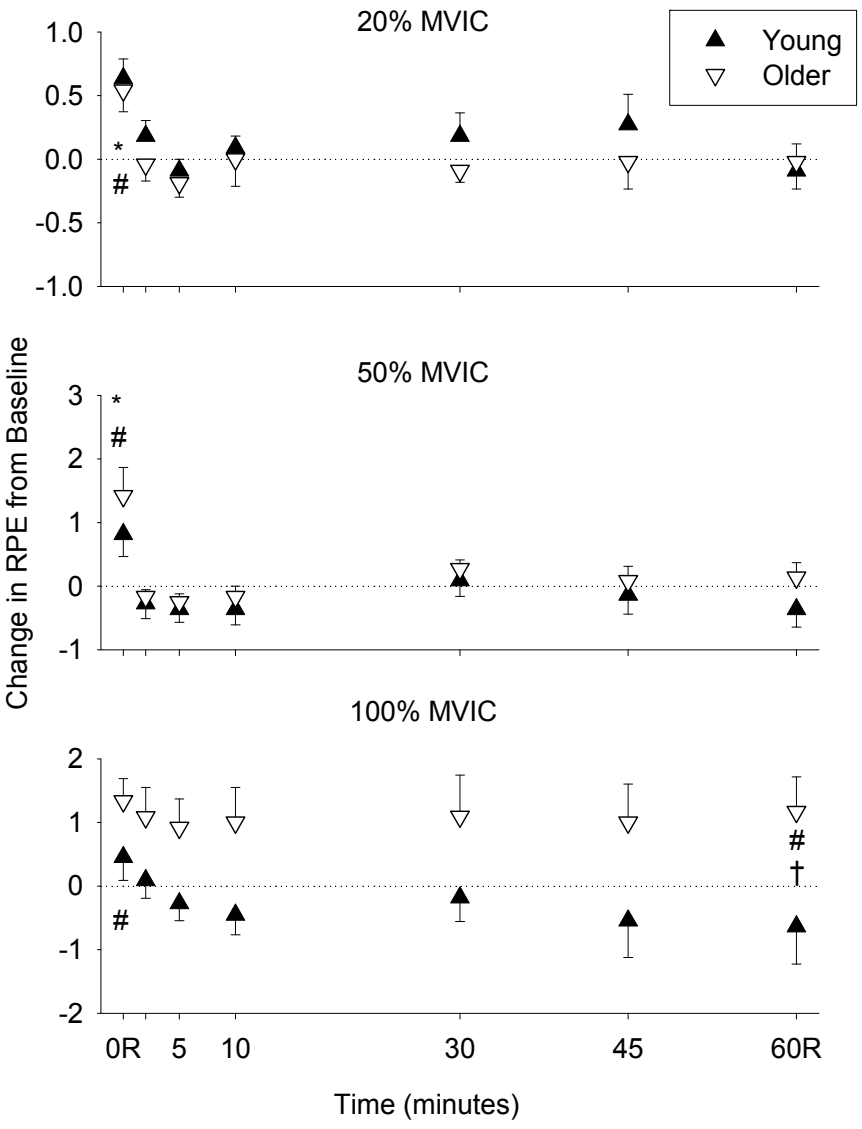

Figure 4.8: Changes in Perceived Exertion. Following fatigue, ratings of perceived exertion increased in both groups to a similar degree at 20% and 50% maximum voluntary isometric contraction torque (MVIC) post-fatigue, but returned to baseline by 60 minutes. At 100% MVIC, RPE increased post-fatigue only in the older group, and remained elevated for the 60 minutes of recovery. Data are mean and SE. At 0 and 60 min of recovery: * indicates young different from baseline; # older different from baseline; † young different from older ($p<0.05$).

CHAPTER 5

RECOVERY OF POWER AND PHYSICAL FUNCTION FOLLOWING NEUROMUSCULAR FATIGUE IN OLDER WOMEN

Abstract

Low muscle power, particularly at high contraction velocities has been linked to functional impairments in older adults. Any delay in the recovery of muscle power following fatiguing exercise could lead to lasting effects on physical function; but this hypothesis has not been evaluated in the context of aging. No study has identified how reductions in power lead to decrements in physical function for an hour after exercise. To test the hypothesis that the recovery from fatigue of power and physical function are linked, 17 healthy older (66-81 years) women completed a 30 min walking protocol designed to induce neuromuscular fatigue, followed by 60 min of recovery. Dynamometry was used to quantify fatigue and recovery of knee extensor muscle power at 3 different velocities. Function was quantified as time to perform 5 chair rises, and by measures of center of pressure (COP) range (mm), COP velocity ($mm \cdot s^{-1}$) and time-to-contact (TtC, s) in the anterior-posterior (AP) and medial-lateral (ML) directions during quiet stance. Power declined at all velocities immediately after walking ($p<0.01$) and remained depressed after 60 min of recovery. Postural stability decreased following the walk, indicated by increased AP and ML range and COP velocity, and showed a mixed pattern of recovery. Following 60 min of recovery, COP range remained elevated, but average COP Velocity in both directions was reduced and AP TtC was elevated, suggesting increased stability relative to baseline. Correlation analyses of high-speed power ($270° \cdot s^{-1}$) and balance measures suggested greater power declines was associated with greater instability immediately following the walk (due to weakness), but greater stability following 60 min of recovery. Decreased high-velocity power was also associated with slower chair rise times both following the walk and after 60 min of

recovery. Walking induced marked declines in muscle power that did not recover for at least 1 hour; and this deficit was associated with transient decrements in physical function. These results provide compelling new evidence of neuromuscular changes in older women that may place them at greater risk for functional deficits following everyday tasks such as walking.

Introduction

As individuals age, they become susceptible to a number of health problems affecting balance and muscle function. More specifically, in older adults, there is increased prevalence of visual, vestibular, and somatosensory dysfunction (6, 111, 137). Impairments in neuromuscular function in older adults include changes in motor unit firing behavior (107), sarcopenia (70), and reduced muscle power (81, 100). Ultimately, the combination of these changes can lead to poor physical function, i.e. the inability to do every day mobility tasks, in this population.

Muscle power, the product of torque and velocity, has been shown to be a predictor of physical dysfunction in older adults (13). For example, older adults with muscle weakness have slower chair rise times and gait speeds (26). This may be related to the concept that a minimum amount of power is necessary to perform a variety of functional tasks (28, 188, 212). Above this minimum, people operate in a "functional reserve," where higher power does not affect performance of a given task. However, when power falls below this threshold, physical function declines, and eventually reaches a point where functional tasks can no longer be performed. Due to muscle weakness, older adults may operate closer to their functional reserve threshold than younger adults during everyday tasks (97). Thus, even small changes in the amount of power they can produce, for instance as a result of fatigue, may have severe impacts on physical function.

Older adults show reduced balance performance compared with young adults. For instance, it has been shown that older adults have greater anterior-posterior (AP) and medial-lateral (ML) range and velocity of their center of pressure (COP) during quiet stance with eyes open (168). Furthermore, older adults have a shorter time to contact

(TtC) of the stability boundary, a measure which takes into account COP position and velocity in relationship to the base of support (203). These changes in COP and TtC characteristics may be indicative of impaired balance (69) and ultimately an increased risk of falls (33). Lower extremity muscle weakness, along with reduced neuromuscular control, proprioception, vision and vestibular function, all contribute to this impaired balance (137). Studies have shown correlations among leg strength and COP sway (137), functional balance batteries (89), as well as improvements in balance following strength training (25).

Transient declines in power, such as those from muscle fatigue in response to exercise, can lead to declines in physical function (91, 154, 163). While it has been shown that older adults fatigue less than young adults during isometric tasks, older adults fatigue to a greater extent during high-velocity dynamic tasks (42), resulting in greater power losses. Thus, the functional consequences of weakness may be amplified following fatiguing dynamic exercise in older adults. Gait characteristics (91) and sit-to-stand transitions (163) are altered following fatiguing exercise in older adults, possibly due to changes in postural control. In addition, several measures indicate balance is altered following fatiguing tasks in both young (153) and older adults (16, 69, 134). While researchers have shown functional effects from muscle fatigue induced in the laboratory by strength machines and dynamometers in older adults, these fatigue protocols may not reflect the activities of daily living, such as walking, that may contribute to fatigue in a "real-world" setting.

It is reasonable to theorize that 1) there are deficits in physical function and power following a fatiguing walking task, and 2) recovery of physical function may require the

recovery of muscle power. We have shown that recovery of power during high-velocity contractions is slower in older adults and incomplete following 60 min of recovery (Foulis, Chapter 4). Because it has been suggested that postural control during quiet stance is achieved, in part, through short ballistic contractions (136), lingering decrements in power at high-velocities could be detrimental to the maintenance of balance after a fatiguing bout of exercise.

We are not aware of any study that has quantified changes in physical function in concert with measures of muscle power following fatiguing exercise in older adults. Thus, the aim of this study was to evaluate the impact of a fatiguing walking task on changes in power, balance, and physical function in older women. We hypothesized that 1) a 30 min walking task would decrease knee extensor muscle power; 2) power at high velocities would be more affected by the walking task than lower velocities; 3) physical function and balance control would be reduce following the walk; and 4) these power declines would be associated with reduced physical function and increased instability. For the purposes of this study, physical function was assessed using chair rise time and measures of balance during quiet stance.

Methods

Participants

Seventeen community-dwelling older (66-81 years) women participated in the study. Women were recruited because older women are at a greater risk for disability than males due to their generally lower muscle strength (108). All participants were relatively healthy, non-smokers and free of any leg injury that could affect physical performance. No participants had a history of metabolic, neurological, cardiovascular

(except for controlled hypertension), or pulmonary disease. With the exception of one participant on a low-dose beta-blocker (atenolol), no participant was on any medication known to affect the outcome measures of this study. All participants read and signed an informed consent document as approved by the University of Massachusetts, Amherst human subjects review board. Physician's consent was obtained prior to participation. Each participant made 4 visits to the Muscle Physiology Lab: one for consenting, one for habituation, and two for testing.

All participants were sedentary to recreationally active by self-report, defined as not currently training or participating in organized athletic activities. No individuals were engaged in any strength training programs. To quantify habitual physical activity, participants wore Actigraph GT1M (Pensacola, FL) uniaxial accelerometers at the hip for 7-10 days. Total daily activity counts, as well as minutes spent in moderate-vigorous activity (MVPA), were calculated using established thresholds for Actigraph accelerometers (75).

All participants completed a habituation visit prior to the two testing visits. Descriptive variables, including anthropomorphic measurements, functional ability, and symptomatic fatigue were collected during this visit. Functional status was quantified using the Short Physical Performance Battery (SPPB; (83, 84)), 10-s foot-tap speed (115), and 400 m walk time (10 loops of a 40 m course; (187)). Symptomatic fatigue was determined using a validated questionnaire (PROMIS 7a short form (34)). In addition, participants were familiarized with the power and functional testing measures.

Muscle Power Measures

Knee extensor torque and power were measured using a Biodex System 3 dynamometer (Biodex Medical Systems, Shirley, NY), as described previously (32). Briefly, participants were seated with the hips at 90° and a resting knee angle of 100° extension. Torque, velocity, and position signals were collected at 2500 Hz using a customized Matlab (Mathworks, Natick, MA) program.

Maximal voluntary isometric contraction torque (MVIC, Nm) was recorded during 3-4s contractions of the knee extensors. Participants were allowed to select the leg to be tested. Verbal encouragement was provided by the investigator and visual feedback about torque production was provided using a lighted box. Participants performed 3 MVICs with 2 minutes of rest between contractions. Additional MVICs were performed if peak torque of 2 of the first 3 were not within 10% of each other. Peak power (W) was measured during dynamic contractions over a 70° range of motion (100°-170° of extension). Participants completed a series of 3 rapid contractions at each velocity. The torque-velocity curve was calculated for each participant using peak torque at 10 velocities from 30-300°$\cdot s^{-1}$ at 30°$\cdot s^{-1}$ intervals (32). Each contraction series was cued by the investigator, and separated by 1 minute of rest. Peak torque at each velocity was expressed relative to MVIC and fit to a second-order polynomial so that the velocity at which 75% of MVIC (V_{75}) was generated could be determined. The V_{75} provided a summary variable representing each individual's overall torque-velocity characteristics, as well as a common relative velocity at which to perform the strength measures at baseline and during recovery.

Physical Function and Balance

The effects of muscle fatigue on physical function were determined by measuring balance during 30s of quiet stance and time to complete 5 rapid chair rises prior to, and throughout 60 min of recovery from the walking task. Balance was using two side-by-side force plates (AMTI, Newton, MA) to measure ground reaction forces under each foot. These forces were used to compute measures of COP excursion and TtC of the base of support. Reflective markers were placed bilaterally on the halluces, metatarsal heads 1 and 5, center of the heels, and medial and lateral malleoli. As is standard procedure for balance measures (44, 201), participants placed one foot on each plate parallel to each other and shoulder width apart. During the recordings, participants were instructed to place their arms across their chest and stand as still as possible for 30 s. Data were recorded at 120 Hz using Qualisys track manager (Qualysis Medical AB, Gothenburg, Sweden).

Changes in COP were quantified by calculating the range (mm) and average velocity ($mm \cdot s^{-1}$) separately for the anterior-posterior (AP) and medial-lateral (ML) directions over the 30 s. Measures of TtC (s) of the COP to the stability boundary were calculated with the Slobounov technique (189), using a rectangular boundary identified by the toe, heel, and fifth metatarsal markers. While COP is often used to measure balance, TtC may be a better measure of balance as it also takes into account spatial and temporal information about the individual's limit of stability as defined by the perimeter of their feet during quiet stance (85). The Slobounov method was selected as it best captures overall postural control by including information about the instantaneous position, velocity and acceleration of the COP; in contrast, other techniques for

calculating TtC omit acceleration, and thus may miss important information (85). From these calculations, average and minimum TtC were calculated, again in the AP and ML separately. Average TtC is a measure of the overall stability and postural control during the 30 s. To capture the periods of least stability, while avoiding transient motions, minimum TtC was calculated as the average of the minima for successive 100 ms epochs throughout the 30 s.

Following the balance test, a chair was brought to the participants and they completed 5 timed chair rises with their arms folded across their chest. Chair rises were selected as a representative measure of physical function because older adults perform that task at a high percentage of their maximal strength (97), and chair rise performance has been shown to be affected by fatigue in young and older adults (163). Chair rise time (s) was recorded as the time required to stand up completely and sit back down in a chair (seat height = 45 cm) 5 times as fast as possible. Time was started by cue of the investigator and stopped when the participant was seated in the chair for the 5^{th} time.

Fatigue Protocol and Recovery Measures

To allow accurate quantitation of fatigue-induced changes in and recovery of both power and physical function (balance, chair rise), participants performed the walking task on two days, and either power of function measures were obtained. The trials were separated by at least 48 hours, and the order of the 2 visits was randomized. The timing of all recovery measures was consistent on both days, occurring 2, 5, 10, 30, 45, and 60 minutes following the walk.

Following a set of baseline measures, the participant began the fatigue protocol, which consisted of 30 min walking on a treadmill. On the first fatigue test day, treadmill

speed (incline = 0°) was increased over the first 30 s until the average overground walking speed from the individual's 400 m walk test was attained. At that point, participants were asked if they thought they could maintain that speed for the full 30 min. If the participant could not, treadmill speed was reduced in 0.045 $m \cdot s^{-1}$ increments every 10s until the participant was confident that they could compete the task. At minutes 7, 17, and 27, the grade of the treadmill was increased to 3% for 1 minute in order to provide a slight challenge and to simulate a hill that the participant might encounter in everyday life. After 1 minute, the grade was returned to level. During the final 30 s, the treadmill was gradually slowed to 0.4$m \cdot s^{-1}$ before stopping. Participants then stepped off the treadmill and continued walking overground for ~2 min at approximately the same pace. This approach allowed us to eliminate potential motion after-effects caused by walking on the treadmill (88), as well as transport the participant to the Biodex or force platforms for their recovery measures. This process was repeated for both fatigue tests; the same treadmill speed was used on both days.

Baseline measures of power or function were collected immediately prior to the walking protocol, using the dynamometer or force platform, respectively. The first recovery measure was collected 2 min following completion of the overground portion of the walk, which allowed time to position the participant for data collection. Additional measures were collected at 5, 10, 30, 45 and 60 min of recovery. To capture the effects of the walking task on muscle function across a range of velocities, peak torque and power were assessed during contractions at at $0° \cdot s^{-1}$ (MVIC), $30° \cdot s^{-1}$, V_{75}, $270° \cdot s^{-1}$. Contraction order was randomized. These four velocities were selected to allow evaluation of velocity-specific deficits in power output in response to the fatiguing walk

on both an absolute and relative scale. The speed for the high-velocity contractions was chosen because it was the fastest velocity all older participants could be expected to attain (129). Fatigue was quantified as any deficit in power production in response to the walk. Following the fatigue protocol on the function testing visit, participants completed a 30 s quiet stance balance test, followed by 5 chair rises at each recovery time. For the balance testing, participants were positioned on the force platforms and stood quietly for 1 minute prior to the start of the 30-s data collection period. On both fatigue days, participants remained seated between each set of recovery measures, and were asked to remain as still and relaxed as possible.

Statistical Analyses

All analyses were performed using SAS software (SAS Institute, Cary, NC), with significance established at the $p \leq 0.05$ level. To test hypothesis 1, separate paired t-tests were used to compare baseline to (2R), in order to determine the fatiguing effects of walking, and baseline to the 60 min recovery (60R) point, to evaluate the completeness of recovery. A two-factor (velocity, time) repeated measures ANOVA was used to test hypothesis 2 regarding velocity-dependent changes in torque or power in response to and during the recovery from the walking task. The velocity x time interaction was partitioned to determine differences in the amount of power deficit across velocities 2R and 60R. Changes in chair-rise, COP, and TtC during the recovery period also were assessed by using paired t-tests to compare 2R and 60R to baseline, in order to test hypothesis 3. Intermediate recovery time-points are reported, but no formal hypotheses were tested for these time-points. To test the relationships among changes in power with changes in the functional and balance measures (hypothesis 4), linear correlation was

used to calculate correlation coefficients. Correlation coefficients (r) and p-values are provided, as well as mean ± SEM or mean and 95% (unadjusted) confidence intervals (CI) for differences from baseline, as appropriate.

Results

Group Characteristics

Participant characteristics are summarized in Table 5.1. Prescription medication use was typical of this age group; medications included anti-hypertensives, antidepressants, anti-inflammatories, synthetic thyroid hormone, and statins. Only 4 of the 17 participants met the American College of Sports Medicine physical activity guidelines, defined as 150 minutes of MVPA per week (156); the group average was 126 weekly minutes of MVPA.

Thirteen of the 17 participants scored 12 out of 12 on the SPPB, suggesting no to minimal impairments in physical function. The remaining individuals scored an 11, with 1 losing a point on the balance subscore and the other 3 on the chair rise test; overall, these individuals had only minor disturbances to physical function (84). Chair rise and 400 m walk times were generally faster than the average times reported from a large-scale study of older women having characteristics similar to those in the present study (193). Likewise, foot tap speed was generally faster than those previously reported in older women (115). The group had an average PROMIS t-score of 43.7±1.8, indicating slightly less than average symptomatic fatigue than the mean of the general United States population (t-score=50). Baseline MVIC (32) and V_{75} (Foulis, Chapter 4) was similar literature values for comparable study cohorts.

Fatigue Task Performance

Average walking speed for the fatigue test was 1.35 ± 0.05 $m \cdot s^{-1}$. For 13 of the 17 participants, this was the same speed as their over-ground 400m test. Speeds for the other 4 participants were reduced by up to 0.13 $m \cdot s^{-1}$. During the protocol, 16 of the 17 completed the full 30 min on the treadmill, including all 3 incline challenges. Due to fatigue in 1 participant, walking was stopped at the 27 minute mark after only 2 of the incline challenges were completed. Walking duration and intensity was matched across both days for all individuals.

Effects of the Walking Task on Muscle Torque and Power

Changes in muscle torque and power in response to the walking task are shown in Figure 5.1. At 2R, torque and power had decreased from baseline at all velocities ($p \leq 0.03$), indicating significant fatigue from the task. The velocity x time rmANOVA indicated no difference in fatigue across velocities ($p=0.75$). At 60R, torque and power had recovered by different amounts across the velocities ($p<0.01$): isometric torque had returned to baseline ($p=0.07$), while peak power for all dynamic contractions remained depressed ($p<0.01$).

Functional Performance

At 2R, COP range (Figure 5.2) increased in both the AP and ML directions during quiet stance ($p \leq 0.03$). This range remained elevated in the AP direction ($p=0.03$) and tended to be elevated in the ML direction ($p=0.06$) at 60R. Average COP velocity (Figure 5.3) differed from baseline in both the AP and ML direction. In the AP direction it tended to increase from baseline at 2R ($p=0.08$) and then decrease below baseline by 60R ($p=0.01$). In the ML direction, average velocity was unchanged from baseline at 2R

(p=0.14) but, as in AP, it decreased to below baseline by 60R (p=0.01). Peak COP velocity did not change from baseline at any point following the walking task (p≥0.28).

Average AP TtC (Figure 5.4) did not differ from baseline at 2R (p=0.51) but tended to be higher at 60R (p=0.09). Average ML TtC did not differ from baseline at either time point (p≥0.41). The average minimum AP TtC for 100 ms epochs (Figure 5.5) was not different from baseline at 2R (p=0.45) and was longer than baseline at 60R (p<0.01). In the ML, minimum TtC did not change from baseline at the 2R or 60R time-point (p≥0.20).

Results of the chair rise task are shown in Figure 5.6. Mean chair rise times did not change from baseline at 2R or following the 60 minutes of recovery (p≥0.45).

Overall, the balance measured indicated that the fatigue task induced increases in COP Range and COP Velocity at 2R; and increases in COP Range and average TtC and decreased COP velocity at 60R. In contrast, chair rise performance was unaffected by the fatigue task.

Relationships among Changes in Muscle Power and Physical Function

As hypothesized, there were associations between fatigue-induced changes in power at $270°\cdot s^{-1}$ and changes in balance and chair rise measures. Changes at 2R in high-velocity power ($270°\cdot s^{-1}$) were associated with the relative increase in AP COP range at this time point (r=-0.54, p=0.02; Figure 5.7). There were no significant relationships with COP range at baseline or 60R in the AP, or at either time-point in the ML (|r|≤0.39, p≥0.13). The relative decrease in average AP COP velocity tended to be correlated with power deficit at $270°\cdot s^{-1}$ (r=0.45, p=0.06) at 60R; however, this was not the case in the ML, or at any other time point in the AP (|r|≤0.33, p≥0.19). There were no relationships

among any of the TtC measures and the strength measures ($|r| \leq 0.33$, $p \geq 0.19$). Individuals with greater decline in power at $270°\cdot s^{-1}$ at 2R and 60R had a greater relative increase in chair rise time at those time-points ($r=-0.55$, $p=0.02$; $r=-0.52$, $p=0.03$, respectively; Figure 5.8).

There were no relationships among any of the functional measures and isometric torque or power at $30°\cdot s^{-1}$ or V_{75} at fatigue or at the end of recovery ($|r| \leq 0.38$, $p \geq 0.13$), except for one significant correlation among power at V_{75} and ML average COP velocity ($r=-0.51$, $p=0.04$) at 60R. Because no other associations were observed in the ML, or at V_{75}, this one relationship likely a spurious result.

Discussion

The results of this study indicate that 30 min of moderate-paced walking causes significant fatigue in the knee extensor muscles of older women. Following 60 minutes of recovery, isometric torque had returned to baseline, but muscle power remained depressed at all three velocities. Balance during quiet stance was altered immediately following the walking task, but these measures recovered to baseline within 60 minutes. Following this fatiguing exercise, changes in balance in the AP, but not ML, direction were associated with changes in muscle power at $270°\cdot s^{-1}$. Although there was no change in mean chair rise time in response to the walking protocol, changes in chair rise time were associated with changes in high-velocity power, both immediately and 60 minutes following the walk. These data provide new evidence of striking alterations in neuromuscular and physical function in older women following a walking task designed to reflect potential physical challenges encountered in everyday life. Both acute changes associated with fatigue in response to the walk and prolonged alterations that could be

expected to impact function in daily activities were observed. The implications of these results include possible changes in the physical activity recommendation in order to suggest avoiding behaviors following exercise which may place older adults at risk for falling; as well as possible design changes in areas where adults do a lot of walking.

Fatigue and Recovery of Muscle Power

A novel finding of this study is that a 30-minute, moderately intense walking task with 3 uphill challenges caused significant muscle fatigue in healthy older women that lingered for at least one hour (Figure 5.1). While isometric torque recovered to baseline within the 60-min recovery period, power at all three contraction velocities did not. There was a significant effect of velocity at 60R but not 2R, indicating that the power loss was greater during high-speed than low-speed contractions. Indeed, rather than recover, power at $270°\cdot s^{-1}$ declined further at 60R compared with 2R. Thus, the mechanism for the depression of high-velocity power may be based more on the failure of the muscle to generate velocity rather than produce force. This concept would be consistent with findings prior studies in our lab, which have shown both greater deficits in the power-velocity curves (129) and greater fatigue at high velocities (32) in older adults compared to young.

Power deficits at 2R ranged from 8% for the MVIC to 13% during the maximal contraction at $270°\cdot s^{-1}$ (Figure 5.1). These values are similar to, or slightly greater, than those observed at the same time point in the knee extensors muscles of older women following a 4-min isovelocity fatigue protocol on a dynamometer (Foulis, Chapter 4). While we did not measure muscle shortening velocity in this study, loaded shortening velocity in older adults during walking was reported to be $97°\cdot s^{-1}$ (103), a value

remarkably similar to the average contraction velocity of $63°\cdot s^{-1}$ during the knee extension fatigue protocol in our recent study (Foulis Chapter 4). These commonalities in methodology and results provide a possible link between these two fatigue protocols and indicate the relevance of results of lab studies to real-world situations. The amount of fatigue we observed in the fatigue protocol was less than the fatigue observed in other studies of knee extensor fatigue at similar velocities (32, 113), most likely due to the rapid recovery of torque that can be expected during the first two minutes of the recovery period.

A key result of this study was that power did not return to baseline after 60 minutes of recovery. Notably, the power deficits at $270°\cdot s^{-1}$ following 60 minutes of recovery (23%) were similar between the current study and our recent study, in which knee extensor fatigue was accomplished using a dynamometer (Foulis Chapter 4). Given the similar fatigue in both protocols, it is likely that the mechanisms governing fatigue and the recovery of muscle power in that study are applicable to the present study. In our previous study and studies by other researchers (165, 167), incomplete recovery of high-speed power coincided with the presence of low-frequency fatigue. This finding would implicate impairments in excitation-contraction coupling in the reduction in the ability to produce power. Excitation-contraction coupling failure has been observed following a variety of exercises (125), and has been shown to last more than 24 hours following fatigue (68). Thus, it is possible that a similar mechanism is responsible here for the decrements in power. Moreover, given that coactivation of antagonist muscles is greater as age, muscle fatigue, and velocity increase (121, 205), antagonist activation of the hamstrings is limiting power production. However, we have no measures of coactivation.

It is also possible that there was muscle damage in response to the walk which led to increased stiffness (98) and therefore decreased power (102). Future studies may want to include measures of excitation contraction coupling, coactivation, and muscle damage in order to determine the exact mechanisms of the incomplete recovery of power after fatiguing lower limb exercise.

This prolonged depression of high-velocity (i.e. $270°\cdot s^{-1}$) power has important implications for physical function in older adults. For example, unloaded knee extension velocity has been shown to be $265°\cdot s^{-1}$ during stair descent in health older adults (103). Falls on stairs, particularly during stair descent, contribute significantly to the number of fall related deaths every year (29). Any weakness at these high-velocities, even for a brief period in response to prior physical activity, could place older adults at increased risk of falling.

Fatigue and Recovery of Functional Performance

The increased COP range and trend for an increase in COP velocity at 2R may represent reduced postural control as a result of exercise. These findings are in agreement with the work of others who have noted increases in COP displacement in older adults following fatiguing calf contractions (152) and a bout of self-paced circuit-training (69). Following 60 minutes of recovery, we found that COP range remained elevated (Figure 5.2). Nardone et al (153) noted an increase in the amount of COP sway in younger individuals following fatiguing treadmill walking. Sway recovered to baseline within 15 minutes. Similarly, our data decreased in that time frame, but then began a secondary increase. While the increased COP range at the 60R time-point would suggest increased instability, that interpretation is contradicted by the decreased average

COP velocity and increased minimum TtC that were also observed at the end of the recovery period, outcomes considered indicative of greater stability. It is possible that that the reduction in these latter variables below baseline is the result of a learning effect, as previously suggested by Nardone et al (154). During repeated balance trials with no exercise perturbation, they observed increased stability over time. In this case, the increased COP range could still represent some degree of increased instability, while the reduced COP velocity would be due to a learning effect. Thus, following 60 min of recovery, older adults may be drifting at a slower velocity, perhaps due to a difference in the nature of their shifts in COP (i.e. trunk vs. full body sway). Another possibility is that these individuals are actually more stable 60 min after walking. A number of investigators have suggested that TtC may be a better measure of balance because it takes into account spatial characteristics (85), and our TtC measure showed increased stability. Thus, it is also possible that balance is not impaired at the 60R time-point, and the increased COP range is instead due to greater exploratory behavior as a result of increased comfort with the measure (202).

We noted that an increase in high-velocity, but not isometric or low-velocity, fatigue was associated with both a greater AP COP range at 2R and slower average AP velocity at 60R. These relationships may indicate that reduced power is related to instability at the 2R time-point, but greater stability at 60R. The potential mechanism for the reversal in this relationship is unclear, but may be due in part to some of the factors responsible for prolonged fatigue. For example, reduced strength may play a prominent role in the immediate instability, but compensation in balance may have occurred through improvements in another mechanism, such as somatosensory or vestibular function, by

60R. Joint proprioception (95) and vestibular input (135) have been shown to be reduced in young adults following exercise. To our knowledge, there are no studies of recovery of these measures following exercise in aging. Following 60 minutes of sitting after the exercise, it is also possible that tissue stiffness, particularly those at the ankle, is increased. This stiffness may hinder power production (102), yet provide stability (209). Loram and Lakie (136) have suggested that resting stiffness of the calf muscles in young adults is insufficient for complete balance control. Thus, immediately following the exercise, weakness may impair balance. However, an increase in muscle stiffness over the following hour may augment balance under quiet stance. This may not be the case when it comes to balance during more challenging dynamic postural conditions and in response to perturbations, when the ability to produce quick forceful motions is instrumental for preventing falls.

We observed relationships among power and balance primarily in the AP direction. Motion in the AP direction has been hypothesized be dependent on muscle strength due to the multiple joint that require muscular support in that direction (58). In particular, balance in the AP was associated with high-velocity power. This result is consistent with Loram and Lakie's hypothesis (136) that rapid ballistic contractions are needed to maintain balance in the AP. The increased instability post-fatigue may be due to the inability to make these rapid postural adjustments. Balance in the ML may be less susceptible to fatigue due because of the mechanical advantage due to the rigid structure of the legs in that direction.

Our changes in COP velocity and TtC characteristics following the walk were modest with respect to the changes in power. It is possible that power was not the

limiting factor in determining changes in these variables. While knee extensor strength has been correlated with postural sway in older adults (137), Menz showed that tactile sensitivity was more predictive of sway than baseline strength (147). Thus, while strength may play a dominant role some tasks, it may play a secondary role in postural control during quiet stance in healthy, older adults. Impaired recovery of power may have a greater effect under more challenging balance conditions, such as with the eyes closed or during reaching tasks, as well as during dynamic balance tests, such as walking. Further research is needed to investigate mechanisms of and the relationships between this power impairment and dynamic balance tests.

We observed a relationship such that greater deficit of power at $270°\cdot s^{-1}$ was associated with slower chair-rise times. Hortobagyi et al (97) showed that a group of older adults used 80% of their leg strength to get up from a chair. Thus, if fatigue in these individuals was greater than 20%, they would not have been able to complete the chair rise without an altered strategy. While our $270°\cdot s^{-1}$ condition is faster than the $138°\cdot s^{-1}$ observed by Hortobagyi et al (97) during the chair rise task in older adults, we did not find a change in mean chair rise time, even though there was an average decline in power of 23%. This may be due to the multiple redundancies inherent in the ability to do tasks (130). In response to fatigue induced by walking, an altered strategy may have been used by our participants in order to minimize decrements in function. Further studies should investigate changes in the way the task is performed in response to fatiguing exercise. It is also possible that our participants had a sufficient functional reserve. If this is the case, then in agreement with the non-linear nature of the functional reserve described by Buchner et al (28), large changes in power (i.e. due to fatigue) could

result in only small changes in physical function. Those individuals with greater slowing of chair rise time may have been closer to their functional reserve. Because we have shown that fatigue is greater following a second fatigue bout performed one hour after the first (Foulis Chapter 4), accumulation of walking bouts over the course of the day may have a greater impact on function over the course of the day.

Several investigators have reported improvements in physical function in response to traditional resistance (35) and high-velocity (94) training to increase muscle power. These interventions might also improve physical function following walking by increasing their functional reserve. However, if these individuals still fatigue beyond their function reserve threshold, it is unclear whether these interventions confer an additional benefit by expediting the recovery of power following fatigue. It is possible that novel interventions may need to be developed to improve recovery of velocity and power.

Limitations

This study did not include a control group of young adults, so we cannot ascertain the extent to which our results are specific to aging. However, given the functional importance of our findings in older adults, we consider this limitation to be minor relative to the importance of the knowledge gained. We did not include measures of perceived effort, or any mechanistic measures of the causes of fatigue, which limits the interpretability of our results to some extent. However, this design decision was made in order to avoid distracting or overloading our participants during the functional tasks, as such distractions could have affected our measures. Given the similar amount of fatigue observed in this and our previous study (Foulis, Chapter 4), we can infer that the

mechanisms contributing to the recovery of power are similar across the two studies. However, future studies that include measures of perceived exertion, neuromuscular activation, and contractile properties in order to evaluate the relationships among symptomatic fatigue, muscle fatigue, and physical function in response to a walking task would be valuable.

By design, all of the participants in this study were healthy and no significant impairment in mobility function, as indicated by their high SPPB scores. None of these women had a history of falls. The effect of 30 min of walking may be greater in individuals with existing mobility impairments. It also is important to note that the first measure following the fatigue test occurred 2 minutes after the participants finished walking. During that time, it is likely that there was some recovery of strength and function that our measures did not capture. In general, torque and power recover rapidly in the first 2 minutes following fatiguing exercise (Foulis Chapter 4, (128, 165)); this recover could translate into recovery of functional measures, as well. Thus, we may have underestimated the effects of the walking task on fatigue and function in this group. During the first few minutes off the treadmill, relationships between power and balance could be confounded by motion after effects (88). By including a 2-min delay and the over-ground walk before the first recovery measure, we suggest that our results are more indicative of the results related to fatigue as opposed to transient impact of this illusory effect.

For technical reasons, power was only measured in the knee extensors. We used the response in the knee extensors to represent all of the muscles responsible for chair rise and balance. Indeed, at baseline, knee extensor power is strongly linked to a number

of functional tasks, particularly in older adults with muscle weakness (50). However, a number of studies have suggested that the ankle dorsi- and plantarflexors may play a more prominent role in maintaining balance during quiet stance (210) under unfatigued conditions, and it may be strength changes in those muscles that most affect balance (137). The difference in muscle groups may alter some of the relationships among changes in power and function. While the walking task would likely also fatigue the muscles at the ankles, it is possible that the fatigue response in those muscle is different from the knee extensors due to differences in activation during walking (185). It is also possible that these distal muscles have different recovery properties, particularly considering that the tibialis anterior and soleus have a greater proportion of type I fibers than the knee extensors (104).

Finally, we had no measures of sensory function in our participants. Sensory function may play a bigger role in postural control than strength in older adults (147). Future studies should assess changes in visual, vestibular, and somatosensory function with fatigue in order to determine how potential changes in the sensory system may affect balance.

Conclusions

We provide novel evidence that 30 min of moderate treadmill walking is sufficient to induce significant fatigue of the knee extensor muscles of healthy older women, and limit their power production in a velocity-dependent manner for at least an hour. Notably, fatigue of high-velocity power was associated with changes in physical function, both at fatigue and at the end of the recovery period. These results indicate that neuromuscular and physical function may be compromised for some period of time in

healthy older adults following a physical challenge as common as walking. While older adults should not be discouraged from physical activity, the results of this study suggest a critical need to determine the mechanisms and duration of this period of vulnerability. Certainly, any additional challenges to physical function may increase risk of mobility impairments to an unacceptable level in this population. It may be important to raise awareness in older adults about the possible effects of walking or other tiring exercise on physical function, so that they may adapt their behavior in order to prevent problems during this recovery period. Additional research is needed to determine how to prevent these lingering decrements in power in order to minimize the risk of falls and disability in older adults.

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Table 5.1: Group Characteristics

	Mean (SEM)	Range
Anthropometrics		
Age (years)	70.7 (1.2)	66 - 81
Height (m)	1.62 (0.02)	1.49 - 1.71
Mass (kg)	67.4 (3.0)	52.2 - 98.2
BMI ($kg \cdot m^{-2}$)	25.8 (1.3)	17.5 - 36.3
Physical Activity		
Activity ($counts \cdot day^{-1} \cdot 1000^{-1}$)	193 (21)	81 - 390
MVPA ($min \cdot day^{-1}$)	18.0 (4.0)	0.9 - 58.7
Symptomatic Fatigue		
PROMIS (t-score)	43.7 (1.78)	29.4 - 63.4
Functional Characteristics		
400m speed ($m \cdot s^{-1}$)	1.37 (0.05)	1.01 - 1.68
Foot Taps ($\#\cdot 10s^{-1}$)	48 (10)	33 - 66
Chair rise, 5x (s)	8.91 (0.78)	4.34 - 16.12
Knee extensor MVIC (Nm)	115.2 (5.52)	80.9 - 149.3
V_{75} ($^{\circ} \cdot s^{-1}$)	54.7 (4.7)	22.4 - 95.1

BMI: Body Mass Index; MVPA: Moderate-Vigorous Physical Activity; PROMIS: Patient Reported Outcomes Measurement Information System (34); MVIC: Maximum Voluntary Isometric Contraction; V_{75}: Velocity at which 75% of MVIC torque was generated.

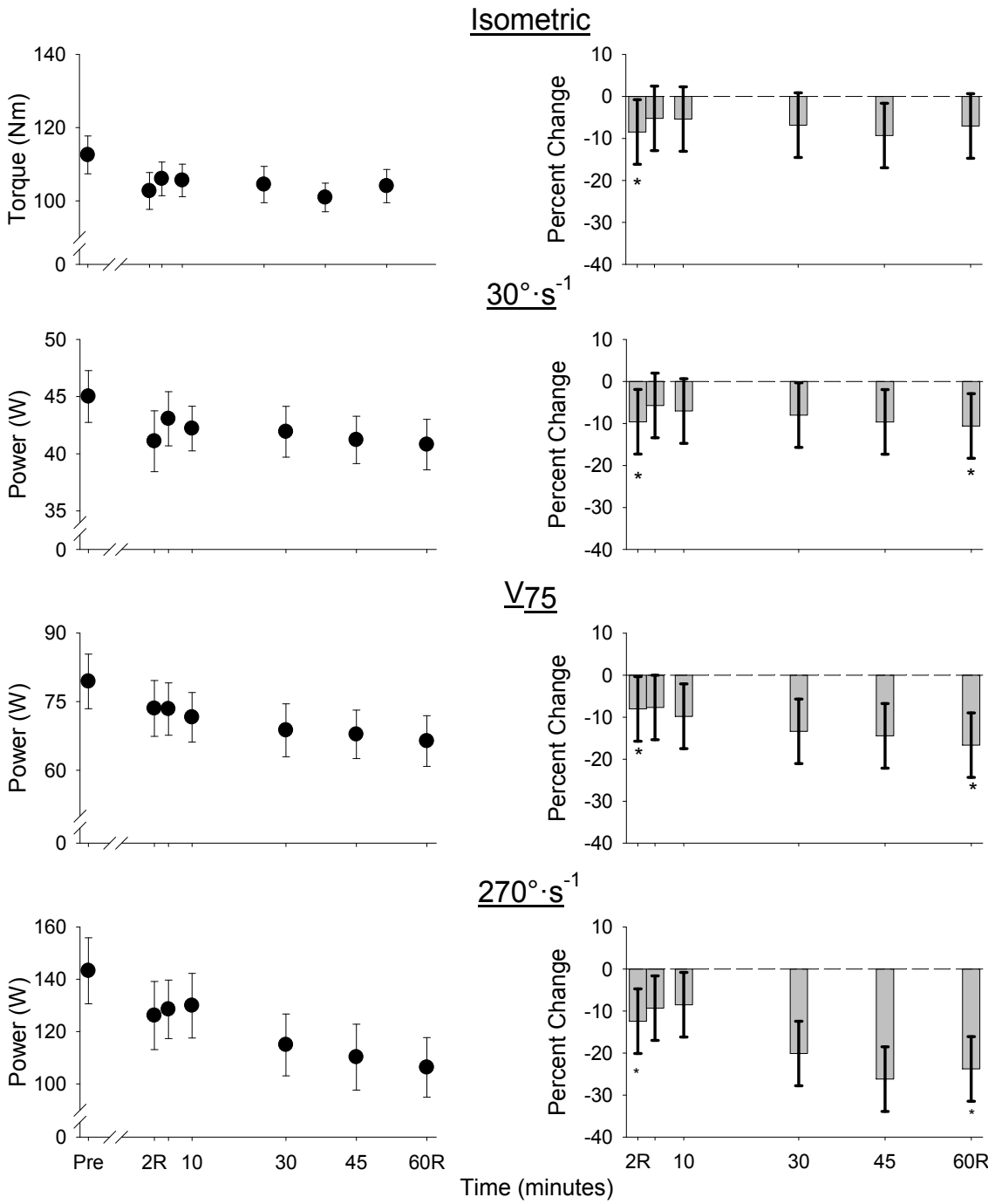


Figure 5.1: Absolute (*left*) and Relative Recovery (*right*) of Torque and Power for the 4 Contraction Velocities. Isometric torque and power at all velocities decreased from baseline following the walk ($p \leq 0.03$, all). Following 60 minutes of recovery, there was differential recovery across velocities such that isometric torque recovered, while dynamic power remained depressed. *Left*: mean ± SEM; *right*: mean and 95% CI for difference from baseline; *$p<0.05$ for difference from baseline. V_{75}: Velocity at which 75% of MVIC torque was generated.

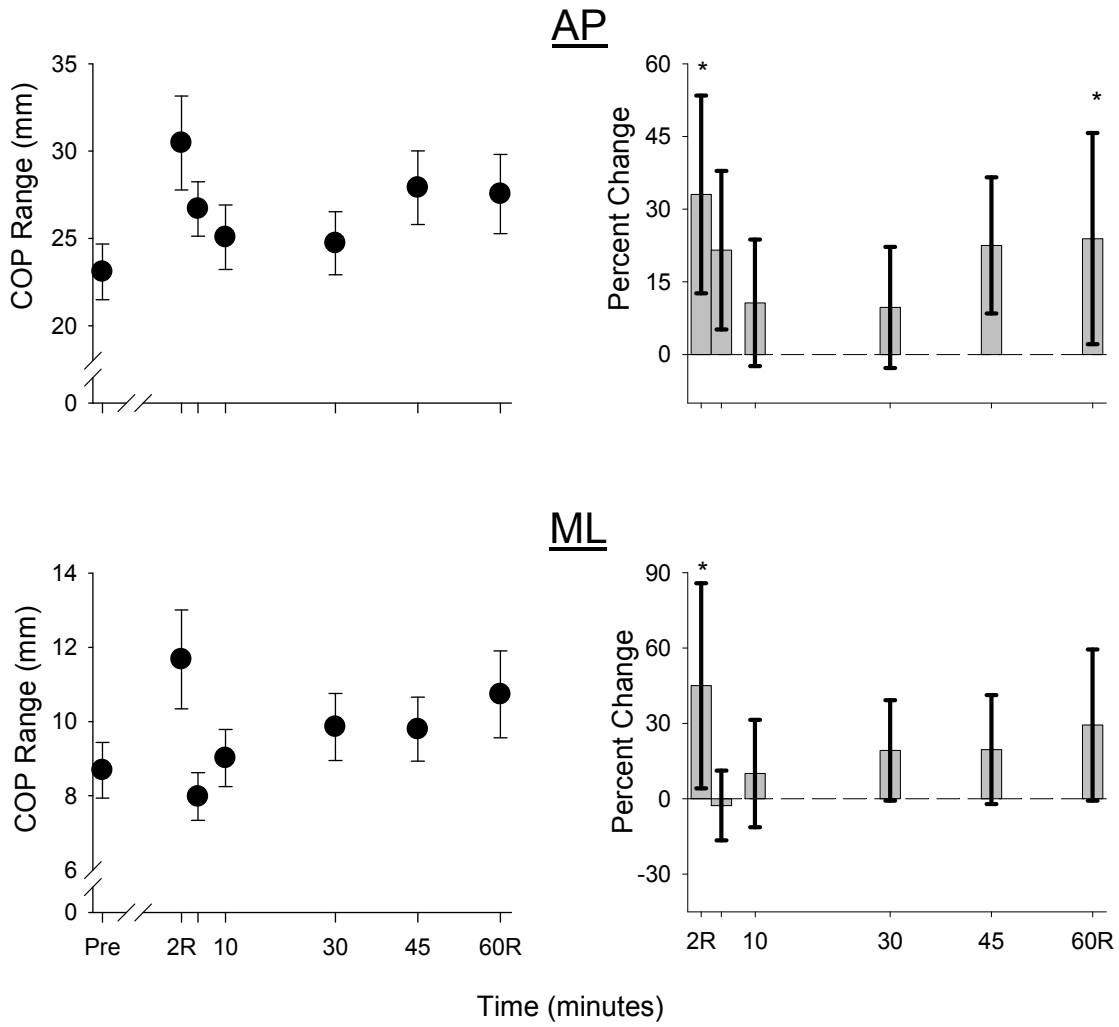


Figure 5.2: Absolute (*left*) and Relative (*right*) Recovery of Center of Pressure (COP) Range in the AP (*top*) and ML (*bottom*) Directions. AP and ML ranges were elevated 2 min after the walking exercise ($p \leq 0.03$). While AP range remained elevated after 60 min of recovery ($p=0.03$), ML range only tended to be elevated ($p=0.06$). *Left*: mean ± SEM; *right*: mean and 95% CI for difference from baseline; *$p<0.05$ for difference from baseline. AP: anterior-posterior; ML: medial-lateral.

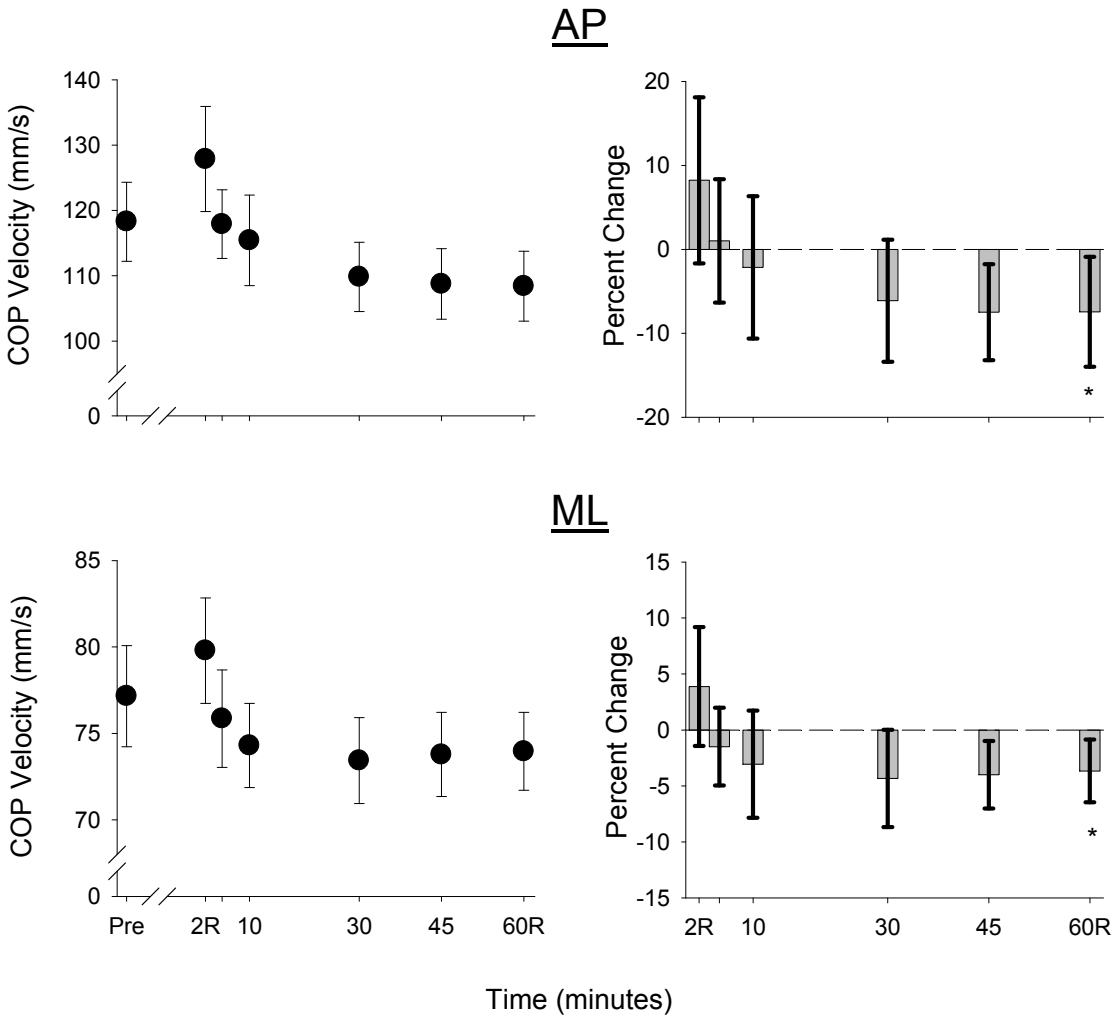


Figure 5.3: Absolute (*left*) and Relative (*right*) Recovery of Average Center of Pressure (COP) Velocity in the AP (*top*) and ML (*bottom*) Directions. Average AP velocity tended to be elevated in the AP ($p=0.08$) but was not different from baseline at 2R. In both directions, velocity decreased with time and was slower than baseline following 60 min of recovery ($p \leq 0.01$). *Left*: mean ± SEM; *right*: mean and 95% CI for difference from baseline; *$p<0.05$ for difference from baseline. AP: anterior-posterior; ML: medial-lateral. Increase in COP velocity is indicative of greater instability.

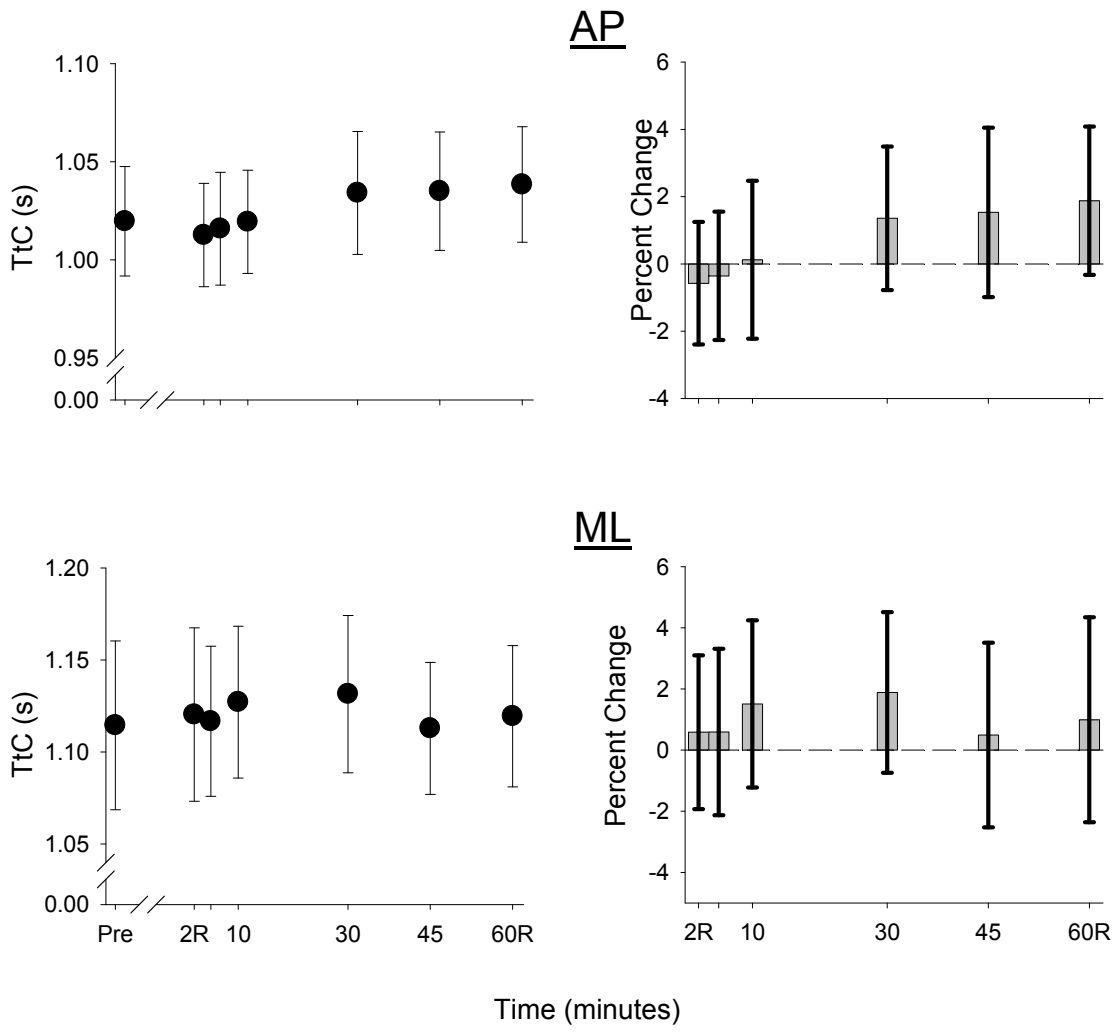


Figure 5.4: Absolute (*left*) and Relative (*right*) Recovery of Average Time-to-Contact (TtC) in the AP (*top*) and ML (*bottom*) Directions. Average AP TtC did not increase immediately following fatigue but tended become longer by 60 min post-exercise (p=0.09). There was no change in ML at either 2R or 60R. *Left*: Mean ± SEM; *Right*: Mean and 95% CI for difference from baseline. AP: anterior-posterior; ML: medial-lateral. Increased tC is indicative of greater stability.

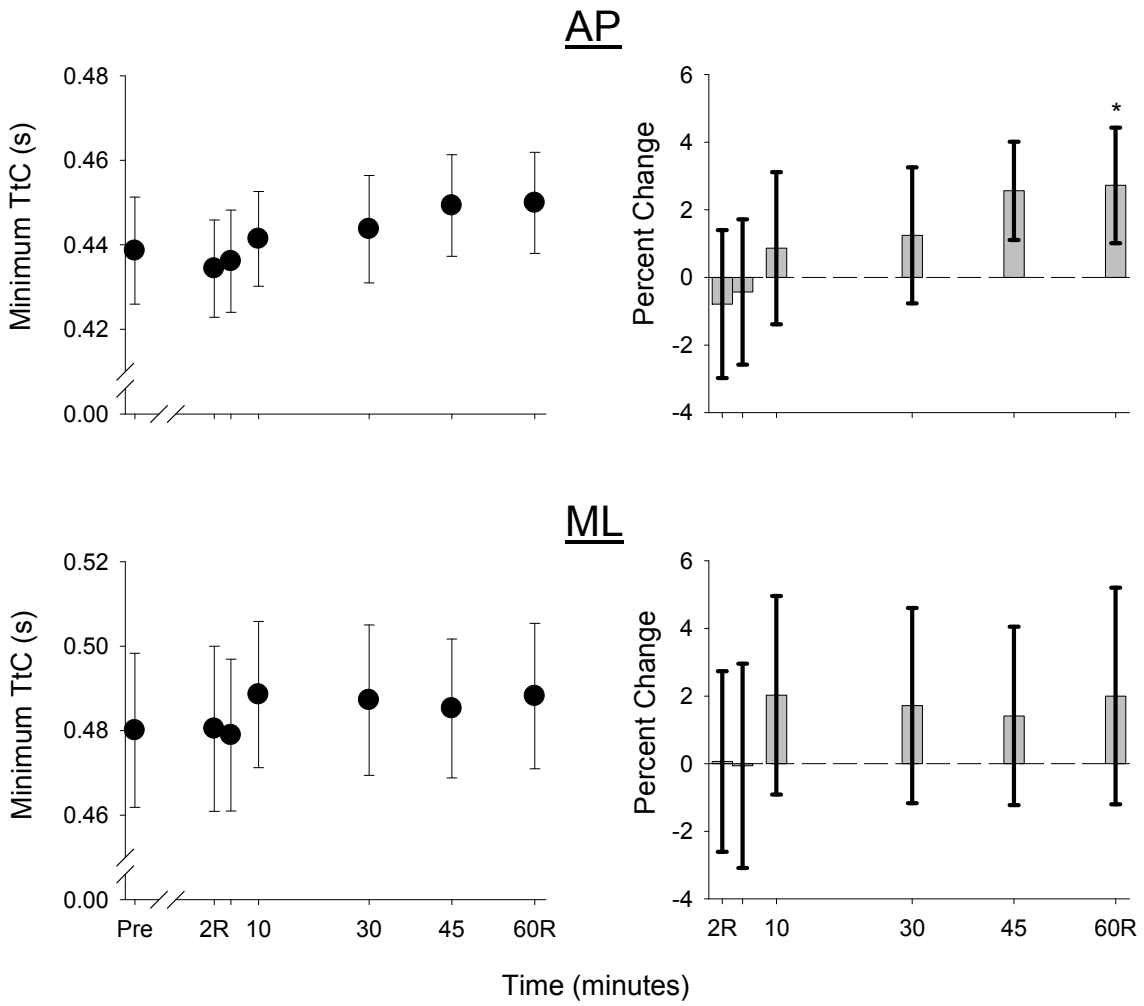


Figure 5.5: Absolute (*left*) and Relative (*right*) Recovery of Minimum Time-to-Contact (TtC) in the AP (*top*) and ML (*bottom*) Directions. AP minimum TtC at 2 min recovery did not differ from baseline ($p=0.40$), but increased throughout recovery to become longer by 60 min post ($p<0.01$). In the ML, minimum TtC was not different from baseline at either 2R or 60R ($p\geq0.20$). *Left*: mean ± SEM; *right*: mean and 95% CI for difference from baseline; *$p<0.05$ for difference from baseline. AP: anterior-posterior; ML: medial-lateral. Increased TtC is indicative of greater stability.

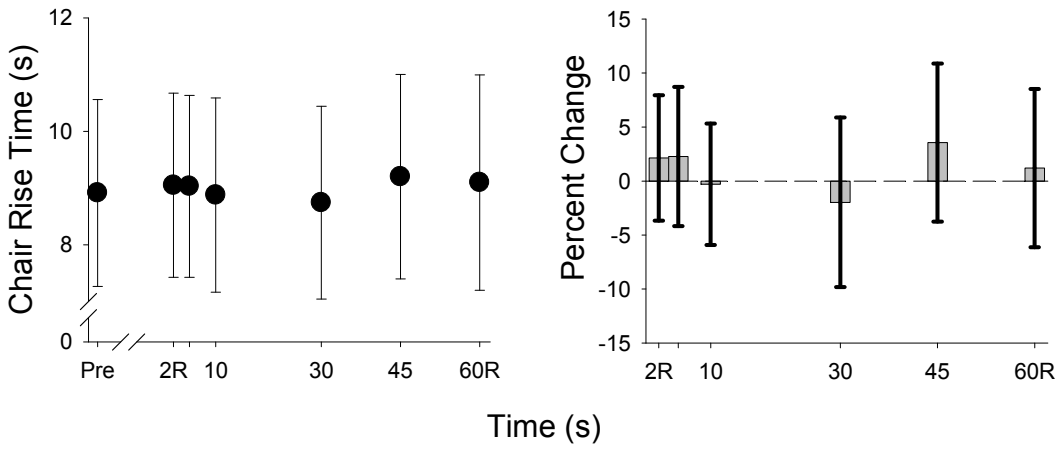


Figure 5.6: Absolute (*left*) and Relative (*right*) Recovery of Chair Rise Time. There was no difference from baseline at 2R or 60R ($p \geq 0.45$). *Left*: mean ± SEM; *right*: mean and 95% CI for difference from baseline.

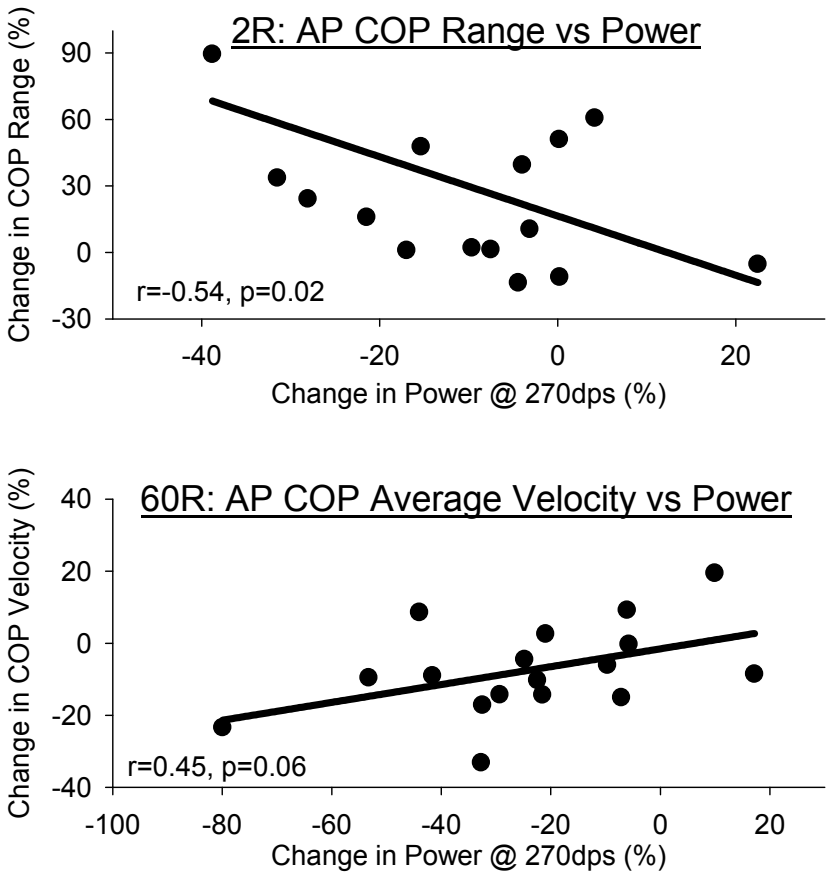


Figure 5.7: Associations Between High-Velocity Power and Balance. The change in high-velocity ($270°\cdot s^{-1}$) power at fatigue was negatively associated with the change in AP COP range (*top*), indicating that fatigue was associated with instability. At 60R, the power deficit at $270°\cdot s^{-1}$ was positively correlated with COP Velocity (bottom), suggesting that greater residual weakness was associated with increased stability.

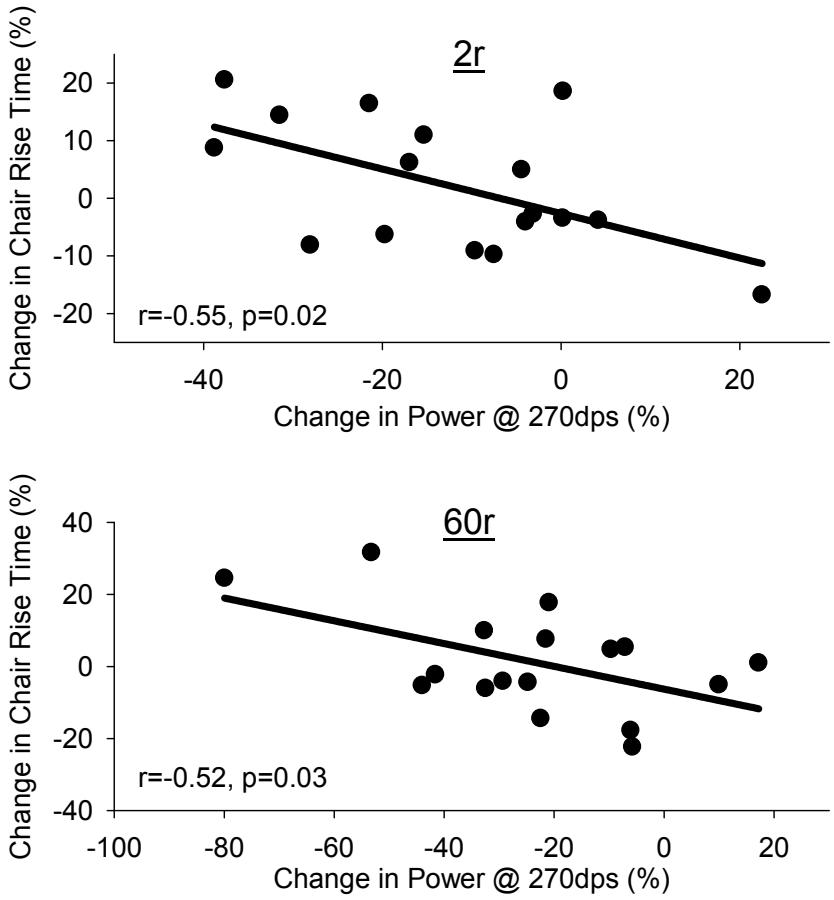


Figure 5.8: Associations Between High-Velocity Power and Chair Rise Time. Correlations of the percent changes of power at $270°\cdot s^{-1}$ and chair rise at 2R (middle) and 60R (bottom) showed a significant relationship such that individuals with a greater decrease in power had a greater slowing of chair rise time.

CHAPTER 6

SUMMARY

The goals of this dissertation were to identify how muscles recover following a bout of fatiguing exercise, determine how this recovery differs in young and older adults, and assess the role of the recovery of force and power in mediating the recovery of physical function. The two studies of this dissertation determined the pattern of recovery of muscle power following two distinct bouts of muscle fatigue. While it has been established that there are velocity-dependent differences in the pattern of fatigue in young and older adults, prior studies had neither investigated recovery of power across a range of velocities, nor the effects of aging on this recovery. Study 1 monitored recovery of power following fatigue induced by maximal knee extensions using a dynamometer. This study also provided details on the possible mechanisms governing recovery during the 60 minutes that follow muscle fatigue. Prior studies have shown that age-related weakness and muscle fatigue can each affect physical function, but no study has attempted to follow both of these factors throughout recovery in older adults. Study 2 examined the relationships among the recovery of power and physical function using a more ecological walking task that caused a similar degree of knee extensor fatigue as the dynamometer-based protocol used in Study 1. Together, these studies provide novel insight about the impact of muscle fatigue on older adults.

A summary of the changes with fatigue and recovery observed during Study 1 are shown in Table 6.1. We observed similar decrements and recovery of power at low velocities in both age groups. However, in support of our hypothesis, recovery was slower (H1.1) and power loss at high-velocities was greater (H1.2) in the older compared

with young women. Thus, we demonstrated an age-related difference in the recovery of power that is velocity dependent. In terms of the mechanisms governing this recovery, the 10:80 Hz ratio declined and did not recover in both groups, indicating the presence of excitation-contraction coupling failure. Contrary to our hypothesis (H1.3), we did not observe similar EC coupling failure in young and old: the ratio tended to decline to a greater extent in the older. This result is consistent with data showing impairments in calcium handling with aging (62, 180). We were correct in hypothesizing a slowing of contractile properties post-fatigue (RFR, and $T_{1/2}$, H1.4); however, there was no difference across age groups. These changes recovered relatively quickly, indicating they were not the primary limiters in power production during the recovery period. Under isometric conditions, we detected an increase in pre-motor time with fatigue that was not different across age-groups (adapted from H1.5). Concurrently, we observed an increase in pre-motor EMG and the voluntary:stimulated rate of force development ratio only in the older women (H1.6). This increase in central drive may reflect a need to increase torque production in compensation for other neuromuscular alterations (such as EC coupling failure) that depress torque with fatigue in this population. Both pre-motor measures recovered to baseline by 60 minutes. This finding was contrary to our hypotheses of reduced and slower neural input to the muscle with fatigue.

None of our exploratory hypotheses for Study 1 were supported. At 20% MVIC we observed no change in the EMG:torque ratio with fatigue (Exploratory H1.1). At 50% MVIC we observed a greater ratio (i.e. reduced efficiency) in only the young group following the fatigue bout, suggesting age-related differences in the neural mechanisms of modulating intermediate levels of torque production following fatigue. In both groups,

this ratio increased during maximal contractions, but to a similar extent. In addition, we observed a transient increase in perceived effort during contractions of 20% and 50% MVIC following the fatigue bout, but these were similar in both groups and recovered within 60 minutes (Exploratory H1.2). In the older group, we observed an increase in perceived effort during maximal contractions that lasted for the full hour. This increase in perceived effort, along with the greater fatigue observed during a second fatiguing exercise bout (Exploratory H1.3), may explain the greater symptomatic fatigue that has been reported previously in older adults (1).

Thus, for Study 1, we observed a greater deficit in older adults in high-velocity power immediately following the kicking exercise, as well as following the 60 minutes of recovery. While it would appear impairments in excitation-contraction coupling may be a mechanism based on our results, we also observed age related changes in the EMG:Torque ratio and pre-motor signaling during isometric contractions. It is likely that some of these neural alterations may also contribute to the long-duration deficit in power. It also possible that some of the variables that showed age-related deficits at baseline, and decreased similarly in young and older following the fatigue bout played a role in the differential deficits between the two groups. Thus changes in contractile properties or time-to-target (i.e. muscle acceleration) may have contributed to the loss in power if the older fell below some critical threshold.

The second study provided evidence of a power decline following 30 minutes of moderately intense walking that was associated with changes in physical function in older women. A summary of the power and functional alterations with fatigue and recovery are found in Table 6.2. The first two hypotheses for this study were supported; decreased

torque and power were observed following the walk (H2.1). Although isometric torque recovered, high-velocity power did not (H2.2), demonstrating again a velocity-dependence on the recovery process. The results from the hypotheses regarding physical function were equivocal. As a group, there was no significant decline in chair rise time following the fatigue bout (H2.3). Notably, however, individual changes in chair rise time were associated with changes in power (H2.4). This relationship was true both 2 and 60 minutes following the fatigue bout, demonstrating the important role of power in maintaining physical function. We also observed increases in COP range and velocity following the walk, indicating increased instability (H2.3). Following 60 minutes of recovery, COP range remained elevated, but COP velocity was reduced and AP TtC was increased, indicating increased stability. While the changes in the AP direction were associated with fatigue of high-velocity power (H2.4), it may be that other processes, such as muscle stiffness, also played a role in the recovery process, as this may decrease power but improve measures of balance.

In summary, in Study 2, we again observed a decrement in muscle power at high-velocities following the treadmill walk that lasted throughout the 60 minutes of recovery. Functionally, changes in high-velocity power were associated with impairments in chair rise and balance. After 60 minutes of recovery, increased musculoskeletal stiffness may improve static balance and while still limiting power production. However, this prolonged power loss may be a hindrance during more challenging, dynamic postural tasks.

Significance

This dissertation addressed the nature of recovery of muscle power following fatigue in young and older women, as well as the potential implications of altered power recovery on physical function in older women. A novel finding of this dissertation was the prolonged impairment of high-velocity power following muscle fatigue in older women. Notably, this slow recovery of power decrement was not present in younger adults, and it occurred both under controlled settings using a dynamometer and in response to treadmill walking designed to mimic real-world activity. Thus, this pair of studies provides "bench-to-bedside" translation of research relevant to the prevention of falls, and ultimately disability, in older adults. Older adults should be aware of this delayed power recovery as it could affect their ability to maintain balance following exercise. While older adults should not be discouraged from physical activity, some behavioral modification might be advised to prevent falls during this recovery period. Modifications could include avoiding unstable positions and increasing active concentration on balance.

The combination of these studies has captured both the mechanisms and implications of recovery from muscle fatigue. Many researchers have studied power loss (32, 105, 128, 166), neuromuscular recovery (7, 150, 167), and functional implications of fatigue (91, 134, 154), but not all three. This dissertation quantified both the changes that occur due to fatigue, and how these changes recover over the course of an hour following two distinct types of exercise. Further, we assessed how recovery is different in older women compared with young women. Specifically, we observed age-related alterations in recovery of pre-motor neural signaling, excitation-contraction coupling, and

neuromuscular efficiency following knee extension contractions which resulted in ~25% drop in muscle power. Functionally, these changes led to increased perceived effort, increased fatigue during a second exercise bout (in both young and old), slowed chair rise times, and impairments in balance in older women. Thus, we have identified key mechanisms for age-related changes in recovery of muscle power, as well as potential functional implications of those alterations. While this list of mechanisms and functional alterations is not complete, it provides an important starting point for identifying changes in the recovery process with aging. The results of this study may prove valuable in developing interventions to prevent the decline in muscle power, and ultimately preventing physical disability, in older adults.

Future Directions

This dissertation provides an important step in understanding the mechanisms and implications of the recovery of muscle power following fatiguing exercise in both young and older adults. Many of our recovery measures provide only indirect assessments of the function of the neuromuscular system. More direct measures of cortical and spinal excitability (transcranial magnetic stimulation), motor unit discharge rates (indwelling electromyography), coactivation (multiple surface electrodes) and muscle calcium handling (biopsy) function may better able to assess quantify the specific mechanisms of neuromuscular recovery that our results indicate may play a role in the recovery process. A neuromuscular model of fatigue and recovery could also be developed to determine the relative influence of each of these processes on muscle power.

The protocol used in Study 2 evaluated only one type of physical function (chair rise) and one test of balance (eyes open, quiet stance). However, there are a number of

activities of daily living that could be affected to varying degrees by fatigue induced by walking. Impairments in these activities may not have been captured using only these two tests. Given the slow recovery of high-velocity power observed in this study, the impact of incomplete recovery of muscle power should be investigated using more difficult balance tasks. These tests could include quiet stance with the eyes closed, reaching, and recovery from perturbations, all of which have been shown to be reduced in older adults in the absence of fatigue (92). Functional tasks of a dynamic nature and those that require rapid movements may be particularly affected by this prolonged loss of power, which could help to precisely identify key moments when older adults are at high risk of falling.

All of the participants in these studies were relatively healthy, with minimal mobility impairments. It remains to be determined whether there are greater decrements in power in older adults showing the signs of physical impairments. These individuals are at a greater risk of falls, even in the absence of muscle fatigue. We have previously shown that mobility impaired individuals produce less torque and have greater torque variability during a dynamic fatigue protocol (113). Whether this variability is indicative of differences in the mechanisms of fatigue and recovery is not known. It is possible that greater variability and power loss could combine to provide momentary weakness, which could lead to falls. The implications of this variability in power production may be particularly true during the prolonged depression of high-velocity power.

The goal of this dissertation was to better understand the recovery from muscle fatigue, in order to provide data that could ultimately be used to prevent disability in older adults. These data suggest that older adults need to be careful in the hour following

exercise as there may be lingering weakness, which could increase their risk of falls. Behavioral modification should be suggested in order to avoid activities that may put older adults at high risk of falls during this hour. In the long term, developing training protocols to target the specific causes of power loss and slowed recovery in older adults may be possible in order to minimize the risk of functional decline and falls associated with old age. This combination of behavioral and physical interventions could lead to increased quality of life in older adults, prevent a number of detrimental health outcomes related to prolonged bed rest and hospital stays that occur as a result of falls, and ultimately decrease the financial burden of health care on society.

Table 6.1: Study 1 Summary

	Baseline	Fatigue (0R)			Recovery (60R)		
	O v Y	Y ΔBaseline	O ΔBaseline	O v Y	Y ΔBaseline	O ΔBaseline	O v Y
Power and Velocity							
Specific Power	NS	↓0, ↓30, ↓V_{75}, *↓270*	↓0, ↓30, ↓V_{75}, ↓270	↓270	↓0	↓0, ↓270	↓270
Time-to-Target Velocity	↑270	↑V_{75}, ↑270	↑V_{75}, ↑270	NS	NS	NS	NS
Neuromuscular Variables							
Central Motor Drive (Vol:Stim RFD)	NS	NS	↑0	NS	NS	NS	NS
Voluntary RFD	NS	NS	↑0	*↑0*	NS	NS	NS
EMG:Torque	↑20%	↑50%, ↑100%	↑100%	↑50%	NS	NS	NS
Pre-Motor Activation (Pre-Motor EMG)	NS	NS	↑0	*↑0*	↑30	NS	↑30
Pre-Motor Delay (Pre-Motor Time)	↑30, ↑270	↑0	↑0	↓270	*↑0*	*↑0*	NS
Stimulated RFD	↑Yes	NS	NS	NS	↑Yes	↑Yes	NS
Stimulated Torque Relaxation (80Hz RFR & $T_{1/2}$)	↓Yes	↓Yes	↓Yes	NS	NS	NS	NS
EC Coupling (10:80 Hz)	↓Yes	↓Yes	↓Yes	↓*Yes*	↓Yes	↓Yes	↓*Yes*
Functional Variables							
Perceived Exertion	↓*50%,* ↓*100%*	↑20%, ↑50%, ↑*100%*	↑20%, ↑50%, ↑100%	↑*100%*	NS	↑100%	↑100%
Power following 2nd Fatigue Bout compared to 1st		↓0, ↓30, ↓V_{75}, ↓270	↓0, ↓30, ↓V_{75}, ↓*270*	NS			

Values represent where differences ($p \leq 0.05$) were present for young compared with older (Y v O), young compared with baseline (Y ΔBaseline), and older compared with baseline (O ΔBaseline). Italicized values represent trends ($p \leq 0.10$). Shaded boxes indicate data not collected. 0: Isometric; 30: $30°\cdot s^{-1}$; V_{75}: Velocity at which 75% of MVIC was generated; 270: $270°\cdot s^{-1}$; 20%: 20% MVIC; 50%: 50% MVIC; 100%: 100% MVIC; RFD: Rate of Force Development; RFR: Rate of Force Relaxation; $T_{1/2}$: Half-relaxation Time. NS: No significant difference

Table 6.2: Study 2 Summary

	Fatigue (2R) ΔBaseline	**Recovery (60R) ΔBaseline**
Specific Power	↓0, ↓30, ↓V_{75}, ↓270	↓30, ↓V_{75}, ↓270
Functional Changes		
Chair Rise Time	NS	NS
Balance		
COP Range	↑AP, ↑ML	↑AP, ↑*ML*
COP Average Velocity (↑: Greater Instability)	↑*AP*	↓AP, ↓ML
TtC Average (↑: Greater Stability)	NS	↑*AP*
TtC Minimum (↑: Greater Stability)	NS	↑*AP*

Values represent where differences ($p \leq 0.05$) compared with baseline. Italicized values represent trends ($p \leq 0.10$). . 0: Isometric; 30: 30°·s^{-1}; V_{75}: Velocity at which 75% of MVIC was generated; 270: 270°·s^{-1}; AP: Anterior-Posterior; ML: Medial-Lateral; COP: Center of Pressure; TtC: Time-to-Contact. NS: No significant difference

APPENDIX A

INFORMED CONSENT DOCUMENT

INFORMED CONSENT DOCUMENT
University of Massachusetts
Amherst, MA 01003

Project Title: Recovery from Muscle Fatigue in Young and Older Women

Principal Investigators: Jane A. Kent-Braun, Ph.D. (413-545-9477)
Stephen A. Foulis, M.S. (413-545-5305)

Your written informed consent is required prior to participation in this project. Please read this document carefully and then sign your name on the last page if you agree to participate. This document is in accordance with the *Assurance of Compliance with the Office of Human Research Protection Regulations* approved by the Faculty Senate of the University of Massachusetts.

Purpose: The purpose of the study is to learn more about how aging affects recovery from muscle fatigue. In particular, we seek to investigate how the recovery process is different in young and older adults, and how that may affect physical function.

Eligibility: To participate in this study, you must be in good physical health and between the ages of 25 and 40 or 65 and 85 years old.

Definitions: The following terms will be referred to throughout the study. These are the names of the main techniques that we will be using:

Isometric contractions. A contraction of your muscle that produces force, but no movement (i.e., static) is referred to as isometric.
Dynamic contractions. A contraction of your muscle that produces force and movement is referred to as dynamic.
Electrical Stimulation. This technique uses self-adhesive, rubber pads applied to the skin of your leg. These electrode pads are used to stimulate your muscle to contract.
Fatigue. This term refers to the drop in strength that normally occurs in response to repeated strenuous muscle contractions.
Physical Function. This term refers to the ability to do everyday activities such as standing up from a chair, or balancing while standing still.
Muscle Activation. Comparisons will be made between the force you can generate with your leg, and that produced by electrical stimulation. This comparison will give information regarding your nervous system's ability to fully activate the muscles of your leg.
EMG- *electromyography*. This technique uses small metal discs that are taped to your leg. These discs record the electrical signal of your muscle during exercise.
MRI- Magnetic Resonance Imaging. This technique uses radio waves and a large magnet to receive information about the size and shape of your muscles.

Procedures:

Pre-Screening - Prior to all studies, you will be screened by telephone interview for general health, medical history, current medications, usual physical activity level, and eligibility for the study. If you are qualified and agree to participate, you will be invited to the Muscle Physiology Laboratory at the University of Massachusetts, Amherst, for further study.

Visit 1 - Screening (Muscle Physiology Lab, UMass) - You will be asked to complete a detailed medical history form, a Physical Activity Readiness Questionnaire, a safety checklist, and fatigue questionnaires. We will measure your height and weight, and the blood pressure in your arm. We will then ask you to perform several tests of physical function:

- Balance: You will be asked to balance with your feet in various placements.
- Walking speed: You will be asked to walk along a 6 meter path.
- Chair Rise: You will be asked to stand up from a seated position and return to the seated position 5 times.

If you are over the age of 65, we will, with your permission, obtain approval from your personal physician before proceeding with any further testing. This visit will take ~1 hour.

Visit 2 – Familiarization, 400 Meter Walk, Activity Monitoring (Muscle Physiology Lab, UMass) – After a brief warmup on an exercise bike, you will undergo tests of your muscle strength and ability to contract your muscles forcefully. You will sit in a comfortable chair and your leg will be fitted to an apparatus that will measure muscle strength. You will be strapped snugly to the chair to reduce extra movement. Three electrodes (EMG) will be placed on your thigh to record the voluntary and stimulated electrical activity of your muscles during this visit. In addition, two self-adhesive electrode pads will be applied to your leg to allow for electrical stimulation to be used to contract the muscles of your thigh. You will perform a series of voluntary contractions of your knee extensor muscles at a range of speeds and will also undergo electrical stimulation to determine some of the properties of your muscle. The electrical stimulation will last for less than one second. It will be uncomfortable, but not dangerous. You will also be introduced to the fatigue protocol described below.

You will then be asked to walk 400 meters, about length of 4 city blocks, at the quickest pace that you can maintain for the entire walk. We will monitor your heart rate and rate of perceived exertion during the walk. If you experience any symptoms (i.e., chest pain, shortness of breath, extreme fatigue, dizziness, etc.) during these procedures, notify the investigator immediately.

Once the walk is complete, you will receive a physical activity monitor (a small portable device that records your motion). You will be asked to wear this monitor around your waist during waking hours for 10 days. In addition, you will be asked to keep a simple diary of your physical activities during those 10 days. You will return the activity monitor and diary at a future visit.

This entire visit will take ~2 hours.

For the remaining visits you will be asked to complete one of two fatigue and recovery protocols:

- ❑ **Protocol A** _____

  (subject initials here)

  Visit 3A – Fatigue & Muscle Recovery (Muscle Physiology Lab, UMass) - After the brief warmup on an exercise bike, you will be seated in the same exercise

chair as Visit 2. Following some resting strength measures, you will complete a 4-minute dynamic muscle contraction protocol designed to fatigue your muscle. At intervals over the hour following the protocol, you will perform voluntary dynamic contractions and undergo stimulated muscle contractions to monitor the recovery of your muscle. At the end of one hour, you will repeat the same fatiguing protocol, and be observed for an additional 10 minutes of recovery. This visit will take ~2 hours.

Visit 4A – Fatigue & Neural Recovery (Muscle Physiology Lab, UMass) - You will again be seated in the same chair as Visit 3A and complete the same resting strength measures and then perform the 4-minute fatigue protocol. During the hour following the protocol, you will perform isometric (static) contractions at 3 different force levels. This visit will take ~2 hours.

Visit 5A – MRI (Amherst Community Health Center, University Drive, Amherst) - While lying still in a large magnet, images of your leg will be taken. During this procedure, you will hear loud banging noises. For this reason you will be given earplugs or a headset to wear. This visit will take ~45 minutes

❑ **Protocol B** _____

(subject initials here)

Visit 3B – Fatigue & Muscle Recovery (Muscle Physiology Lab, UMass) - After a brief warmup on an exercise bike, you will be seated in the same exercise chair as Visit 2. Following some resting strength measures, you will be moved to a treadmill where you will walk for up to 30 minutes. While on the treadmill, the investigator will be at your side to assist as needed. At the end of the walk, you will be re-seated on the exercise chair. At intervals over the hour following the protocol, you will perform voluntary dynamic contractions to monitor the recovery of your strength. This visit will take ~2 hours.

Visit 4B – Fatigue & Functional Recovery (Muscle Physiology Lab and Motor Control Lab, UMass) – After a brief warmup and resting strength measures as done in Visit 3B, you will perform resting measures of 2 measures of physical function:

- *Standing Balance:* You will stand still on a force platform which is capable of detecting small changes in your balance.
- *Chair Rise:* You will be asked to rise and sit down in a chair 10 times, as fast as you can.

You will be moved to a treadmill and complete the same walking task from Visit 3B. At the end of the walk, and at intervals over the hour following the walk, you repeat the 3 measures of physical function. This visit will take ~2 hours.

Study Timeline: All testing will be completed within 3 weeks.

Testing Day	Procedure	Approximate Duration
1	Screening	1 hour
2	Familiarization, 400 Meter Walk, Activity Monitoring	2 hours
3	Fatigue & Recovery Test 1	2 hours
4	Fatigue & Recovery Test 2	2 hours
5* (Protocol A only)	MRI *(Amherst Community Health Center)*	45 minutes

Possible Risks and Discomforts: The following risks and discomforts may be associated with the procedures described above.

- *Physical Function Testing* – During any type of exercise, especially strenuous exercise, there are slight health risks, along with the possibility of fatigue, cardiovascular events, muscle soreness, and falls. These risks are minimal during the type of self-paced testing used here, particularly in healthy individuals. Study personnel will be monitoring you closely for your safety and guarding to prevent falls.

- *Muscle Contractions and Fatigue Protocol* – You may experience slight muscle soreness during and/or after this portion of the testing; the soreness will not interfere with your daily activity, and will subside within 2-3 days. You will feel a strong buzzing during the electrical stimulation. The discomfort with electrical stimulation is of a moderate degree. We expect that your muscle will fatigue during the fatigue testing. During the walking protocol, there are slight risks of cardiovascular events and falls. These risks are small in individuals with no prior history of cardiovascular, respiratory, or musculoskeletal disease or injury. To minimize the risk of any adverse events, you will be given a warmup period, and your heart rate will be monitored during the fatigue task. You are also encouraged to report any abnormal discomfort. If the researchers see anything abnormal, or you ask us to stop, the session will be stopped immediately.

- *Magnetic Resonance Imaging (MRI)* – The United States Food and Drug Administration (FDA) has set guidelines for magnet strength and exposure to radio waves, and we carefully observe those guidelines. There are no known negative effects at the amount of exposure you will see during this study. Some people may feel uncomfortable or anxious during the MRI. If this happens to you, you may ask to stop the study at any time and we will take you out of the MR scanner. On rare occasions, some people might feel dizzy, get an upset stomach, have a metallic taste or feel tingling sensations or muscle twitches. These sensations usually go away quickly but please tell the research staff if you have them.

  MRI poses some risks for certain people. If you have a pacemaker or some metal objects inside your body, you may not be in this study because the strong magnets in the MR scanner might harm you. Another risk is a metallic object flying through the air toward the magnet and hitting you. To reduce this risk we require that all people involved with the study remove all metal from their clothing and all metal objects from their pockets. Nothing metal can be brought into the magnet room at any time. Also, once you are in the magnet, the door to the room will be closed so that no one from outside accidentally goes near the magnet.

  We want you to read the questions on the MR Safety Questionnaire and answer them very carefully. Those questions are for your safety. Take a moment now to be sure that you have read the MR safety sheet and be sure to tell us any information you think might is important. Even if you think that it is probably okay, we would rather have you ask us to make sure.

  Please note: The MRI is for research purposes only and is not in any way a clinical scan to diagnose diseases for you. The scans in this study are not designed for diagnosis. If we see something on your scan that might be medically significant, we will ask a radiologist or another physician to review the

relevant images. If that person recommends that you should seek medical advice, then the primary investigator, or consulting physician, will contact you, talk with you about the situation, and recommend that you seek medical advice as a precautionary measure. At that point, the decision to seek advice or treatment is completely up to you and your doctor. The researchers for this project, the consulting physician, or the Amherst Community Health Center are not responsible for any exam or treatment that you receive based on these findings.

Confidentiality: Your records will be kept as confidential as is possible under the law. No individual identities will be used in any reports or publications resulting from this study.

In Case of Injury: In the unlikely event of an injury resulting directly from participation in this study, we will do everything we can to assist you in seeking medical treatment. The University of Massachusetts does not have a program for compensating subjects for injury or complications related to human subjects research.

Benefits: You will receive no direct benefit from participating in this study. You may receive more precise information about your muscle function and a clearer idea about how it may be influenced by age. Any information that is obtained from this study will be made available to your physician upon request. The purpose of these studies is to provide the investigators with information which may have a positive impact on the management of muscle fatigue in aging.

Costs and Reimbursement: No costs will be charged to you if you participate in this study. You will receive $50 for completion of the entire study. In the event that you do not complete the study, you will be compensated $10 for each visit you complete. A check will be mailed to your home in about six weeks.

Withdrawal of Participation: Participation in this research is voluntary. You have the right to refuse or to withdraw at any point in this study without prejudice. You will be compensated for the portions of the study that you have completed as described above.

Information: You are encouraged to ask questions about the study. The investigators will attempt to answer all of your questions to the best of their knowledge. The investigators fully intend to conduct the study with your best interest, safety, and comfort in mind. Please address any questions regarding the study to Stephen Foulis, M.S. at (413) 545-5305 or Jane Kent-Braun, Ph.D. at (413) 545-9477. If you would like to discuss your rights as a participant in a research study or wish to speak with someone not directly involved in the study, you may contact the Human Subjects Administrator at humansubjects@ora.umass.edu (413) 545-3428.

_____

Participant's Name Address

_____

Signature Phone Number

_____

Witness Date

The investigator has read and understands the regulations for the Protection of Human Research Subjects (45 CFR 46) and agrees to comply with all the clauses of the said document to the best of her ability. The investigator also pledges to consider the best interests of the subject beyond the explicit statement contained in the aforementioned regulations and to exercise professional expertise to protect the rights and welfare of the subject.

_____

Jane Kent-Braun, Ph.D. Date
or
Stephen A. Foulis, MS

Principal Investigators
Department of Kinesiology

APPENDIX B

TELEPHONE SCREENING FORM

Date: _____ Screened by: _____ Group: _____ Status: _____

TELEPHONE SCREENING

1) Explain: all visits: paperwork/SPPB, Habituation (stim.); Fatigue, Time commitment

Contact Info:
Name _____
Phone # _____
Email _____
Address _____

Descriptive Info:
Sex _____ Age_____ DOB_____
Height_____ Weight _____
BMI_____

Qualifying Questions:

1) How would you describe your current health status in general?
   _____

2) Do you have any physical limitations that keep you from doing usual activities of daily living?
   _____

3) Has your doctor ever told you not to exercise? Y ____ N ____ If so, why?
   _____

4) How often, if at all, do you exercise? And what do you do?

Type:	Frequency:	Duration/Intensity:	Since when?

5) Do you smoke/have you ever been a smoker? Y___N___ How long ago? (must be 2 yrs ago)_____

6) Have you ever had an MRI? Y___N___ Are you able to receive an MRI? Y___N___ (metal fragments, implants, claustrophobia)?
   _____

7) Do you have any problems with your lower legs, feet, ankles, or knees?
   _____

   VL leg ____R____L____

8) Does your medical history include any of the following?

Surgeries:	Diabetes?	Neurological/ Neuromuscular?	Pulmonary?	Coronary?	Joint Problems?

If yes, explain:
_____

8) Current Medications:

Drug Name	Classification	Dosage	Frequency	Duration	Prescribed for?

9) Is fatigue a problem for you?_____ Leg fatigue?_____

10) Doctor's Info:

Name:	Office:	Last Visit:

Recruiting Purposes:

1) How did you hear about the study? _____

2) Have you ever participated in a research study before? Y ____ N ____

3) Would you be willing to participate in the future? Y____ N ____

Next step:

1) If we call you back and miss you, is it OK to leave a message? (privacy) Y____N____

2) Do you have any questions or concerns about what we'll be doing/asking you to do throughout this process?

_____

Follow up, if approved:

1) Need transportation? Y___N___ If yes: from where? _____ If no: Parking Pass _____

2) Scheduling:

First Visit Date/Time _____

APPENDIX C

PHYSICAL ACTIVITY READINESS QUESTIONNAIRE

1. Has a doctor ever said you have a heart condition and recommended only medically supervised activity?

   YES_____ NO_____

2. Do you have chest pain brought on by physical activity?

   YES_____ NO_____

3. Have you developed chest pain in the last month?

   YES_____ NO_____

4. Do you tend to lose consciousness or fall over as a result of dizziness?

   YES_____ NO_____

5. Do you have a bone or joint that could be aggravated by the proposed physical activity?

   YES_____ NO_____

6. Has a doctor ever recommended medication for your blood pressure or a heart condition?

   YES_____ NO_____

7. Are you aware through your own experience, or a doctor's advice, of any other physical reason against your exercising without medical supervision?

   YES_____ NO_____

Note: If you have a temporary illness, such as a common cold, or are not feeling well at this time – POSTPONE.

APPENDIX D

MEDICAL HISTORY FORM

Please fill out and sign in ink. This record is confidential.

Do you take any prescribed or over-the-counter medications? Please include vitamins, herbs, or other dietary supplements. If yes please list the dose, frequency and the duration of use.

_____
_____

Have you ever been told by a physician that you should not exercise?
Yes ____ No ____ If yes, please explain: _____
_____

Do you have or have you EVER had any of the following problems? Check if YES and provide details below.

____ Heart disease/rheumatic fever	____ Thyroid disorder	____Asthma
____ High blood pressure	____ Claustrophobia	____Allergies
____ Elevated Cholesterol	____ Anemia	____Stroke
____ Epilepsy or seizure disorder	____Diabetes	___Dizziness

____ Blurred or double vision
____ Orthopedic or joint problems (e.g., arthritis)
____ Shortness of breath or difficulty in breathing
____ Phlebitis, blood-clots, varicose veins, peripheral vascular disease

Lifestyle

Do you smoke cigarettes? Yes ____ No ____
Do you drink alcohol? Yes ____ No ____
Do you get regular exercise? Yes ____ No ____
If yes, number of times per week _____
Have you had surgery? Yes ____ No ____
If yes, when was this? _____

Is there any other information or concerns you have that you feel we should know about before you participate in the study? If yes please explain.

_____
_____

APPENDIX E

MRI SAFETY QUESTIONNAIRE

Yale University School of Medicine
Magnetic Resonance Research Center
300 Cedar Street
New Haven, CT 06510

Name: _____ **Date of birth:** _____
Today's date: _____

Please read the following questions carefully. It is very important for us to know if you have any **metal devices** or **metal parts** anywhere in your body. If you do not understand a question, please ask us to explain!

1. Yes ☐ No☐ Do you have a heart pacemaker? (if you have a pacemaker, **you cannot have an MRI**)
2. Yes ☐ No☐ Did you ever have a device implanted somewhere in your body like a heart defibrillator?
3. Yes ☐ No☐ Did you ever have an aneurysm clip implanted during brain surgery?
4. Yes ☐ No☐ Do you have a Carotid Artery Vascular clamp?
5. Yes ☐ No☐ Do you have nerve stimulators (neuron-stimulators also called TENS or wires)?
6. Yes ☐ No☐ Do you have any devices to make bones grow (like bone growth or bone fusion stimulators)?
7. Yes ☐ No☐ Do you have implants in your ear (like cochlear implants)?
8. Yes ☐ No☐ Do you have a Vagus nerve stimulator to help you with convulsions or with epilepsy?
9. Yes ☐ No☐ Do you have a filter for blood clots (Umbrella, Greenfield, bird's nest)?
10. Yes ☐ No☐ Do you have embolization coils (Gianturco) in your brain?
11. Yes ☐ No☐ Do you have implants in your eyes? Have you ever had cataract surgery?
12. Yes ☐ No☐ Do you have any stents (small metal tubes used to keep blood vessels open)?
13. Yes ☐ No☐ Do you have an implanted pump to deliver medication?
14. Yes ☐ No☐ Do you have an artificial arm or leg?
15. Yes ☐ No☐ Do you wear colored contact lenses?
16. Yes ☐ No☐ Do you wear a patch to deliver medicines through the skin?
17. Yes ☐ No☐ Do you have shrapnel or metal in your head, eyes or skin?
18. Yes ☐ No☐ Have you ever worked with metal? (For example in a machine shop)? If yes, we need to obtain Orbit x-rays.
19. Yes ☐ No☐ Have you ever had metal removed from your eyes by a doctor?
20. Yes ☐ No☐ Have you ever had a gunshot wound? Or a B-B gun injury?
21. Yes ☐ No☐ Do you have body-piercing or jewelry on your body?
22. Yes ☐ No☐ Do you have permanent eye liner?
23. Yes ☐ No☐ Do you use a hearing aid?
24. Yes ☐ No☐ Do you wear braces on your teeth or have a permanent retainer?
25. Yes ☐ No☐ Do you have a "shunt" (a tube to drain fluid) in your brain, spine or heart?
26. Yes ☐ No☐ Do you have metal joints, rods, plates, pins, screws, nails, or clips in any part of your body?
27. Yes ☐ No☐ Do you have a tattoo? (We need to make sure it does not heat up during the MRI)
28. Yes ☐ No☐ Do you get upset or anxious in small spaces?
29. Yes ☐ No☐ Do you have asthma? Have you ever had an allergic reaction? If yes, to what? _____
30. Yes ☐ No☐ Have you ever had any surgery? Please list all _____

FOR WOMEN

31. Yes ☐ No☐ Are you breastfeeding?
32. Yes ☐ No☐ Do you use a diaphragm, IUD, or cervical pessary?
33. Yes ☐ No☐ Do you think there is any possibility that you might be pregnant? Date of last menstrual period _____

FOR MEN

34. Yes ☐ No☐ Do you have a penile implant?

Weight _____ Height _____

Signature: _____ **Date:** _____

APPENDIX F

PROMIS FATIGUE QUESTIONNAIRE

Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue Short Form

Please respond to each question by marking one box per row. You may skip questions.

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
1.	How often did you feel tired?	☐	☐	☐	☐	☐
		1	2	3	4	5
2.	How often did you experience extreme exhaustion?	☐	☐	☐	☐	☐
		1	2	3	4	5
3.	How often did you run out of energy?	☐	☐	☐	☐	☐
		1	2	3	4	5
4.	How often did your fatigue limit you at work (include work at home)?	☐	☐	☐	☐	☐
		1	2	3	4	5
5.	How often were you too tired to think clearly?	☐	☐	☐	☐	☐
		1	2	3	4	5
6.	How often were you too tired to take a bath or shower?	☐	☐	☐	☐	☐
		1	2	3	4	5
7.	How often did you have enough energy to exercise strenuously?	☐	☐	☐	☐	☐
		1	2	3	4	5

APPENDIX G

SUPPLEMENTAL MATERIAL FROM STUDY 1

Main effects, Interaction, and 95% Confidence Intervals for Changes from Baseline for Specific Torque and Power by Age Group and Collapsed by Group

Isometric Group: p=0.89 Time: p<0.01 Group x Time: p=0.53

Torque	**Younger**		**Older**		**Collapsed**	
	Lower CI	**Upper CI**	**Lower CI**	**Upper CI**	**Lower CI**	**Upper CI**
0r	-25.77	-11.53	-23.86	-10.23	-22.78	-12.92
2r	-11.54	-0.63	-11.35	-0.90	-9.88	-2.33
5r	-9.64	0.72	-7.75	2.17	-7.21	-0.04
10r	-9.26	0.19	-9.03	0.02	-7.79	-1.25
30r	-10.95	-0.58	-12.36	-2.43	-10.17	-2.99
45r	-11.03	-1.63	-8.53	0.47	-8.44	-1.93
60r	-9.88	-0.07	-10.92	-1.53	-8.99	-2.21

30°·s^{-1} Group:p=0.97 Time: p<0.01 Group x Time p=0.59

Power	**Younger**		**Older**		**Collapsed**	
	Lower CI	**Upper CI**	**Lower CI**	**Upper CI**	**Lower CI**	**Upper CI**
0r	-23.09	-8.81	-23.65	-9.98	-21.32	-11.44
2r	-8.51	5.15	-7.69	5.39	-6.14	3.32
5r	-10.62	3.29	-7.80	5.52	-7.22	2.41
10r	-4.64	8.32	-4.15	8.26	-2.54	6.43
30r	-10.24	1.93	-9.21	2.45	-7.98	0.45
45r	-10.41	7.77	-12.34	5.07	-8.77	3.81
60r	-7.58	3.53	-7.17	3.47	-5.79	1.91

V_{75} Group: p=0.95 Time: p<0.01 Group x Time: p=0.64

Power	**Younger**		**Older**		**Collapsed**	
	Lower CI	**Upper CI**	**Lower CI**	**Upper CI**	**Lower CI**	**Upper CI**
0r	-28.31	-10.25	-31.01	-13.72	-27.07	-14.57
2r	-15.83	5.01	-9.59	10.37	-9.72	4.70
5r	-15.13	-0.44	-12.82	1.24	-11.87	-1.70
10r	-13.89	4.94	-9.88	8.15	-9.19	3.85
30r	-16.25	3.07	-16.03	2.47	-13.37	0.00
45r	-13.28	5.70	-15.39	2.77	-11.62	1.52
60r	-12.08	6.61	-15.17	2.73	-10.94	1.99

270°·s^{-1} Group: p=0.01 Time: p<0.01 Group x Time: p=0.04

Power	**Younger**		**Older**		**Collapsed**	
	Lower CI	**Upper CI**	**Lower CI**	**Upper CI**	**Lower CI**	**Upper CI**
0r	-26.76	1.49	-52.08	-23.84	-35.28	-15.31
2r	-12.45	1.84	-21.25	-6.97	-14.76	-4.66
5r	-11.14	15.72	-37.34	-10.47	-20.30	-1.31
10r	-13.20	16.63	-31.73	-1.90	-18.10	2.99
30r	-15.97	14.04	-39.68	-9.68	-23.43	-2.21
45r	-10.05	22.32	-34.84	-2.46	-17.70	5.19
60r	-5.90	19.92	-36.08	-10.27	-17.21	1.04

Main effects, Interaction, and 95% Confidence Intervals for Changes from Baseline for Voluntary RFD by Age Group and Collapsed by Group

Group: p=0.59 Time: p<0.01 Group x Time: p=0.07

	Younger		Older		Collapsed	
	Lower CI	**Upper CI**	**Lower CI**	**Upper CI**	**Lower CI**	**Upper CI**
0r	-24.86	52.10	11.72	85.40	4.45	57.73
2r	-24.09	16.08	-10.32	28.13	-11.45	16.35
5r	-24.58	14.36	-11.21	26.07	-12.32	14.64
10r	-5.85	21.49	2.12	28.29	2.05	20.98
30r	3.78	34.18	-13.00	16.10	-0.25	20.79
45r	-7.47	32.63	-13.77	24.62	-4.87	22.89
60r	-11.25	28.97	-13.60	24.90	-6.66	21.17

Main effects, Interaction, and 95% Confidence Intervals for Changes from Baseline for Stimulated:Voluntary RFD by Age Group and Collapsed by Group

Group: p=0.71 Time: p=0.04 Group x Time p=0.02

	Younger		Older		Collapsed	
	Lower CI	**Upper CI**	**Lower CI**	**Upper CI**	**Lower CI**	**Upper CI**
0r	-27.58	36.63	8.19	75.53	-0.07	46.45
5r	-30.26	-0.41	-27.89	4.52	-24.53	-2.50
10r	-16.07	10.12	-10.77	16.69	-9.49	9.48
30r	-6.80	27.66	-28.02	9.23	-12.17	13.20
60r	-19.26	20.09	-29.47	11.80	-18.47	10.05

Main effects, Interaction, and 95% Confidence Intervals for Changes from Baseline for Time-to-Target Velocity by Age Group and Collapsed by Group

30°·s^{-1} Group:p=0.25 Time: p=0.52 Group x Time p=0.32

	Younger		Older		Collapsed	
	Lower CI	**Upper CI**	**Lower CI**	**Upper CI**	**Lower CI**	**Upper CI**
0r	-59.47	69.17	-1.64	121.52	-12.13	76.92
2r	-31.98	27.14	-0.44	56.16	-7.74	33.18
5r	-21.21	30.80	-3.07	46.73	-4.69	31.31
10r	-33.23	32.54	-1.57	61.41	-7.98	37.55
30r	-21.53	38.93	-0.56	57.33	-2.38	39.47
45r	-14.79	39.18	-6.28	45.38	-2.81	34.55
60r	-7.91	35.98	-11.04	30.98	-3.19	27.20

V_{75} Group: p=0.23 Time: p=0.65 Group x Time: p=0.23

	Younger		Older		Collapsed	
	Lower CI	**Upper CI**	**Lower CI**	**Upper CI**	**Lower CI**	**Upper CI**
0r	4.29	30.64	-9.75	15.48	1.05	19.29
2r	-12.38	20.43	-15.15	16.26	-9.07	13.65
5r	-5.53	30.79	-11.52	23.26	-3.32	21.82
10r	-5.18	36.22	-24.94	14.70	-9.13	19.53
30r	-1.64	36.98	-19.64	17.34	-5.10	21.63
45r	-10.46	27.54	-14.31	22.07	-6.94	19.36
60r	-6.86	26.01	-14.67	16.80	-6.06	16.70

270°·s^{-1} Group: p=0.48 Time: p=0.01 Group x Time: p=0.88

	Younger		Older		Collapsed	
	Lower CI	**Upper CI**	**Lower CI**	**Upper CI**	**Lower CI**	**Upper CI**
0r	9.53	43.20	7.05	41.61	13.29	37.41
2r	0.17	31.30	-4.60	26.52	2.34	24.35
5r	1.86	25.35	0.23	23.73	4.48	21.10
10r	-3.35	20.01	-4.89	18.47	-0.70	15.82
30r	7.19	36.48	-3.02	26.27	6.37	27.09
45r	0.11	32.08	-8.77	23.20	0.35	22.96
60r	-1.78	24.78	-11.07	15.49	-2.53	16.25

Main effects, Interaction, and 95% Confidence Intervals for Changes from Baseline for Pre-motor Time by Age Group and Collapsed by Group

Isometric Group: p=0.65 Time: p=0.07 Group x Time: p=0.64

	Younger		Older		Collapsed	
	Lower CI	**Upper CI**	**Lower CI**	**Upper CI**	**Lower CI**	**Upper CI**
0r	-27.26	103.01	36.08	149.95	22.19	108.70
2r	-20.53	69.47	-16.44	70.64	-5.52	57.09
5r	-56.82	157.47	-7.64	198.76	-1.44	147.33
10r	-26.02	95.37	3.33	119.55	6.05	90.08
30r	-31.97	172.76	-2.13	194.37	12.32	154.20
45r	-10.99	236.17	-30.42	207.59	14.81	186.37
60r	-52.40	171.42	-22.54	191.76	-5.40	149.53

30°·s^{-1} Group: p=0.13 Time: p=0.23 Group x Time p=0.17

	Younger		Older		Collapsed	
	Lower CI	**Upper CI**	**Lower CI**	**Upper CI**	**Lower CI**	**Upper CI**
0r	-27.63	89.11	-74.45	38.17	-34.25	46.85
2r	-19.84	89.59	-81.59	23.93	-34.98	41.03
5r	-22.69	30.81	-28.95	23.21	-18.08	19.27
10r	-5.31	70.44	-49.51	23.01	-16.56	35.87
30r	-17.27	96.64	-68.76	40.30	-26.70	52.15
45r	-29.63	68.38	-72.24	21.60	-36.90	30.95
60r	-37.09	34.14	-48.67	19.52	-32.68	16.63

V_{75} Group: p=0.43 Time: p=0.37 Group x Time: p=0.31

	Younger		Older		Collapsed	
	Lower CI	**Upper CI**	**Lower CI**	**Upper CI**	**Lower CI**	**Upper CI**
0r	-55.85	39.97	0.07	91.81	-14.16	52.17
2r	-33.24	28.83	-24.88	34.55	-20.17	22.80
5r	-80.05	55.20	-29.22	102.90	-35.06	59.47
10r	-38.25	61.89	-2.76	93.11	-6.16	63.15
30r	-26.41	41.86	-29.56	35.80	-18.21	29.05
45r	-26.03	69.39	-40.26	51.10	-19.47	46.57
60r	-16.15	53.10	-15.76	50.54	-6.03	41.90

270°·s^{-1} Group: p=0.05 Time: p=0.08 Group x Time: p=0.07

	Younger		Older		Collapsed	
	Lower CI	**Upper CI**	**Lower CI**	**Upper CI**	**Lower CI**	**Upper CI**
0r	-29.34	22.82	-42.02	11.18	-27.97	9.29
2r	-19.72	27.11	-53.70	-6.87	-29.85	3.26
5r	-7.12	45.05	-60.87	-8.70	-26.35	10.53
10r	-17.84	26.90	-23.42	21.31	-14.08	17.55
30r	-15.43	37.48	-53.37	-1.57	-26.73	10.29
45r	-13.00	51.93	-54.69	8.64	-24.46	20.90
60r	-34.10	29.46	-32.41	29.81	-24.05	20.43

Main effects, Interaction, and 95% Confidence Intervals for Changes from Baseline for Pre-motor EMG by Age Group and Collapsed by Group

Isometric Group: p=0.09 Time: p=0.02 Group x Time: p=0.62

	Younger		Older		Collapsed	
	Lower CI	**Upper CI**	**Lower CI**	**Upper CI**	**Lower CI**	**Upper CI**
0r	-65.14	76.96	21.20	161.43	-1.30	98.52
2r	-52.32	10.40	-7.95	54.77	-20.95	23.40
5r	-54.14	9.65	-15.24	48.55	-25.35	19.76
10r	-47.51	63.00	0.93	111.44	-7.10	71.03
30r	-21.10	68.84	-4.89	86.96	0.31	64.59
45r	-34.30	34.06	-15.21	53.14	-14.74	33.59
60r	-53.96	18.69	-30.07	42.58	-31.38	20.00

30°·s^{-1} Group: p=0.61 Time: p<0.01 Group x Time p<0.01

	Younger		Older		Collapsed	
	Lower CI	**Upper CI**	**Lower CI**	**Upper CI**	**Lower CI**	**Upper CI**
0r	-13.11	95.51	-13.84	90.16	2.08	77.28
2r	-25.22	39.32	-11.30	51.26	-8.95	35.99
5r	-42.25	18.18	-22.35	35.50	-23.65	18.19
10r	-38.70	20.19	-28.25	28.13	-25.04	15.73
30r	-40.07	85.65	-62.79	57.58	-33.42	53.61
45r	-58.82	12.01	-43.70	24.11	-41.11	7.92
60r	-67.83	-15.36	-20.19	30.05	-36.49	-0.17

V_{75} Group: p=0.82 Time: p=0.14 Group x Time: p=0.04

	Younger		Older		Collapsed	
	Lower CI	**Upper CI**	**Lower CI**	**Upper CI**	**Lower CI**	**Upper CI**
0r	-25.47	46.04	-17.53	53.08	-11.09	39.16
2r	-22.49	33.82	-29.54	26.78	-17.77	22.05
5r	-48.45	15.93	-31.68	32.70	-30.64	14.89
10r	-52.38	14.75	-35.45	31.68	-34.08	13.38
30r	-53.07	9.38	-32.46	30.73	-33.57	10.85
45r	-32.62	36.67	-54.94	14.35	-33.63	15.36
60r	-37.92	24.44	-42.63	19.74	-31.14	12.96

270°·s^{-1} Group: p=0.79 Time: p=0.05 Group x Time: p=0.19

	Younger		Older		Collapsed	
	Lower CI	**Upper CI**	**Lower CI**	**Upper CI**	**Lower CI**	**Upper CI**
0r	-32.47	56.10	-12.83	72.91	-9.89	51.75
2r	-23.07	41.78	-17.85	44.24	-11.17	33.72
5r	-38.05	30.82	-31.62	34.32	-24.97	22.71
10r	-25.72	33.92	-35.03	22.07	-21.83	19.45
30r	-61.46	24.64	-28.82	53.16	-32.84	26.60
45r	-7.86	71.40	-42.60	30.50	-14.09	39.82
60r	-49.65	26.31	-19.90	52.82	-23.90	28.68

Main effects, Interaction, and 95% Confidence Intervals for Changes from Baseline for EMG:Torque Ratio by Age Group and Collapsed by Group

20% MVIC Group: p=0.28 Time: p<0.01 Group x Time: p=0.33

	Younger		Older		Collapsed	
	Lower CI	**Upper CI**	**Lower CI**	**Upper CI**	**Lower CI**	**Upper CI**
0r	-6.03	24.72	-11.83	17.61	-4.53	16.76
2r	-15.11	2.19	-16.68	-0.12	-13.42	-1.44
5r	-13.75	7.23	-19.97	0.12	-13.85	0.67
10r	-9.37	9.95	-22.07	-3.58	-12.95	0.42
30r	-2.57	21.60	-11.47	11.67	-3.56	13.17
45r	-11.20	25.09	-22.08	12.67	-11.44	13.68
60r	-17.04	9.39	-21.43	3.88	-15.45	2.85

50% MVIC Group: p=0.19 Time: p<0.01 Group x Time p<0.01

	Younger		Older		Collapsed	
	Lower CI	**Upper CI**	**Lower CI**	**Upper CI**	**Lower CI**	**Upper CI**
0r	19.64	43.45	-4.16	18.63	11.15	27.63
2r	-16.51	3.01	-10.03	8.66	-10.47	3.04
5r	-4.88	16.45	-16.59	3.84	-7.68	7.09
10r	-4.96	17.20	-14.65	6.58	-6.63	8.71
30r	-0.47	23.30	-8.80	13.95	-1.23	15.22
45r	-9.50	19.79	-16.92	11.12	-9.02	11.26
60r	-16.48	14.59	-20.00	9.74	-13.79	7.71

100% MVIC Group: p=0.94 Time: p<0.01 Group x Time: p=0.93

	Younger		Older		Collapsed	
	Lower CI	**Upper CI**	**Lower CI**	**Upper CI**	**Lower CI**	**Upper CI**
0r	17.51	48.49	18.30	47.96	22.35	43.79
2r	-7.55	13.81	-3.14	17.31	-2.29	12.50
5r	-11.93	5.72	-9.90	6.99	-8.39	3.83
10r	-10.48	12.72	-9.84	12.37	-6.84	9.22
30r	-4.24	19.22	-7.27	15.19	-2.39	13.85
45r	-9.51	17.83	-8.51	17.67	-5.09	13.83
60r	-10.39	20.04	-9.25	19.88	-5.46	15.60

Main effects, Interaction, and 95% Confidence Intervals for Changes from Baseline for Stimulated Measures by Age Group and Collapsed by Group

RFD Group: p=0.54 Time: p=0.01 Group x Time: p=0.54

	Younger		Older		Collapsed	
	Lower CI	**Upper CI**	**Lower CI**	**Upper CI**	**Lower CI**	**Upper CI**
0r	-0.28	23.38	-14.01	12.15	-3.51	14.13
5r	5.14	25.29	-0.20	22.25	5.58	20.66
10r	1.84	23.64	-1.44	22.67	3.55	19.80
30r	-0.56	19.62	-1.36	21.02	2.15	17.22
60r	0.63	19.18	-0.36	20.15	2.99	16.81

RFR Group: p=0.11 Time: p<0.01 Group x Time p=0.12

	Younger		Older		Collapsed	
	Lower CI	**Upper CI**	**Lower CI**	**Upper CI**	**Lower CI**	**Upper CI**
0r	-37.73	-21.61	-38.41	-20.59	-35.59	-23.58
5r	-6.56	1.17	-0.12	8.57	-2.14	3.67
10r	-7.87	10.52	1.75	22.08	-0.23	13.47
30r	-6.87	14.04	0.19	23.36	-0.12	15.48
60r	-7.81	3.50	-3.77	8.72	-4.05	4.37

$T_{1/2}$ Group: p=0.44 Time: p<0.01 Group x Time: p=0.23

	Younger		Older		Collapsed	
	Lower CI	**Upper CI**	**Lower CI**	**Upper CI**	**Lower CI**	**Upper CI**
0r	13.91	51.47	18.64	60.17	22.05	50.04
5r	-11.43	6.10	-10.96	8.87	-8.47	4.76
10r	-12.06	1.21	-18.66	-3.98	-13.32	-3.43
30r	-7.95	8.23	-20.02	-2.03	-11.49	0.60
60r	-2.10	16.42	-16.13	4.35	-6.27	7.54

10:80Hz Ratio Group: p=0.07 Time: p<0.01 Group x Time: p=0.82

	Younger		Older		Collapsed	
	Lower CI	**Upper CI**	**Lower CI**	**Upper CI**	**Lower CI**	**Upper CI**
0r	-22.59	-4.71	-32.42	-12.65	-24.76	-11.43
5r	-9.16	3.07	-18.93	-4.26	-12.09	-2.54
10r	-21.99	-9.89	-26.46	-13.07	-22.36	-13.34
30r	-21.65	-8.49	-26.39	-11.64	-21.98	-12.10
60r	-16.08	-4.64	-20.73	-8.09	-16.65	-8.13

Main effects, Interaction, and 95% Confidence Intervals for Changes from Baseline for Ratings of Perceived Exertion by Age Group and Collapsed by Group

20% MVIC Group: p=0.43 Time: p<0.01 Group x Time: p=0.20

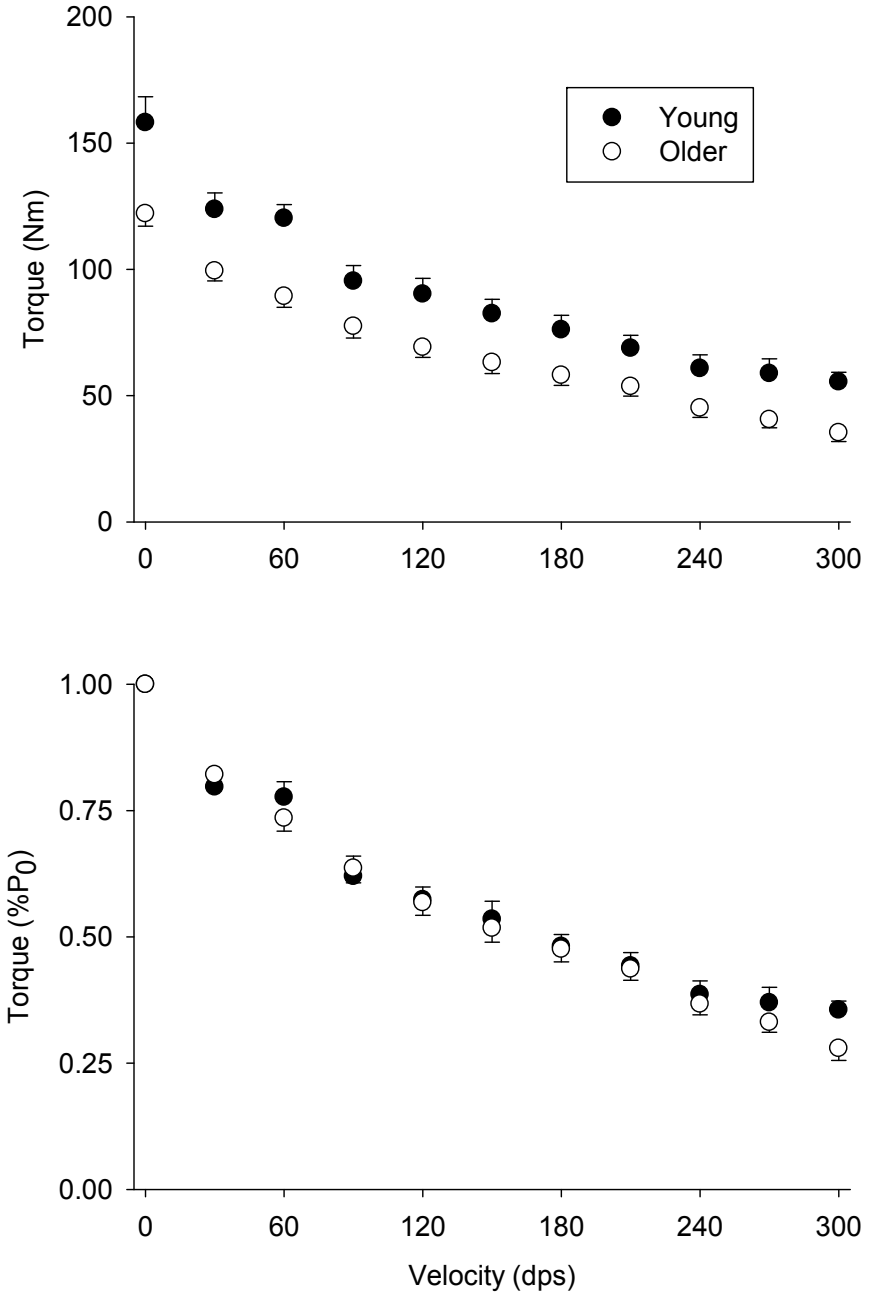
	Younger		Older		Collapsed	
	Lower CI	**Upper CI**	**Lower CI**	**Upper CI**	**Lower CI**	**Upper CI**
0r	0.29	0.98	0.21	0.87	0.35	0.83
2r	-0.09	0.45	-0.30	0.22	-0.12	0.26
5r	-0.31	0.13	-0.40	0.02	-0.29	0.01
10r	-0.27	0.45	-0.34	0.34	-0.20	0.29
30r	-0.13	0.50	-0.47	0.14	-0.21	0.23
45r	-0.21	0.75	-0.48	0.44	-0.21	0.46
60r	-0.54	0.36	-0.45	0.41	-0.37	0.26

50% MVIC Group: p=0.30 Time: p<0.01 Group x Time p=0.69

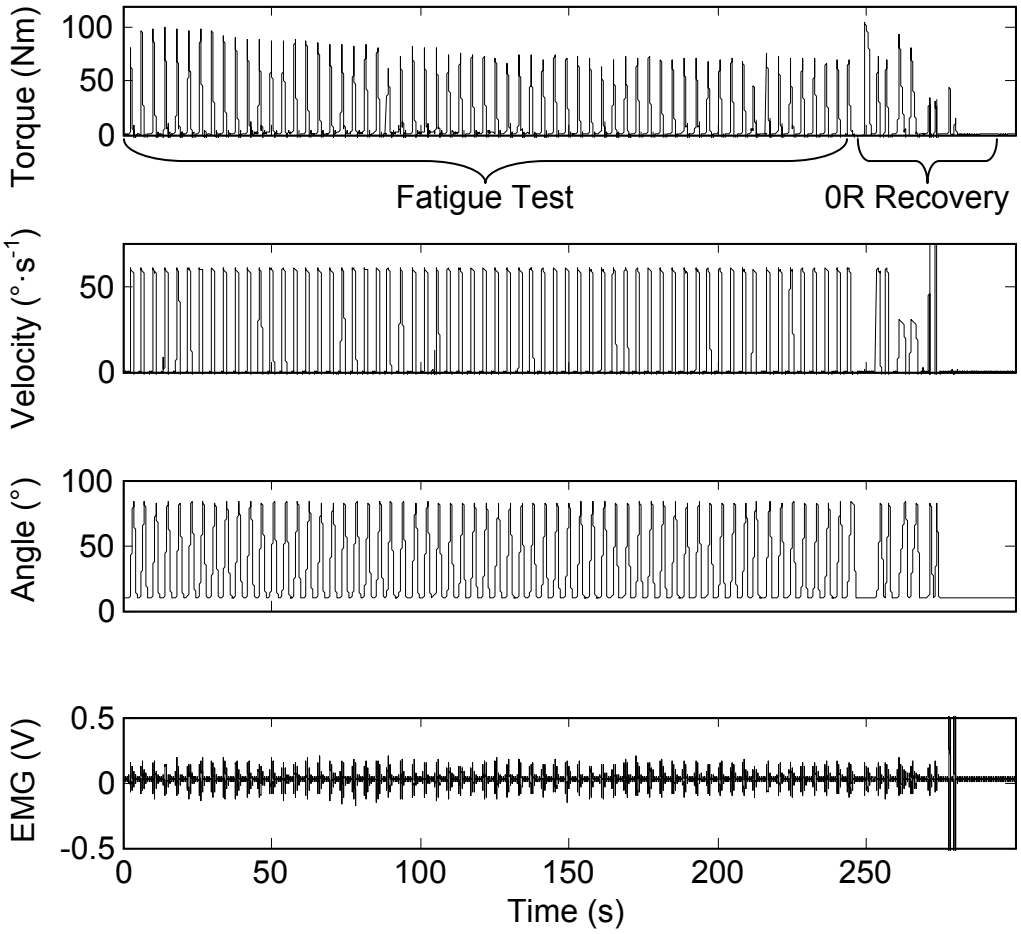
	Younger		Older		Collapsed	
	Lower CI	**Upper CI**	**Lower CI**	**Upper CI**	**Lower CI**	**Upper CI**
0r	-0.05	1.69	0.58	2.25	0.51	1.72
2r	-0.66	0.11	-0.53	0.20	-0.49	0.05
5r	-0.72	-0.01	-0.59	0.09	-0.55	-0.06
10r	-0.80	0.07	-0.59	0.25	-0.57	0.04
30r	-0.33	0.51	-0.18	0.65	-0.13	0.46
45r	-0.70	0.43	-0.46	0.62	-0.42	0.36
60r	-0.90	0.17	-0.45	0.58	-0.52	0.22

100% MVIC Group: p=0.05 Time: p=0.04 Group x Time: p=0.33

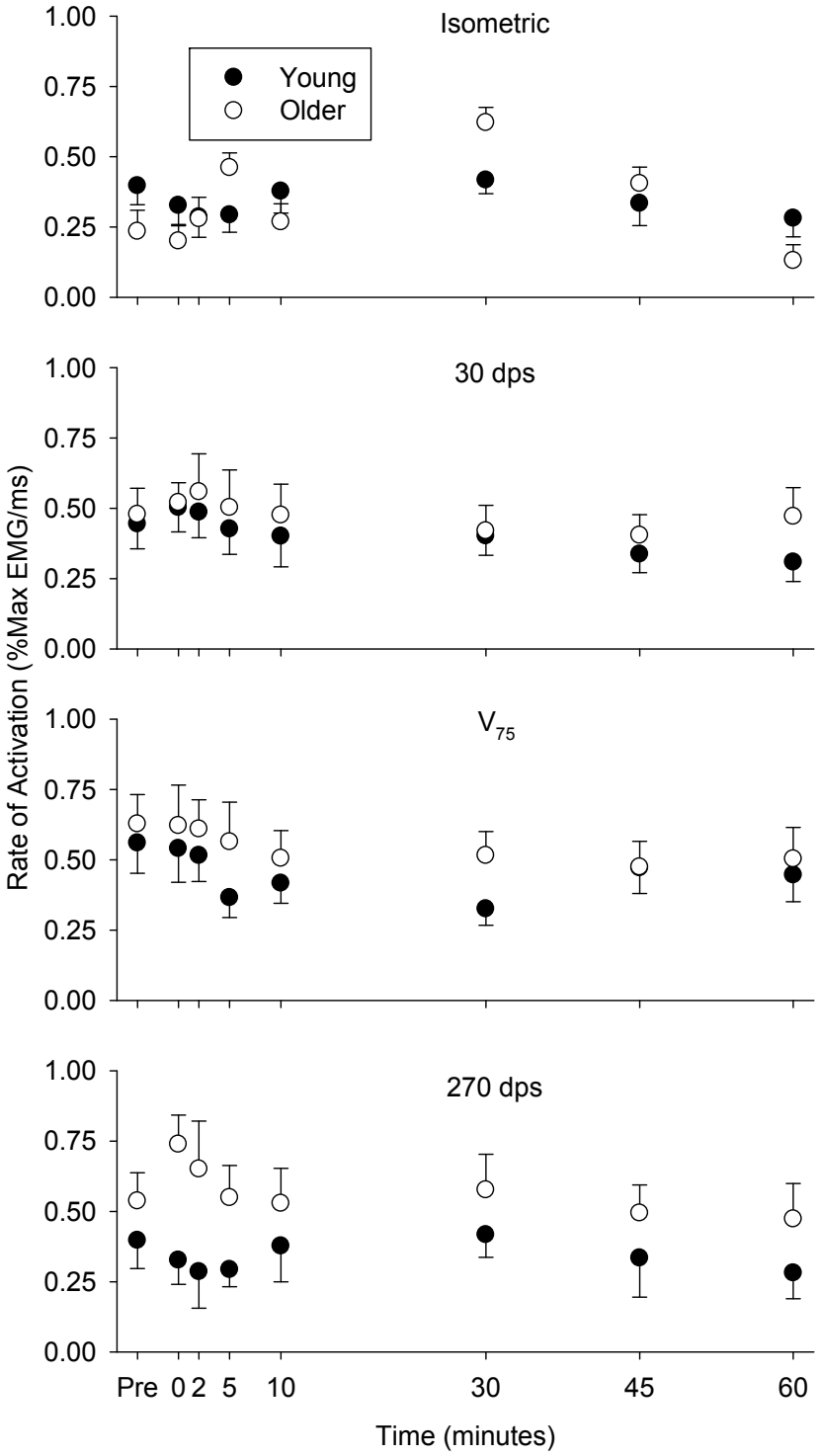
	Younger		Older		Collapsed	
	Lower CI	**Upper CI**	**Lower CI**	**Upper CI**	**Lower CI**	**Upper CI**
0r	-0.31	1.22	0.60	2.07	0.36	1.42
2r	-0.75	0.93	0.28	1.89	0.00	1.17
5r	-1.08	0.54	0.14	1.69	-0.24	0.88
10r	-1.43	0.52	0.07	1.93	-0.40	0.95
30r	-1.40	1.04	-0.43	1.91	-0.57	1.12
45r	-1.80	0.71	-0.21	2.21	-0.64	1.10
60r	-1.85	0.57	0.01	2.33	-0.57	1.10



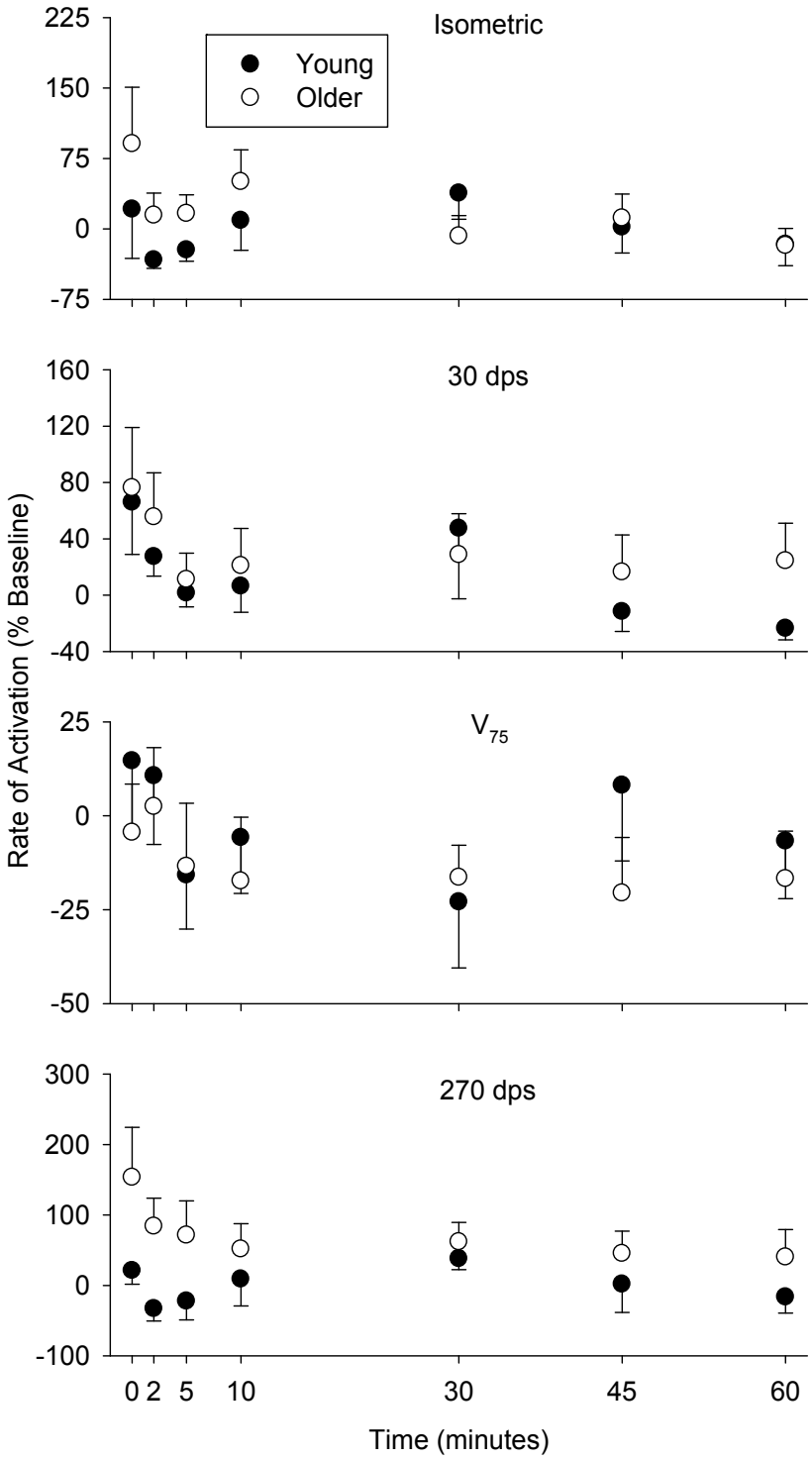
Absolute (top) and Relative (bottom) Torque-Velocity Curves



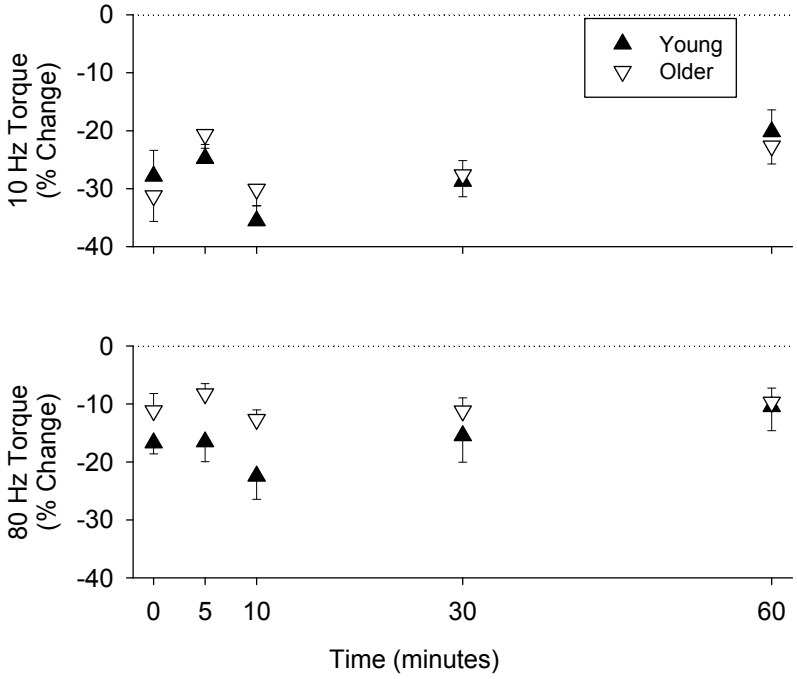
Sample Fatigue Data and 0r Measures from 1 Participant with a V_{75} of 60°·s^{-1}



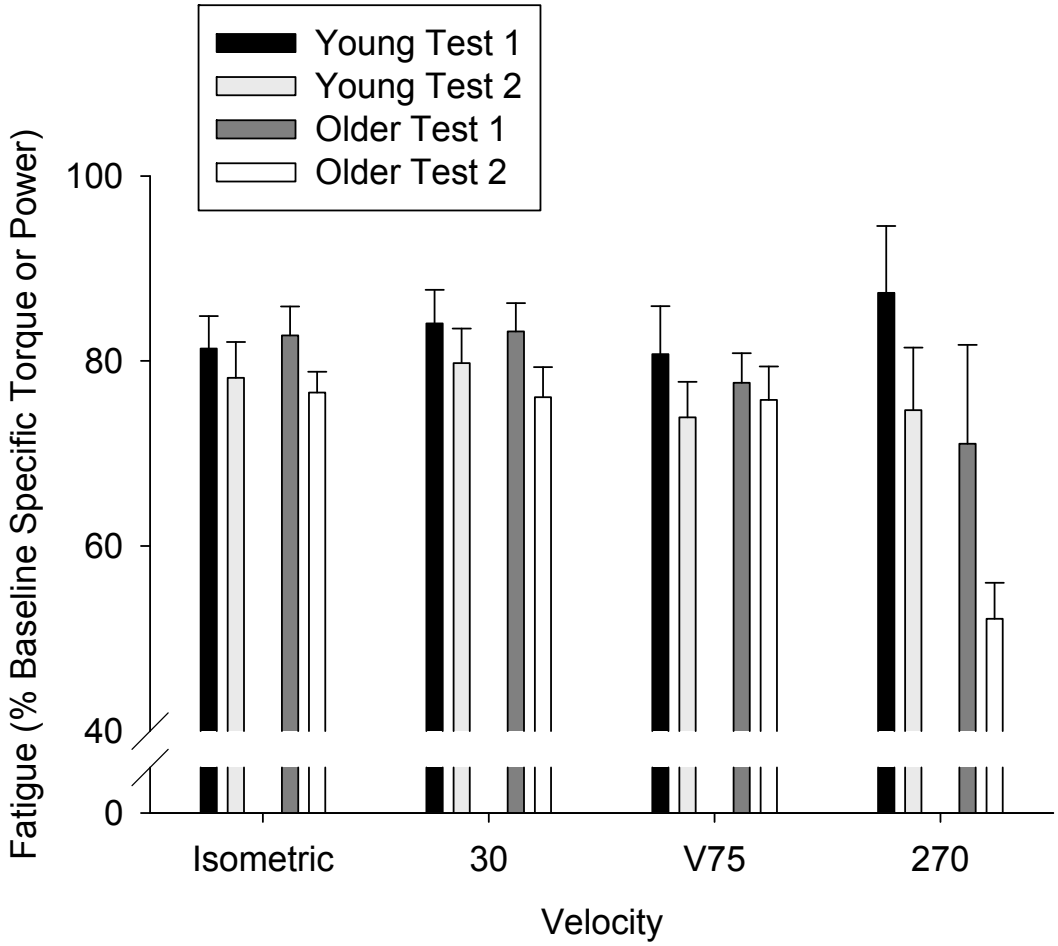
Recovery of Rate of Activation in Absolute Units. This measure was proposed in Chapter 4, but due to a lack of confidence in the measure, this data was excluded from the document.



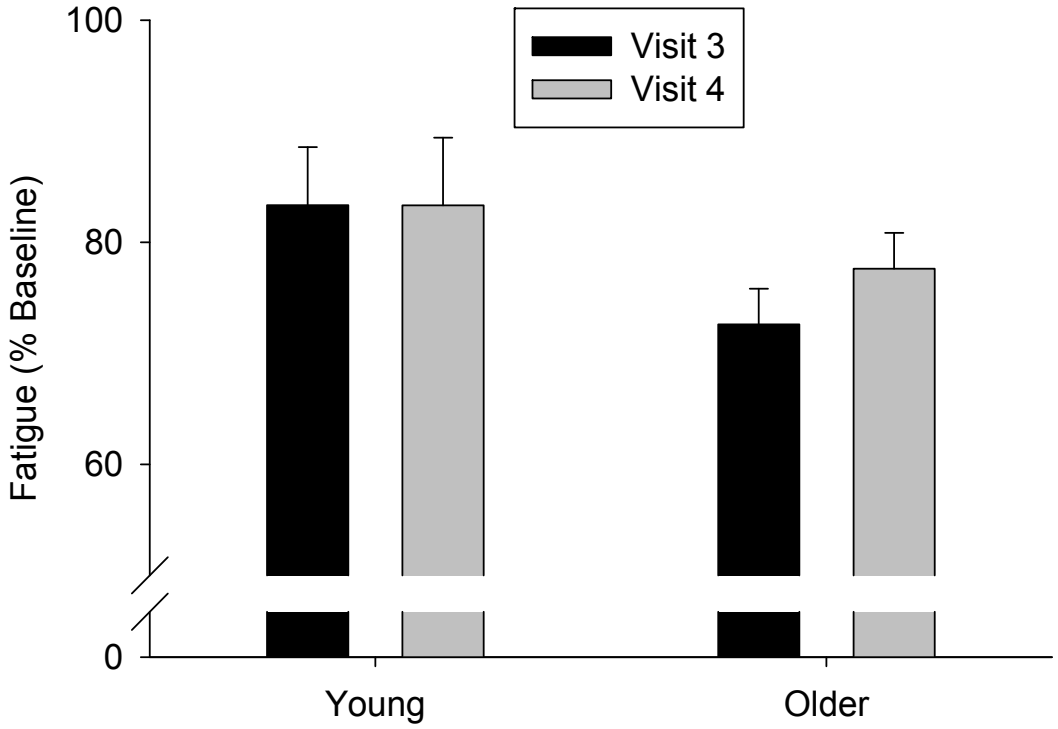
Recovery of Rate of Activation Relative to Baseline. This measure was proposed in Chapter 4, but due to a lack of confidence in the measure, this data was excluded from the document.



Recovery of 10 and 80Hz Tetanic Torque Relative to Baseline. There were no differences by group at either frequency ($p \geq 0.18$). At both frequencies, the 0R and 60R torques were lower than baseline in both groups ($p < 0.01$).



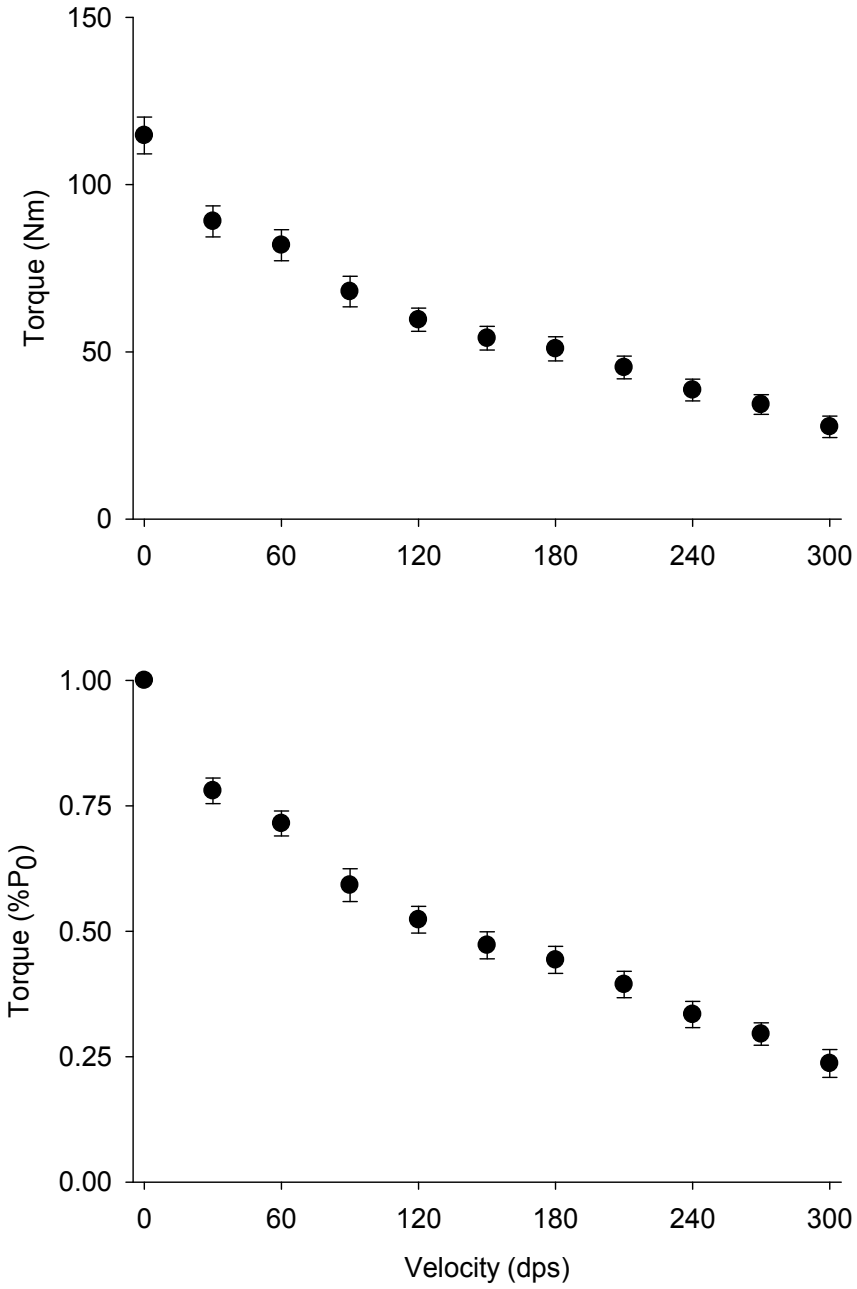
Effects of a Repeated Fatigue Bout on Torque and Power Following 60 Minutes of Recovery. There was a significantly greater fatigue during the second bout for all velocities ($p \leq 0.03$).



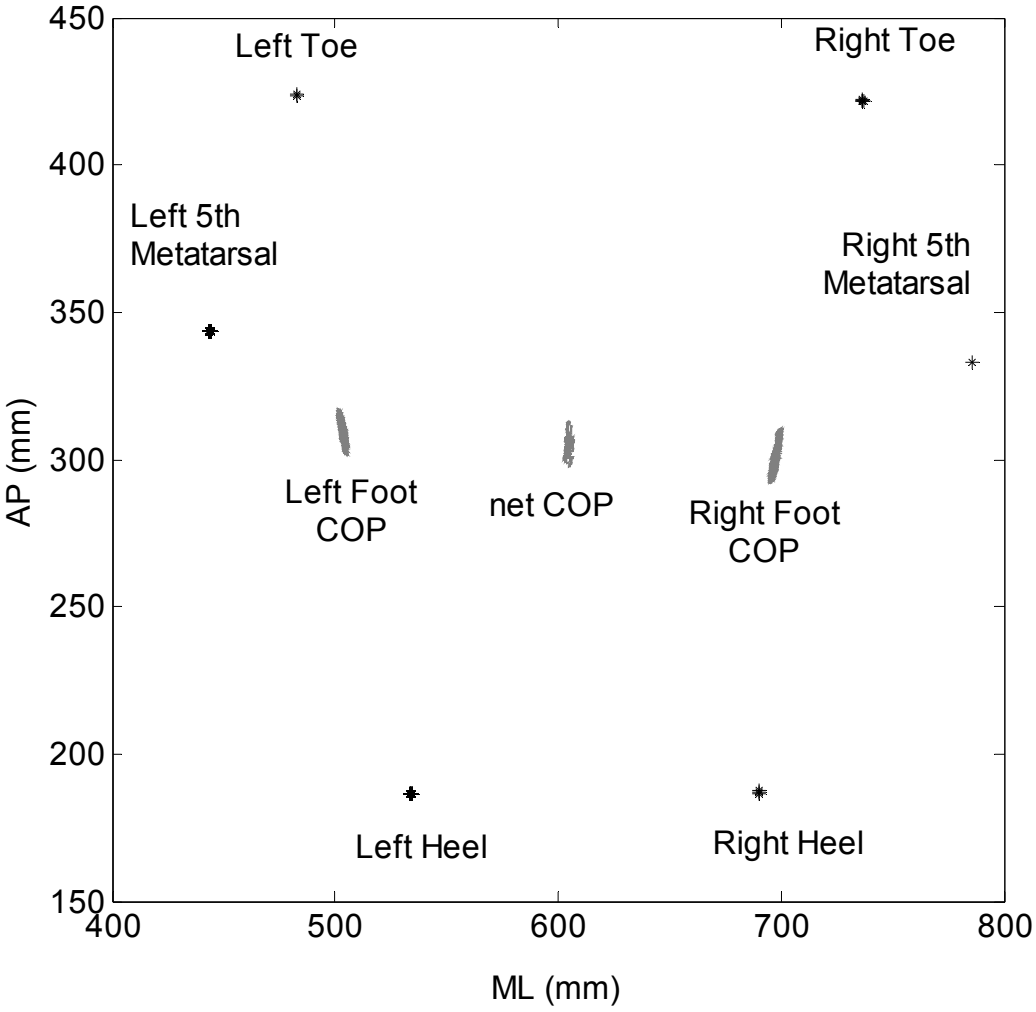
Comparison of Fatigue Bouts across Visits. There was no difference in fatigue by group (p=0.12) or visit (p=0.28).

APPENDIX H

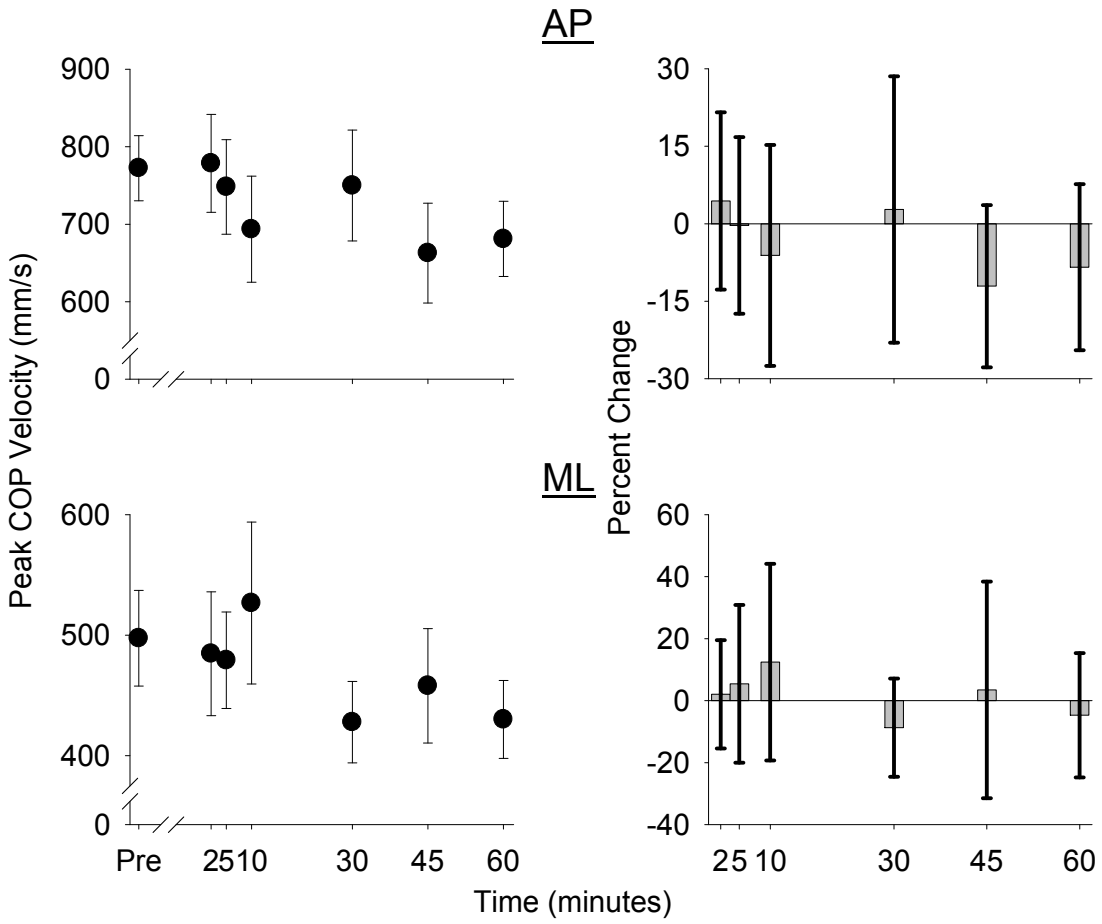
SUPPLEMENTAL MATERIAL FROM STUDY 2



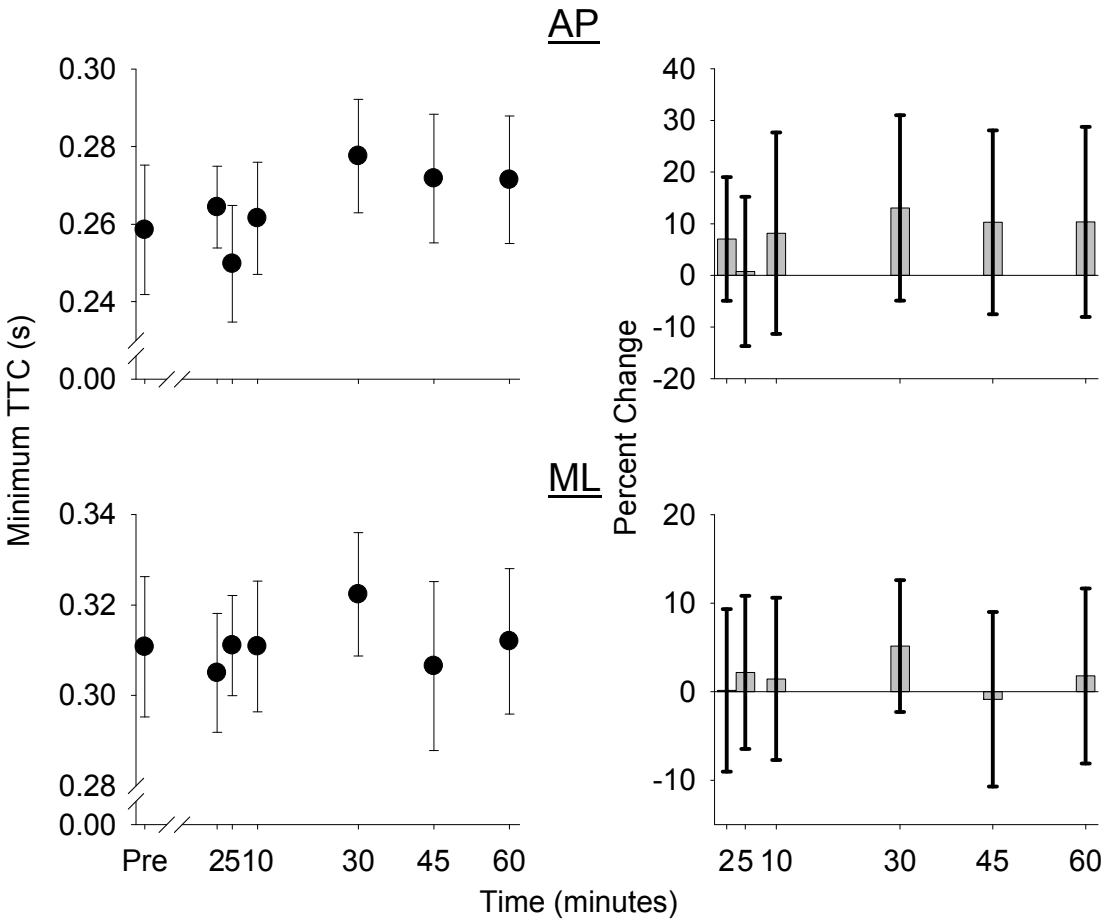
Absolute (top) and Relative (bottom) Torque-Velocity Curves



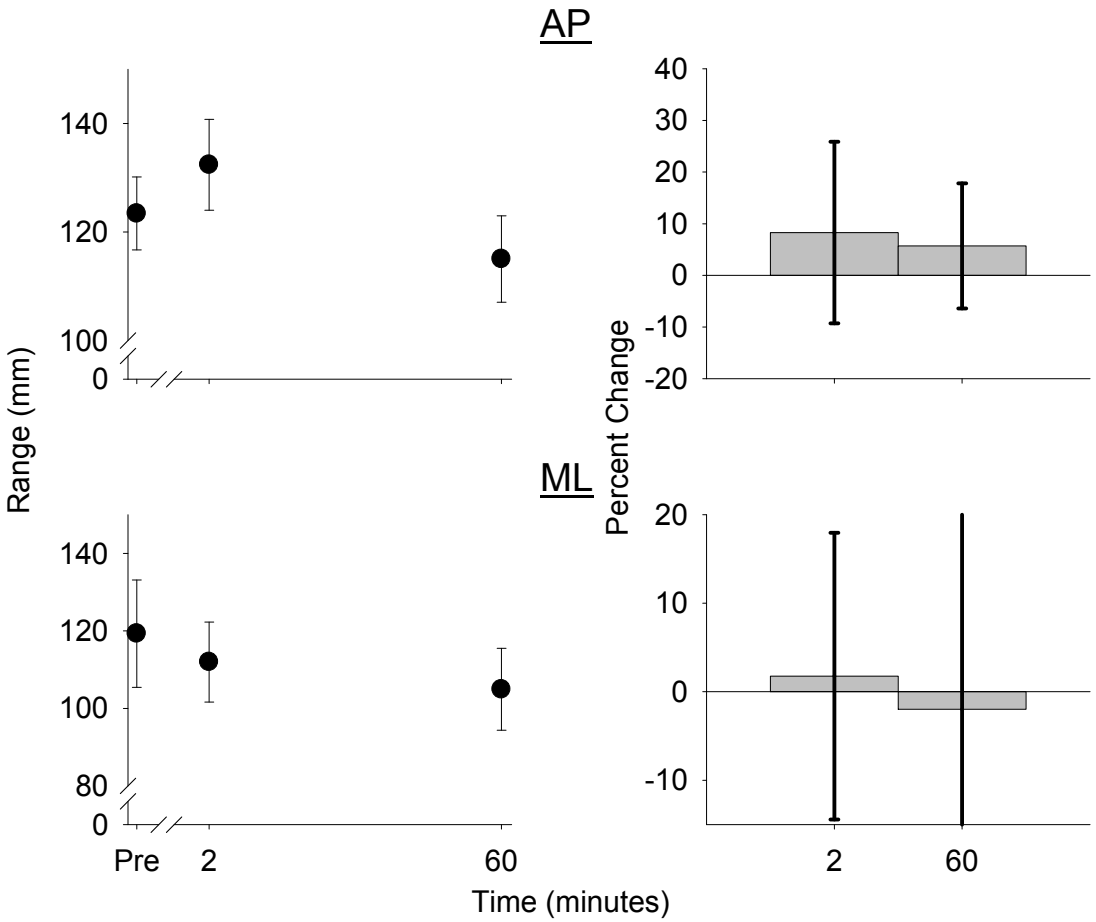
Sample Baseline COP Recording from 1 Older Participant. Location of the markers and COP are labeled.



Recovery of Peak COP Velocity. There were no differences from baseline at 2r or 60r ($p \geq 0.28$)



Recovery of Minimum TtC Based on a Single Point within the 30 Second Recording Period. There were no significant changes from baseline in either direction at the 2r or 60r ($p \geq 0.23$).



Preliminary Data Assessing Recovery of COP Range During the Chair Rise Task. Range was assessed only during the times when the participant was supporting at least 25% of their body weight. There was no significant change from baseline at either time-point ($p \geq 0.32$).

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