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An Examination of Sex-Differences in Quadriceps Fatigability During High- and Low-Intensity Contractions

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AN EXAMINATION OF SEX-DIFFERENCES IN QUADRICEPS FATIGABILITY DURING HIGH- AND LOW-INTENSITY CONTRACTIONS

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LIST OF ABBREVIATIONS

HT	High Torque
LT	Low Torque
MVIC	Maximal Voluntary Isometric Contraction
VL	Vastus Lateralis
VM	Vastus Medialis
VA	Voluntary Activation
ITT	Interpolated Twitch Technique
TQ_{MAX}	Maximum Torque
TQ_{MEAN}	Mean Torque
EMG	Electromyography
AMP	Amplitude
RMS	Root Mean Square
MPF	Mean Power Frequency
PTT	Peak Twitch Torque
pPTT	Potentiated Peak Twitch Torque
TQ_{IMP}	Total Torque Impulse
TQ_{CV}	Torque Coefficient of Variation

ABSTRACT

Kennedy, Katie Grace, M.S., University of South Alabama, August 2022. An Examination of Sex-Differences in Quadriceps Fatigability during High and Low-Intensity Contractions. Chair of Committee: Ryan Colquhoun, Ph.D.

The purpose of the current study was to compare sex-differences in quadriceps fatigability following both high- and low-intensity repeated, isometric contractions. Twenty-four (12 males, 12 females) participants completed two experimental visits consisting of repeated, isometric contractions of the knee extensors at 30% (LT) and 70% (HT) of maximal voluntary force (MVIC) until failure. Prior to, and immediately following the fatiguing contractions, strength, voluntary activation (VA), and peak twitch torque (PTT) were assessed while measuring surface electromyographic amplitude of the vastus lateralis (VL_{AMP}) and vastus medialis (VM_{AMP}). Fatiguing bouts were assessed via mean torque (TQ_{MEAN}), total repetitions completed, torque coefficient of variation (TQ_{CV}), EMG amplitude (VL_{AMP}; VM_{AMP}) and integrated EMG (iEMG) signal, and torque impulse (TQ_{IMP}). Repeated measures Analysis of Variance analyses indicated females completed nearly double the repetitions of males during LT contractions ($p = 0.001$). Greater central fatigue was experienced during the LT contractions than HT ($p = 0.050$), despite having lower EMG amplitude throughout the fatiguing bout ($p < 0.001$). A sex difference may be present during LT repeated isometric contractions, but further investigation is needed.

CHAPTER I

INTRODUCTION

Muscular fatigue is defined as the decrease in force production capabilities, such as following an exercise bout (Gandevia, 2001). This degradation of performance can be quantified by the degree of decrease in muscle force production, commonly assessed via maximal voluntary contraction (MVC) strength (Hunter, 2018). While fatigue is a complex phenomenon, it is widely accepted that females exhibit greater resistance to fatigue than males when completing a similar isometric task (Hunter, 2014), in spite of the fact that numerous studies have demonstrated that males have greater absolute strength during identical relative intensity muscle actions (Albert et al., 2006; Ansdell et al., 2017; Wüst et al., 2008). However, when matching males and females for strength (Ansdell et al., 2017), a sex difference in fatigability remains. Additionally, physiological differences such as males' decreased proportion of Type I muscle fibers (Staron et al., 2000) likely contributes to the decreased fatigue resistance, further complicating the issue. Further investigations are needed to further understand the mechanisms underlying sex-differences in fatigability.

Task failure (i.e. when force cannot be maintained within 5% of the target force (Rudroff et al., 2011)) from exercise-induced fatigue may occur via central or peripheral factors, such as within the contractile unit of the muscle itself (Bigland-Ritchie et al., 1986; Hunter, Duchateau, & Enoka, 2004). Delivering electrical stimulation to peripheral nerves surrounding or during (interpolated twitch technique) an MVC can provide insight as to the mechanisms of fatigue and potential causes of task failure, as the cause of task failure is known to be dependent very specifically on the nature of the task completed (Hunter, Duchateau, & Enoka, 2004). For example, failure of the contractile elements of skeletal muscle have been reported during repeated contractions at various intensities (Ansdell et al., 2019; Bigland-Ritchie et al., 1986). Further, peripheral factors have been cited as a primary culprit for increased fatigability in males at both submaximal intensities (i.e., 20% MVC; (Akagi, 2019)) and maximal intensities (Solianik et al., 2017), while other studies have cited a combination of both central and peripheral fatigue (Søgaard et al., 2006).

The exact mechanisms behind differing fatigue responses are specific to the nature of demands of the task (Hunter, 2014). For example, the muscle group being utilized influences the outcome of the fatiguing task (Albert et al., 2006; Avin et al., 2010; Dearth et al., 2010). Specifically, sex differences have been shown to be minimal in smaller muscles such as the plantar flexors (Ha et al., 2021), making the translation of fatigue between muscle groups difficult at best. Thus, future studies are needed within specific muscle groups of interest, such as the quadriceps group. Additionally, the nature of the contraction, whether sustained (Clark et al., 2005; Dearth et al., 2010; Senefeld et al., 2018) or repeated (Hunter et al., 2006), influences the fatigue sustained from the contractions (Ansdell et al., 2017). The intensity of the task completed is additionally important as previous work directly comparing low-intensity to moderate-intensity contractions appear to demonstrate greater sex differences at higher intensities (Ansdell et al., 2017). This is in contrast to previous work citing a decrease in sex differences as intensity increases (Yoon et al., 2007). Further confounding the issue, intensity has been shown to be a significant factor in muscle activation, as recent data has suggested that completing low-intensity contractions to failure has not been shown to obtain the same response as a high-intensity contraction (Miller et al., 2020). Thus, further investigation is necessary to understand the impact contraction intensity has on decrements in force and differences in muscle activation throughout the fatigue process.

The ability to understand the underlying mechanisms of fatigue and their sex differences is important to proper exercise prescription, as well as a deeper understanding of the physiology of fatigue. Females are severely under-researched, and it is clear from the overall lack of original data on females that creating evidence-based recommendations for females by generalizing male fatigability properties is questionable at best (Ansdell et al., 2019). For example, it has additionally been shown females have a greater time to task failure during varying types of fatiguing exercise (Ansdell et al., 2017, 2019; Clark et al., 2005; Hunter, Critchlow et al., 2004). Therefore, it is unclear if differing training intensities should be prescribed for females to allow for proper motor unit recruitment (Muddle et al., 2018a), while simultaneously allowing for a feasible training prescription. Thus, further data is needed to define a training intensity that provides "optimal" muscle recruitment, while also being feasible to complete.

Because of the numerous variables associated with performance fatigue and conflicting evidence, there is a large gap in the research investigating sex-differences at differing intensities when both completed to failure. Therefore, the purpose of this study was to compare sex-differences in quadriceps fatigability following both high- and low-intensity repeated, isometric contractions. We hypothesize that, while males will possess greater quadriceps strength, females will be more fatigue resistant than males at both intensities, completing a greater number of reps and total work at each intensity. Additionally, we hypothesize that muscle activation will be greater during high-intensity contractions in both males and females. This study will provide data on the underlying physiological mechanisms associated with fatigue and in turn, be utilized to improve recommendations for resistance training prescription and move closer to a more optimal training intensity for maximal activation of the quadriceps in males and females.

CHAPTER II

REVIEW OF THE LITERATURE

2.1 Neuromuscular Function and Fatigue

2.1.1 Bigland-Ritchie et al., 1986

The purpose of this study was to determine central and peripheral factors of fatigue during repeated submaximal isometric contractions of the quadriceps. All participants completed baseline maximal isometric strength testing with electrical stimulations delivered before, during, and after the contractions. Additionally, resting twitch trains were delivered. The fatiguing task was completed at 50% of the measured force value from baseline testing. Subjected repeatedly maintained a 50% contraction for six seconds, then rested for four seconds until they could no longer maintain the force. A superimposed twitch was delivered during the last three seconds of contraction, and during rest, either a train or single twitch was delivered. Surface electromyography was obtained from the vastus lateralis, and stimulations were delivered transcutaneously. MVC force declined linearly, and the difference in MVC and their corresponding twitch decline were not significantly different. EMG values were not significantly different between maximal contraction during the fatiguing bout and maximal contraction at baseline. The authors concluded that these findings signified contractile failure by the muscle, and that force generation changes were not due to a lack of muscle activation.

2.1.2 Jenkins et al., 2015

The purpose of this study was to determine electromyographic amplitude, mean power frequency, and muscle activation of the quadriceps before and after three sets of repetitions to failure at 80% and 30% of one repetition maximum leg extension. Eighteen men and women completed one repetition maximum testing of the leg extension of their dominant leg, followed by isometric testing. On two randomized testing days to follow, participants completed three sets of leg extension to failure, with each set separated by a rest of two minutes. Surface electromyography was obtained from the vastus lateralis, vastus medialis, and rectus femoris. Muscle activation was measured by the amplitude of EMG activity. EMG amplitude increased between the very first and very last repetitions in the 80% condition but remained steady from start to mid-bout followed by an increase from mid-bout to the final repetition in the 30% condition. During every set and rep, EMG AMP was greater in the 80% condition than the 30%. EMG MPF began to decrease halfway through the 30% condition, while MPF decreased in all muscles from the start in the 80% condition. At the final rep, EMG MPF was lower in the 30% condition when compared to the 80%. Overall, muscle activation was greater during 80% 1RM exercise when compared to the 30% 1RM condition. The authors concluded that the mechanisms behind fatigue vary based on the intensity of exercise performed.

2.1.3 Kent-Braun, 1999

The purpose of this investigation was to determine the contributions of central and peripheral nervous system factors to fatigue from sustained maximal contractions of the ankle dorsiflexor muscles. Nine participants volunteered and underwent three supramaximal twitch responses via the peroneal nerve, four baseline maximal voluntary isometric contractions for strength, and a measure of tetanus via a superimposed train of twitches. Following these measures, participants sustained the maximal isometric contraction for four minutes, during which surface electromyography was measured. A superimposed tetanic stimulation was delivered at the end of the four minutes. The difference between tetanic stimuli fatigue and voluntary strength fatigue, as well as the central activation ratio, were used to determine the mechanisms behind the decline in strength. MVC strength decreased nearly 80% from baseline, and tetanus values decreased by about 37%. Twitch contraction time decreased from pre- to post-fatiguing task. The central activation ratio also significantly declined during the task. Voluntary fatigue was seen to be greater than the electrically stimulated fatigue, given the greater decline in MVC than tetanic values. Because of these findings, the authors concluded that an estimated 20% of the force decline during this task could be attributed to mechanisms of central fatigue.

2.1.4 Smith et al., 2016

The purpose of this investigation was to investigate the time-course of neuromuscular responses to fatigue during intermittent isometric contractions of the knee extensors. Following a warm-up, eleven men performed baseline maximal isometric contractions of the knee extensors, which were then used to calculate a target torque at 60% MVIC. Participants then completed 50 isometric, intermittent contractions consisting of six seconds of work and two seconds of rest. During contractions, surface EMG was measured at the vastus lateralis. EMG RMS was increased quadratically during repetitions 5-50 compared to the first. Additionally, EMG MPF was lower in repetitions 20-50 when compared to repetition one. The authors concluded that two phases of fatigue occurred during the fatiguing bout. The study was able to identify the time points in which neuromuscular measures and activation strategies likely change.

2.1.5 Søgaard et al., 2006

The primary purpose of the present study was to understand the development of peripheral and central fatigue following a sustained 15% MVC contraction of the elbow flexors for a total of 43 minutes. Five males and four females completed baseline testing consisting of an MVC, stimulation of the brachial plexus and motor cortex, a 50% MVC, and five 15% MVCs. While the sustained task was completed, MVCs were performed and motor cortex, brachial plexus, or motor point stimuli were delivered. Surface electromyography was measured at the biceps brachii, brachioradialis, and triceps brachii. Maximum EMG increased in all muscles during the sustained contraction. Motor evoked potential area increased during the contraction in the biceps brachii. Superimposed twitch also increased, nearly doubling during the first 20 min of sustained contraction. Both resting twitch and MVC torque of the brief contractions declined as the sustained contraction continued. Cortical inhibition increased as the silent period increased as the sustained contraction continued. The authors concluded that the sustained contraction caused both central and peripheral fatigue. Output by the motor cortex decreased, likely causing the decline in voluntary activation of the muscle.

2.2 Motor Unit Behavior and Fatigue

2.2.1 Adam & De Luca, 2005

The purpose of this study was to evaluate the motor unit firing rates of the vastus lateralis in young men during isometric constant torque contractions to failure. The study evaluated five men tracing displayed force trajectories during which surface and intramuscular electromyography was recorded at the vastus lateralis, vastus medialis, rectus femoris, and biceps femoris muscles. Subjects ramped up force to 50% of measured maximal voluntary contraction strength and briefly maintained force before lowering to 20% of MVC at which they maintained force for 50 seconds. These contractions were repeated until target force could not be maintained twice within ten seconds of a recording. During the initial ramp, nine motor units were activated, while all but 2 were derecruited at the low torque plateau of 20% MVC. Motor unit peak firing rates first decreased at start before increasing as contractions progressed towards exhaustion. As new motor units fired during the task, they discharged at a lower firing rate than the ones previously active. The authors concluded an inverse relationship between firing rates and recruitment threshold was displayed even while the task was being taken to failure.

2.2.2 Contessa et al., 2016

The purpose of this study was to develop a better understanding of the impact of fatiguing isometric contraction on the motor units of the vastus lateralis. Surface electromyography was used to decompose 1,890 motor unit firing trains in five healthy men and women. Force trajectories were followed by participants, beginning by linearly increasing force to 30% of measure maximal voluntary isometric strength of the knee extensors. Participants maintained this force for 48 seconds before decreasing linearly to resting levels. Contractions were repeated until fatigue was reached and force decreased 5% from the target. The firing rates of similar amplitude motor units increased throughout the fatiguing bout. Additional lower firing rate motor units were recruited while subjects both increased and maintained force. Additionally, similar amplitudes of motor unit action potentials were recruited at lower force thresholds as the fatigue bout continued. The authors suggested these results indicate that motor unit firing properties change as fatigue sets in to compensate for a decline in the mechanical properties of the muscle. The size-principle is still maintained while a muscle is experiencing fatigue.

2.2.3 Miller et al., 2020

The purpose of this study was to determine whether moderate contractions to fatigue and a single higher-intensity contraction could activate the motor unit pool similarly. Nine subjects performed one trapezoidal isometric contraction of the leg extensors at 90 percent of measured maximal voluntary contraction strength and repeated 50% MVIC contractions to failure. Surface electromyography was recorded on the vastus lateralis. No differences were present between the final rep of 50% and the single rep at 90% MVC in EMG amplitude or the relationships between mean firing rate, action potential amplitude, and recruitment threshold. However, during the 90% contractions there were increased firing rates but similar action potential amplitudes in the motor unit pool in comparison to the final 50% MVC repetition. Finally, the 90% contraction experienced greater average and maximum action potential amplitudes. The authors concluded that this is evidence to suggest that moderate-intensity contractions to failure and high-intensity contractions do not produce the same neural drive.

2.2.4 Muddle et al., 2018

The purpose of this investigation was to determine differences in motor unit recruitment and firing behavior of the vastus lateralis between high and low-torque isometric contractions to failure. Volunteers included eighteen resistance-trained men completing both contraction intensities in a randomized order. Participants completed repeatedly tracked displayed torque trajectories at the prescribed intensity as many times as possible. Surface electromyography was collected on the vastus lateralis. The total work was similar between both completed intensities, but the lower torque contractions experienced longer time to task failure. Motor unit recruitment threshold was not related to time to task failure, and mean firing rates were greater during high torque contractions. On average, larger motor units were recruited during the high torque than low torque tracings, while recruitment threshold and motor unit recruitment decreased more significantly during the low torque visit. While higher threshold motor units were recruited in low torque exercise performed to failure, high torque contractions elicited greater recruitment of the largest motor units.

2.2.5 Murphy et al., 2021

The purpose of this study was to determine differences in motor unit recruitment during 70% and 30% of maximal voluntary isometric contraction strength during knee extension performed to momentary failure. Adult, resistance trained males volunteered to perform continuous isometric contractions at both 30% and 70% of determined MVC on the same visit day, separated by a rest of 20 minutes with MVC being performed before each condition. Participants maintained the targeted force until they were unable. Wavelet based analysis was completed via surface electromyography from the vastus lateralis, vastus medialis, and rectus femoris. The results showed that those who completed the 30% condition first maintained the contraction for 46% longer than when done after 70%. The 70% trial was, on average, 26% longer when done first. Wavelet analysis suggested that motor unit recruitment patterns were different between high and low-torque contractions. The intensity of the mean signal frequency was greater during 30% contractions for all muscles, suggesting that more motor units were recruited to continue torque production. However, a wider range of motor units were recruited during the high-torque contractions. The authors concluded that motor unit recruitment during these conditions may be similar as the highest threshold motor units are recruited, however with different recruitment patterns as the muscle fatigues.

2.2.6 Stock & Mota, 2017

The aim of this study was to observe differences in the slope and y-intercept of recruitment threshold versus decruitment threshold in the vastus lateralis motor units. Nine healthy, untrained men completed repeated contractions of the knee extensors at 50% of measured maximal voluntary contraction strength. At baseline, five of these subjects had a greater recruitment than derecruitment threshold while three had greater derecruitment thresholds than recruitment. However, as fatigue took place motor units fired and greater rates and this regression line experience decreased slope. The authors concluded that these changes in this relationship demonstrate motor unit adjustments necessary to maintain force as the muscle is fatigued.

2.2.7 Vila-Chã et al., 2012

The purpose of this study was to understand the effects of training on motor unit properties during fatiguing contractions of the knee extensors. Thirty men volunteered to participate and were randomized to one of three groups: a control group with no intervention, a strength training group, and an endurance training group. Training consisted of 18 total sessions across 6 weeks. The resistance training program consisted of leg press, leg extension, and leg curl for three to four sets of eight to fifteen repetitions. At baseline and after six weeks, participants completed maximal voluntary contractions and maintained a constant contraction at 10% of MVC for 70 seconds. They then performed an isometric hold at 30% MVC for as long as possible. Intramuscular and surface EMG were both recorded. After strength training, time to task failure did not increase but overall MVC strength increased. The decline in discharge rates of motor units was not impacted by any training. Training only exhibited an effect on conduction velocity in the higher force of 30% MVC. Conduction velocity reduced to a lesser extent over time after training when compared to before training. The authors concluded that the decline in motor unit conduction velocity during sustained fatiguing exercise could be reduced following training.

2.3 Sex Differences in Fatigue

2.3.1 Akagi et al., 2019

The purpose of this study was to determine if sex differences in muscle fatigability can be attributed to sex-based differences increases in the shear modulus of the knee extensors. Eighteen males and 23 females performed baseline maximal voluntary isometric contractions followed by a sustained contraction at 20% of MVC strength until the endurance limit. Surface electromyography was collected from the vastus lateralis, vastus medialis, and rectus femoris. Voluntary activation and evoked peak torque were also collected. There was no sex difference in time to task failure. However, males experienced a greater decline in peak torque following fatigue compared to females. When normalized to Mmax, RMS-EMG of the RF was greater before fatigue than after in men, with no difference in women. Men had greater Mmax at baseline than women for the VL. VM Mmax decreased similarly between males and females following fatigue. After fatigue, only male VL shear modulus was increased. Decreases in evoked torque were greater in males than females. The authors of the study concluded that sex differences in the fatiguability of the knee extensors are due to peripheral fatigue factors, especially within in the VL.

2.3.2 Albert et al., 2006

The purpose of this study was to understand sex differences in both upper and lower muscle fatigability and recovery during sustained isometric contractions.

Participants completed fatiguing exercise of the knee extensors, elbow flexors, or both. Force transducers were secured to the appropriate limb for all maximal voluntary isometric strength testing. Electrical stimulation and electromyography were completed via surface electrodes. The fatiguing bout required participants to maintain 50% of their tested isometric contraction strength for 30 seconds a total of 10 times, interspaced with 30s of rest. The interpolated twitch technique was performed during all maximal voluntary contractions, as well as during the peak and five seconds after relaxation of the repeated, submaximal contractions. This was also completed after the fatiguing bout had ended. No sex differences existed in upper or lower body mean root mean squared or mean median frequency EMG amplitude, nor in motor unit activation. However, males had greater force levels both pre- and post-fatigue in the upper and lower body. Despite this, peak twitch torque amplitude was greater in males than females at pre-, as well as 30- and 45-minutes post-fatigue. While males had greater evoked twitch during fatigue, they were still more fatigable when performing the task. The authors concluded that absolute force in males was greater than females, but the relative force during recovery was greater in females than males at all time points except for 30-minutes post-fatigue. Females were more fatigue resistant and were better able to maintain target force levels.

2.3.3 Ansdell et al., 2017

The purpose of this study was to investigate potential sex differences present when performing intermittent, fatiguing isometric contractions at the submaximal intensities of 30% and 50% of maximal voluntary isometric contraction strength for thirty minutes and until failure, respectively. Ten males and eight females performed both intensities randomized across two separate days. Following MVC attempts, participants performed the prescribed intensity while maintaining force for three seconds and resting for two, with an additional MVC attempt performed after every 60 seconds. Surface electromyography was recorded from the vastus lateralis. Males had greater target forces than females at both intensities. Males had a greater reduction in force following 30% contractions, as well as following the 50% task, despite having lesser time to task failure than females. EMG increases were similar between sexes in both conditions. However, the increase in root mean square EMG activity in females occurred at a slower rate during the 50% condition, given that females exercised for longer than males. The authors concluded that females are less fatigable at both 30% and 50%, and these sex differences could not be explained by absolute strength.

2.3.4 Ansdell et al., 2019

The purpose of this study was to determine differences in critical intensity during intermittent, isometric contractions of the knee extensors between males and females. Ten males and ten females performed four trials of knee extension between 40% and 80% of maximal voluntary isometric contraction strength to determine their critical intensity. Participants maintained target force for three seconds and rested for two, with electrical stimulation and an MVC attempt at each minute of the task, as well as additional measures at task failure. The force-impulse relationship was used to estimate participants' critical intensity and curvature constant to set the intensity of their fatiguing task. Participants completed isometric contractions of the knee extensors 10% above and below their determined critical intensity to failure, with MVC and electrical stimulation at the end of each minute. Females had a greater time to task failure than males during the contractions above critical intensity, while all participants were stopped at the cutoff of 45 minutes for subcritical intensity. However, females also demonstrated a greater relative critical intensity than males. Males had greater impairment of contractile function after fatigue and had greater deoxygenation during exercise. The authors concluded that females experienced greater resistance to fatigue even while adjusting for critical intensity rather than maximum force.

2.3.5 Clark et al., 2005

The primary purpose of this study was to determine sex differences in the fatigability and neuromuscular activation patterns of the quadriceps femoris. Surface electromyography was recorded at the vastus lateralis, vastus medialis, rectus femoris, and biceps femoris. Maximal strength of both the knee flexors and extensors was measured. Following this, target force for the fatiguing task was calculated as 25% of maximal force. Participants followed a solid line at 25% of maximal force for as long as possible. The coefficient of variation in force was calculated for the first-, middle-, and last-third of the fatiguing bout. Root mean squared was calculated for electromyography. Males were significantly stronger than females, but females experienced a 21% greater time to task failure than males. At task failure, females had a greater amplitude of EMG activity of the rectus femoris than males by nearly 40%. When pooled, females had overall greater muscle activation at failure than males. While both males and females had an increase in force fluctuation during the last third of the fatiguing task, females had greater coefficient of variation in force fluctuation than males during this phase. The authors concluded that females could better recruit the rectus femoris with fatigue than males, while simultaneously being more fatigue resistant and experiencing greater force fluctuations when approaching failure than males.

2.3.6 Dearth et al., 2010

The purpose of this investigation was to determine sex differences in time to task failure of a sustained isometric contraction of the elbow extensors. Participants completed maximal strength testing of the elbow flexors to determine 15% of their strength to be used as the fatiguing task target force. Surface electromyography was obtained from the triceps brachii during all contractions. Electrical stimulation was delivered to the brachial plexus, as well as supraspinal via transcranial stimulation, measuring both maximal stimulation and motor evoked potential for all participants. Participants then sustained an isometric contraction at the target force of 15% for as long as possible. Nerve stimulation and TMS were delivered periodically during the fatiguing task, as well as during recovery. While men were stronger than women, there was no difference in time to task failure and similar decrease in force following fatigue. Maximal electrical stimulation was larger in men as well. No sex differences were present at baseline nor during the fatiguing task for motor evoked potential. The authors concluded these findings to suggest that no sex differences in fatigue are present for the elbow extensors.

2.3.7 Ha et al., 2021

The purpose of the present investigation was to determine what, if any, sex differences are present during fatigue and recovery following both isometric and isotonic contractions of the plantar flexors. Twelve males and fourteen females performed maximal voluntary isometric contractions with their dominant foot secured to a footplate. Following this, they performed a two-minute sustained MVIC for the isometric protocol or 120 isotonic contractions at 30% MVIC randomized across two testing days. Surface electromyography was collected from the medial gastrocnemius and soleus. Post-testing included an MVIC and five maximal isotonic contractions immediately, as well as 2.5, 5, and 10 minutes after exercise. Males experienced greater decrease in rate of EMG rise in the medial gastrocnemius during isotonic contractions and faster recovery after isometric contractions than females. Otherwise, no sex differences were present. The authors concluded that sex differences may be less significant in muscles such as the plantar flexors as minimal sex differences were detected.

2.3.8 Hunter, Critchlow, et al., 2004

The purpose of this study was to determine differences in time to task failure between males and females when completing intermittent submaximal contractions of the elbow flexors. 10 males and 10 females with similar physical activity levels were strength-matched for analysis after completing maximal voluntary isometric contraction of the elbow flexors. Surface electromyography was recorded from the biceps brachii long and short heads, as well as the triceps brachii and brachioradialis. MVCs were completed three times for the elbow flexors, followed by the extensors. The fatiguing task consisted of six seconds at 50% of MVC strength, followed by four seconds of rest until the subject could no longer maintain this force. An additional MVC was completed each minute within the fatiguing protocol. An MVC was completed every minute for three minutes when the fatiguing task ended. Male MVC torque declined more rapidly during the fatiguing task. Time to task failure was significantly longer in females. Menstrual cycle was not seen to alter time to task failure in females. Average rectified EMG increased more quickly in males and was greater at the time of task failure than females. The authors concluded that the difference in time to task failure between sexes must be due, not to strength, but other mechanisms. At task failure, males required a greater amount of the motorneuron pool to maintain torque production.

2.3.9 Hunter et al., 2006

The purpose of this study was to determine mechanisms of sex differences during sustained isometric voluntary contraction of the elbow flexors. Eight women and nine men completed isometric strength testing of the elbow flexors with a linear strain gauge. Participants were electrically stimulated at the brachial plexus and transcranially. Surface electromyography was measured at both the biceps and triceps brachii. Prior to the fatiguing bout, the maximal potential of the biceps and triceps was measured, as well as motor evoked potentials of the muscles. Transcranial magnetic stimulation (TMS) was delivered at contractions of 60% and 80% of maximal strength before and after fatigue. Following this, maximal contractions lasting 22s were repeated a total of 6 times with 10s of rest separating each contraction. During the rest periods, brief contractions were performed at 60% and 80% of maximal strength during which TMS was again delivered. Contractions were also performed during a recovery period lasting ten minutes after the fatiguing protocol. Voluntary activation was calculated from the superimposed twitches frequently delivered during both fatigue and recovery. Males had greater strength but recovered more slowly following the fatiguing contractions. Male and female superimposed twitches were similar during the fatiguing bout, as well as during recovery. Voluntary activation decreased during fatigue and increased during recovery in a similar manner in both men and women. Men experienced greater decreases in resting twitch amplitude during fatigue. The authors concluded that females were less fatigable than males, while having lower absolute strength. However, voluntary activation changes were similar between sexes. Men experienced greater peripheral fatigue, while at the supraspinal level, males and females experienced similar changes.

2.3.10 Inglis & Gabriel, 2021

The purpose of this investigation was to understand sex differences in the variability of motor unit discharge and its impact on force steadiness. Electromyography was measured with intramuscular needles while participants performed three maximal voluntary isometric contractions of the dorsiflexors. Following this, they completed submaximal contractions at 20, 40, 60, and 80% of MVIC for eight seconds each. Females had a greater variability in motor unit discharge than males. Females also had a greater variation in force than males. Males had more steadiness when contractions ranged from 60 to 80% of MVIC, while females were less steady at the lower and higher ends of submaximal contractions. The authors concluded that these differences may occur at the neural level to compensate for muscular differences between males and females.

2.3.11 Parra et al., 2020

The purpose of this study was to determine sex differences in motor unit behavior during submaximal contractions of 10% and 70% of maximal contraction strength in the first dorsal interosseous muscle. Eleven males and twelve females performed three maximal voluntary isometric contractions to set target force. Participants then completed one 10% and one 70% MVIC trapezoidal tracings in a randomized order. Surface electromyography was recorded from the first dorsal interosseous. Cross sectional area was also measured via ultrasonography. Y-intercepts of the mean firing rate versus recruitment threshold were greater for females than males during 70% MVC contractions. Females also had greater initial firing rates than males during 70% contractions. Males had greater initial MVIC strength and greater cross-sectional area. The authors concluded that sex differences in action potential amplitude were due to the recruitment threshold and the intensity of the contraction. Because low threshold motor units were similar sized in males and females unlike higher threshold motor units, differences in action potential amplitude may explain differences in motor unit control to maintain high- versus low-intensity contractions.

2.3.12 Senefeld et al., 2018

The purpose of this study was to determine if sex differences surrounding fatigability during dynamic and isometric knee extension could be explained by supraspinal mechanisms. Fourteen males and seventeen females completed maximal voluntary isometric contractions of the leg extensors, followed by baseline electrical stimulation of the femoral nerve. Superimposed stimulations from TMS and femoral stimulation were delivered to measure voluntary activation. A minute long sustained isometric contraction was performed with TMS delivered during the maximal contraction. MVICs were also performed immediately after and through 10 minutes post. The dynamic task involved 120 fast-velocity concentric contractions at 20% of MVIC.

There were no differences between male and female torque during the isometric task, but males had greater reductions in torque than females during both isometric and dynamic tasks. Voluntary activation was lower in males than females following the isometric task. Resting twitch decreased to a greater extent in males than females following dynamic exercise. The authors concluded that the increased fatiguability in males was due to supraspinal factors. However, fatigue mechanisms are task specific as the slower recovery in males after the dynamic task was due to contractile fatigue.

2.3.13 Solianik et al., 2017

The purpose of the present study was to compare age and sex differences in central and peripheral fatigue following sustained maximal isometric knee extension. Both young and older adults of both sexes completed an identical fatiguing task. At baseline, following placement of surface electromyography electrodes on the right quadriceps femoris, an electrical stimuli train was delivered directly to the muscle to determine stimulated peak torque. Participants completed two baseline maximal voluntary isometric contractions with a superimposed twitch. The fatiguing task of a 120-s maximal isometric hold was completed with superimposed twitches delivered roughly every 30 seconds of the contraction. Five minutes later, post-testing was conducted via an additional stimuli train and an MVC attempt with a superimposed stimulus. Decline in torque was greater in males than females. Regardless of age, males were more fatigable than females. At the five-minute post-task mark, torque had not recovered in either sex. Central activation ratio was measured and experienced no sex-related decline. No sex difference was found in root mean squared EMG of the quadriceps femoris. The decline in twitch response by peripheral stimulation was greater in males at both intensities of 20 and 100 Hz. The recovery of MVC strength was associated most with the recovery of stimulation at 20 Hz. The authors therefore concluded that males experienced more peripheral fatigue than females and recovery of torque in young adults was based primarily on peripheral factors.

2.3.14 Wüst et al., 2008

The purpose of this study was to determine fatigue susceptibility differences between men and women following electrical stimulation of fatigue. Thirty-five women and 29 men volunteered for quadricep cross sectional area scans via MRI. Next, participants completed maximal voluntary isometric contractions of the knee extensors at three randomized knee joint angles. The interpolated twitch technique was used to assess voluntary activation via electrical stimulation to the quadriceps. The fatigue protocol involved evoked isometric contractions of the quadriceps at a pattern of one second on, one second off for 60 contractions. No sex differences were present in voluntary activation at baseline. Female musculature contracted at a slower rate than males following stimulation at 30 Hz, as measured by relaxation rate. Males experienced a greater decrease in torque following fatigue. An additional fatigue test was performed in which recovery time was decreased to 0.5 seconds. This caused the onset of fatigue to occur sooner, as well as the sex difference becoming apparent more quickly. Additionally, the individuals with larger and stronger muscles tended to fatigue more quickly. The authors concluded that men are less fatigue resistant than females, even when matched with physical activity level and age. The authors attributed this difference in fatigue resistant to peripheral factors.

2.3.15 Yacyshyn et al., 2018

The purpose of this study was to investigate sex differences in central fatigue and motorneurons in the elbow flexors and extensors after a sustained maximal contraction. Participants received electrical stimulus to the brachial plexus to assess peripheral excitability. Additionally, stimulation was delivered to the muscle belly of both the biceps and triceps brachii. Transcranial magnetic stimulation was used to determine motor cortex excitability. The fatiguing task consisted of a sustained, two-minute MVC of the elbow flexors or extensors, while electrical stimulation was delivered via a rotating pattern of muscle belly stimulation brachial plexus stimulation, TMS, and cervicomedullary stimulation were delivered in fifteen second intervals until reaching 118 seconds. Females had lower reductions in torque following fatigue when compared to males. Females had higher voluntary activation than males after the fatiguing task of the elbow flexors. The authors concluded that this investigation did not provide evidence to suggest that sex differences following fatigue will alter the behavior of Group III/IV afferents differently in men and women.

CHAPTER III

METHODOLOGY

3.1 Experimental Design

This study utilized a randomized, counterbalanced, within-subjects design to compare the effects of high- (HT) and low-torque (LT) fatiguing exercise on neuromuscular properties of the knee extensors between males and females. All participants completed a familiarization session followed by 2 experimental sessions that consisted of repeated, intermittent, isometric contractions at either 70% (HT) or 30% (LT) of their maximum voluntary isometric contraction (MVIC) strength. Each visit was separated by at least 48 hours and completed at the same time of day (±1 h). The first visit was comprised of a familiarization day in which participants arrived to the laboratory following a fast of, at minimum, eight hours, including abstaining from alcohol, tobacco, and caffeine. Participants were allowed to drink water ad libitum and were asked to refrain from any exercise for 48 hours prior to the visit. Participants completed an informed consent, as well as questionnaires regarding their health history, physical activity, and menstrual cycle (if applicable) and the necessary paperwork to complete a Dual-Energy X-ray Absorptiometry (DEXA; Hologic Inc., Marlborough, MA, USA) scan. Participants' height and weight were measured prior to DEXA scan completion. Following a three-minute warm-up on a stationary bike, sensors were placed on the participants' vastus lateralis (VL) and vastus medialis (VM), with each location marked in semi-permanent ink for future placement. Participants were then seated in a calibrated isokinetic dynamometer (Biodex System 3, Biodex Medical Systems, Shirley, NY, USA), where they completed three warm-up contractions each at 25, 50, and 75% of their perceived maximum strength.

The remaining two visits were experimental visits in which participants arrived to the laboratory following a four hour fast and having refrained from lower body exercise for 48 hours prior. Surface electrodes were placed in previously marked locations, and participants completed a three-minute bike warmup and warmup contractions in the dynamometer (as described previously). Following the warmup, participants completed two maximal MVICs to determine their target torque and baseline strength. Voluntary activation (VA) was determined via the interpolated twitch technique (ITT). Following baseline testing and a five-minute rest period, the fatiguing protocol began. Participants were instructed to follow trapezoidal contractions lasting 20 seconds, with a 3 second inactive period prior to and following each contraction. Contractions were repeated until the participant could no longer maintain force within 5% of the target. Immediately following failure, VA and MVIC strength were completed to measures changes due to the fatiguing task. The final experimental visit was identical to the first, with the participant completing the alternate condition.

3.2 Participants

Twenty-four young, recreationally-active adults (12 males & 12 females) were recruited to participate in the investigation. Volunteers were considered recreationally-active if they participated in regularly structured exercise for at least 30 minutes twice per week for the previous 6 months. All participants were healthy and free of any neuromuscular or musculoskeletal injuries. Additionally, participants were excluded if they had any known metabolic disorders or diseases, had any relative or absolute contraindications to exercise described by the American College of Sports Medicine, consumed any supplement with ergogenic effect in the two weeks prior to collection, or regularly consumed any heart, pulmonary, thyroid, anti-hyperlipidemic, hypoglycemic, anti-hypertensive, endocrinologic (e.g, thyroid, insulin, etc), neuromuscular/neurological, or androgenic medications (anabolic steroids). Participants abstained from any exercise 48 hours prior to the familiarization session and any lower body exercise 48 hours prior to experimental sessions 1 and 2. Additionally, participants were asked to arrive to the laboratory following an 8-hour fast and 4 hour-fast for the familiarization session and experimental sessions, respectively. All experimental procedures were thoroughly explained prior to enrollment and signing of the Informed Consent. This protocol followed the standards of the Declaration of Helsinki and was approved by the University of South Alabama's Institutional Review Board, Radiation Safety Committee, and the State of Alabama Department of Public Health prior to any testing.

3.3 Isometric Testing

Isometric strength testing was completed with participants seated in a calibrated isokinetic dynamometer (Biodex System 3, Biodex Medical Systems, Shirley, NY, USA) while secured with straps across the chest and waist to avoid additional movement. The distal portion of the participant's leg, approximately 3cm above the medial malleolus of the right ankle, was secured to the arm of the dynamometer with the knee and hips at 90^{o} and 105^{o} of flexion, respectively. All dynamometer settings were recorded and held constant throughout all testing visits for each participant. Once seated and secured, participants completed 3 warm-up contractions at 25, 50, and 75% of their perceived maximal effort (Tomko et al., 2018). Following a brief rest, participants complete two 3-5 s. MVICs separated by 60 s. of rest. Participants were instructed to kick out as hard as possible with real-time feedback of their torque output displayed on a television monitor approximately 2 meters from the dynamometer. Strong verbal encouragement was provided to ensure maximum effort possible from the participant. The 0.50 s. epoch with the highest torque was recorded as their maximum torque (TQ_{MAX}). Following the fatiguing bout, one final MVIC was completed.

3.4 Interpolated Twitch Technique (ITT)

After isometric testing and an additional minute of rest, VA was assessed via ITT, in which a maximal electrical stimulus was administered to the femoral nerve via anode-cathode configuration (Sierra Summit, Cadwell Industries Inc, Kennewick, WA, USA) before, during, and 3-5 s. after the force plateau of an additional MVIC. During each visit, the optimal current was found by progressively increasing the stimulus until there was no longer a visible increase in the maximal m-wave at rest. The current was then recorded and utilized for the duration of the visit. VA was estimated from the superimposed and potentiated twitches as (1-[superimposed twitch/potentiated twitch])*100 (Behm et al., 1996). This was repeated following the fatiguing bout to detect changes in VA.

3.5 Fatiguing Exercise Bouts

Participants completed intermittent, isometric high-torque (HT) and low-torque (LT) fatiguing bouts. The order of conditions was randomized and counterbalanced within each sex. Participants completed 'trapezoidal' isometric contractions ramping up at 10% MVIC per second up to a torque plateau at the intended intensity. Contractions were time-matched, with each contraction lasting a total of 20 seconds. Thus, the torque plateaus were 6 s. and 14 s. for the HT and LT conditions, respectively. Six seconds of rest was given between each contraction. Participants completed trapezoidal contractions to failure, defined as the inability to maintain force within 5% of the targeted intensity during the torque plateau.

3.6 Surface Electromyography

Specialized, pre-amplified surface electromyographic (EMG) sensors (Delsys Trigno Galileo Sensor, Natick, MA) were placed on the VL and VM muscles of the participant's right leg to record EMG signals at the surface of the skin during all evoked and voluntary contractions. All sensors were placed in accordance with the recommendations of Zaheer and colleagues (Zaheer et al., 2012). A reference electrode was placed on the skin near the muscle of interest in accordance with the manufacturer's recommendations. To reduce inter-electrode impedance and increase the signal-to-noise ratio (De Luca & Contessa, 2012), local areas of the skin were shaved, abraded, and cleaned with isopropyl alcohol prior to the placement of the electrodes.

3.7 Signal Processing

EMG and torque signals were recorded during all evoked and voluntary testing. The EMG and torque signals were sampled simultaneously at 2222 Hz via a Delsys Trigno Acquisition Base System (Delsys Inc., Natick, MA, USA), recorded on a personal computer, and processed off-line with custom-written software (Labview v.2020, National Instruments, Austin, TX, USA). The EMG signals were amplified (x1000), zero-meaned, and digitally band-pass filtered with a zero-phase shift, 4^{th} order Butterworth filter using a band-pass of 10–499 Hz. The force signals were low-pass filtered (zero-phase shift 4th-order Butterworth filter) with a 15 Hz cutoff. All subsequent analyses were completed on the filtered and scaled signals. The EMG amplitude, quantified as the root mean square (RMS), was calculated for each muscle (VL_{AMP} and VM_{AMP}, respectively). During the fatiguing bouts, EMG amplitude of the VL and VM was normalized to MVIC (%MVIC). During the voluntary MVICs, VL_{AMP} and VM_{AMP} values were calculated from the 500 ms epoch corresponding to the MVIC plateau. Peak twitch torque was determined from the torque signal as the greatest average 5 ms torque value following the initial (PTT) and final (pPTT) doublet stimuli delivered during the %VA assessment. The total muscle excitation was quantified by summing the integrated EMG (iEMG) signal for each muscle across each fatiguing bout. The total work performed during the fatiguing protocol was quantified by summing the total torque impulse (TQ_{IMP}) from all repetitions in each condition. Additionally, the mean torque (TQ_{MEAN}) and coefficient of variation (TQ_{CV}) during the plateau of each repetition was calculated.

3.8 Statistical Analysis

To assess pre- and post-exercise changes in MVIC, VA, and PTT, three separate 2 (HT vs. LT) × 2 (PRE vs. POST) × 2 (M vs. F) repeated measures analysis of variance (ANOVA) analyses were run. VL_{AMP} and VM_{AMP} were assessed via a 2 (HT vs. LT) × 2 (VL vs. VM) × 2 (PRE vs. POST) × 2 (M vs. F) repeated measures ANOVA.

Separate 2 (HT vs. LT) × 4 (FIRST vs. MIDDLE vs. LAST vs. FAILURE) × 2 (M vs. F) repeated measures ANOVAs were run to examine TQ_{MEAN} and TQ_{CV} across the fatiguing bouts. Normalized VL_{AMP} and VM_{AMP} were assessed by a 2 (HT vs. LT) × 2 (VL vs. VM) × 4 (FIRST vs. MIDDLE vs. LAST vs. FAILURE) × 2 (M vs. F) repeated measures ANOVAs. Total work (repetitions completed and TQ_{IMP}) was assessed via separate 2 (HT vs. LT) × 2 (M vs. F) repeated measures ANOVAs. Total muscle excitation (i.e., iEMG) was analyzed via a 2 (HT vs. LT) × 2 (VL vs. VM) × 2 (M vs. F) repeated measures ANOVA.

For all ANOVA analyses, significant interactions were decomposed with follow-up, lower order ANOVAs, and/or Bonferroni-corrected dependent- and independent-samples t-tests on the simple main effects. Estimated marginal means were analyzed for variables not involved in significant interactions. Partial eta squared was calculated when appropriate. All ANOVAs, Bonferroni-corrected t-tests, and partial eta squared effect sizes were calculated using IBM SPSS Statistics (Version 27; IBM, Inc., Armonk, NY, USA). The alpha level for all tests was set a priori at $p \leq 0.05$.

CHAPTER IV

RESULTS

All data is presented as Mean ± standard deviation unless noted otherwise. Only significant interaction and main effects are discussed. Descriptive characteristics of the subjects are displayed below in Table 1.

Table 1. Baseline descriptive characteristics and body composition of subjects. *Indicates significant difference between sexes ($p < 0.05$).

	Females (n = 12)	**Males (n = 12)**	**P-value**
Age (y)	20.8 ± 1.9	22.0 ± 1.9	0.147
Height (cm)	167.1 ± 5.4	173.8 ± 7.4	0.018*
Weight (kg)	70.3 ± 12.0	82.3 ± 13.8	0.034*
Fat Free Mass (kg)	44.98 ± 5.31	60.7 ± 7.97	< 0.001*
Fat Mass (kg)	25.36 ± 9.07	21.62 ± 8.14	0.300
Fat Mass (%)	35.2% ± 7.6%	25.6% ± 6.5%	0.003*
Right Leg Fat Free Mass (kg)	7.11 ± 1.09	9.50 ± 1.46	< 0.001*
Right Leg Fat Mass (kg)	4.97 ± 1.83	3.53 ± 1.29	0.037*
Right Leg Fat Mass (%)	39.0% ± 7.5%	25.5% ± 6.6%	< 0.001*

4.1 Pre- and Post-Fatigue Assessments

4.1.1 Maximal Voluntary Isometric Contraction (MVIC) Strength

There was no significant three-way interaction effect for MVIC strength ($p = 0.172$). There were significant interaction effects for both Condition × Time ($F_{1,22} = 56.1$; $p < 0.001$; $\eta^2 = 0.72$) and Sex × Time ($F_{1,22} = 7.0$; $p = 0.015$; $\eta^2 = 0.24$). When collapsed across sex, post-hoc analyses indicated that MVIC was significantly greater at LT_{PRE} (227.2 ± 69.7 N·m) when compared to HT_{PRE} (217.5 ± 69.4 N·m; $p = 0.050$) and LT_{POST} (133.4 ± 45.9 N·m; $p < 0.001$). The differences observed in MVIC strength are presented in Figure 1 below. Additionally, MVIC was significantly greater at HT_{PRE} when compared to HT_{POST} (155.9 ± 45.9; $p < 0.001$). MVIC was also significantly lower at LT_{POST} when compared to HT_{POST} ($p < 0.001$; Figure 1). When collapsed across condition, males had significantly greater MVIC strength than females at both PRE (M: 263.2 ± 48.5 N·m; F: 181.5 ± 62.0 N·m; $p = 0.002$) and POST (M: 169.3 ± 29.9 N·m; F: 120.0 ± 42.5 N·m; $p = 0.003$). However, MVIC decreased from PRE to POST for both males and females ($p < 0.001$ for both).

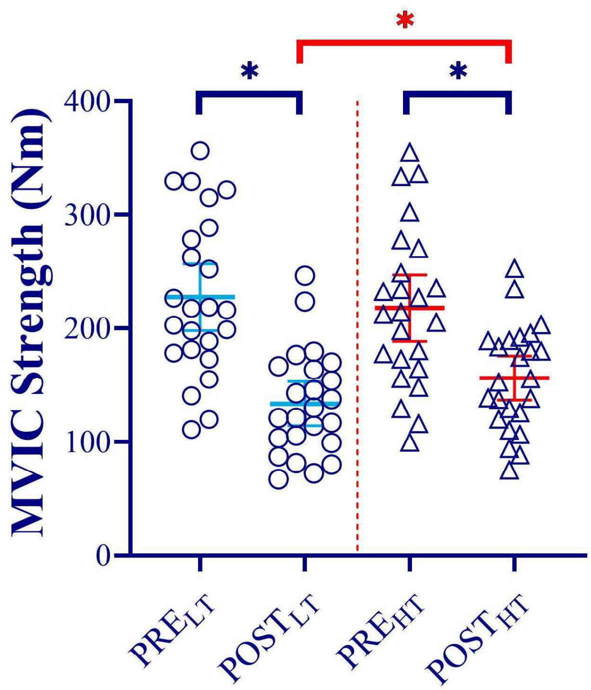

Figure 1. Individual and mean (±95% CIs) MVIC values prior to and immediately following exercise in the low torque (LT) and high torque (HT) conditions. *Denotes significant difference between time points ($p<0.05$)

4.1.2 Peak Twitch Torque (PTT)

There was no significant three-way interaction effect for PTT ($p = 0.861$). There were significant interaction effects for both Condition × Time ($F_{1,21} = 9.5$; $p = 0.006$; $\eta^2 = 0.31$) and Sex × Time ($F_{1,21} = 14.0$; $p = 0.001$; $\eta^2 = 0.40$). Post-hoc analyses indicated that, when collapsed across sex, PTT significantly declined from LT_{PRE} (72.9 ± 23.4 N·m) to LT_{POST} (34.1 ± 15.8 N·m; $p < 0.001$), and from HT_{PRE} (63.1 ± 29.5 N·m) to HT_{POST} (36.3 ± 16.8 N·m; $p < 0.001$) as presented below in Figure 2. When collapsed across condition, males had significantly greater PTT than females at PRE (M: 81.6 ± 21.0 N·m;

F: 53.2 ± 12.7 N·m; p = 0.001). PTT significantly decreased from PRE to POST in both males (40.2 ± 11.8 N·m) and females (29.7 ± 12.8 N·m; p < 0.001 for both).

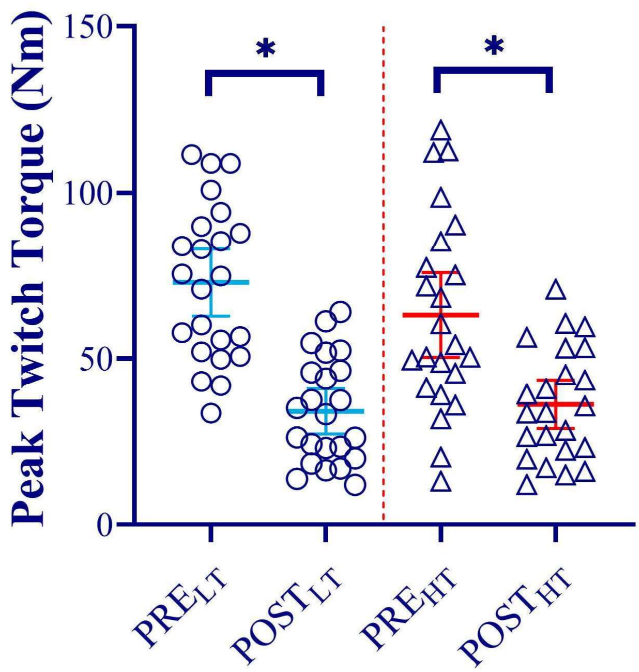

Figure 2. Individual and mean (±95% CIs) PTT changes prior to and immediately following low- (LT) and high-torque (HT) exercise.
*Denotes significant difference between time points (p<0.05).

4.1.3 Voluntary Activation (VA)

There was no significant three-way interaction effect for VA (p = 0.299). There was a significant interaction effect for Condition × Time ($F_{1,22} = 6.5$; p = 0.018; $\eta^2 = 0.23$). Post-hoc analysis indicated that, when collapsed across sex, VA significantly decreased from LT_{PRE} (93.7 ± 7.1%) to LT_{POST} (86.4 ± 15.0%; p = 0.014). Additionally, VA was greater at HT_{POST} (93.0 ± 7.7%) than LT_{POST} (p = 0.050) as depicted below in Figure 3.

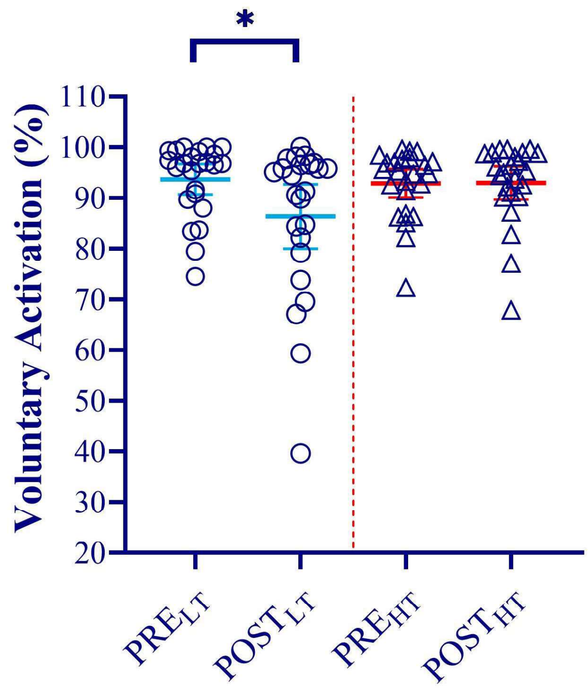

Figure 3. Individual and mean (±95% CIs) VA changes prior to and immediately following low-(LT) and high-torque (HT) contractions.
*Denotes significant differences between time points (p<0.05).

4.1.4 VL (VL_{AMP}) and VM (VM_{AMP}) EMG Amplitude during MVIC

There were no significant four-way (p = 0.239) or three-way interaction effects (p = 0.191-0.689) for VL_{AMP} or VM_{AMP}. There was a significant Muscle × Sex interaction effect ($F_{1,22} = 7.0$; p = 0.015; $\eta^2 = 0.24$). Post-hoc analyses indicated that, when collapsed across time and condition, both VL_{AMP} and VM_{AMP} were significantly greater in males

(VL: 0.11 ± 0.03 μV VM: 0.22 ± 0.11 μV) than females (VL: 0.07 ± 0.02 μV, $p = 0.003$; VM: 0.09 ± 0.04 μV; $p = 0.002$). Additionally, males had greater VL_{AMP} than VM_{AMP} ($p = 0.004$). There was a significant main effect for Time ($F_{1,22} = 4.6$; $p = 0.043$; $\eta^2 = 0.17$). When collapsed across muscle, sex, and condition, EMG amplitude decreased from PRE (0.13 ± 0.07 μV) to POST (0.12 ± 0.06 μV; $p = 0.039$).

4.2 Measures during Fatiguing Task

4.2.1 Mean Torque (TQ_{MEAN})

There was no significant three-way interaction effect for TQ_{MEAN} ($p = 0.128$). There were significant interaction effects for Sex × Time ($F_{1.3,24.2} = 4.0$; $p = 0.048$; $\eta^2 = 0.17$), Condition × Sex ($F_{1,19} = 10.2$; $p = 0.005$; $\eta^2 = 0.35$), and Condition × Time ($F_{1.3,24.8} = 20.2$; $p < 0.001$; $\eta^2 = 0.52$). Post-hoc analyses indicated that when collapsed across condition, males had significantly greater TQ_{MEAN} than females at all timepoints ($p = 0.003$-0.004). In males, TQ_{MEAN} was significantly different at all timepoints ($p = 0.001$-0.042), aside from the FIRST and MID repetitions ($p = 0.597$). There were no significant differences between any timepoints in females ($p = 0.082$-0.533).

When collapsed across time, both males and females exhibited greater TQ_{MEAN} during HT (M: 168.2 ± 26.8 N·m; F: 114.6 ± 41.0 N·m) when compared to LT (M: 76.0 ± 13.2 N·m; F: 53.3 ± 18.6 N·m; $p < 0.001$ for all). Additionally, males exhibited significantly greater TQ_{MEAN} than females during both conditions ($p < 0.001$ for all).

When collapsed across sex, TQ_{MEAN} was significantly greater during HT than LT at all timepoints ($p < 0.001$). TQ_{MEAN} was significantly lower at LT FAIL (62.6 ± 18.8 N·m) than all other LT timepoints ($p = 0.002$-0.003). TQ_{MEAN} was significantly lower at

HT FAIL (131.2 ± 39.1 N·m) than at all other HT timepoints ($p < 0.001$ for all). During the HT condition, both the FIRST (148.1 ± 46.9; $p = 0.003$) and MID (147.5 ± 47.9 N·m; $p = 0.002$) reps were significantly greater than LAST (143.9 ± 45.4 N·m).

4.2.2 Torque Coefficient of Variation (TQ_{CV})

There were no significant three-way ($p = 0.384$) or two-way ($p = 0.658$-0.198) interaction effects for TQ_{CV}. There were significant main effects for both Condition ($F_{1,19} = 6.6$; $p = 0.019$; $\eta^2 = 0.26$) and Time ($F_{1.1,21.4} = 17.1$; $p < 0.001$; $\eta^2 = 0.47$). When collapsed across time and sex, LT (5.89 ± 4.28%) had significantly greater TQ_{CV} than HT (4.43 ± 3.94%; $p = 0.019$). When collapsed across condition and sex, the FAIL rep (8.79 ± 6.33 %) had significantly greater TQ_{CV} than all other timepoints ($p = 0.002$-0.011). Further, the LAST repetition (5.04 ± 2.25%) had significantly greater TQ_{CV} than both FIRST (3.24 ± 1.23%; $p < 0.001$) and MID (3.58 ± 1.60%; $p = 0.002$) repetitions.

4.2.3 VL (VL_{AMP}) and VM (VM_{AMP}) EMG Amplitude during Torque Plateau

There were no significant four-way ($p = 0.810$) or three-way interaction effects ($p = 0.188$-0.594) for VL_{AMP} or VM_{AMP}. There was a significant interaction effect for Condition × Muscle ($F_{1,19} = 4.4$; $p = 0.049$; $\eta^2 = 0.19$). Post-hoc analyses indicated that, when collapsed across sex and time, both VL_{AMP} and VM_{AMP} were significantly greater during HT (VL: 102.7 ± 25.3%; VM: 95.9 ± 16.9%) than LT (VL: 50.4 ± 16.7%; VM: 54.9 ± 22.4%; $p < 0.001$ for both), illustrated below in Figure 4. There were no differences between muscles within the condition ($p = 0.220$-0.319). There was a significant main effect for both Time ($F_{1.4,26.3} = 31.5$; $p < 0.001$; $\eta^2 = 0.62$). Post-hoc analyses indicated that when collapsed across condition, muscle, and sex, all timepoints significantly differed ($p < 0.001$-0.001), with the exception of the LAST (86.17 ± 35.64%) and FAIL repetitions (86.73 ± 35.92%, $p = 0.999$).

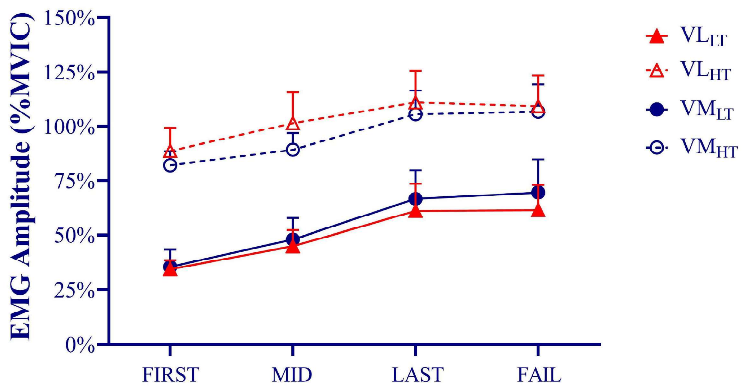

Figure 4. Mean (±95% CIs) changes of VL and VM EMG amplitude during plateaus of FIRST, MID, LAST, and FAIL repetitions during low-(LT) and high-torque (HT) contractions.
*Denotes significant differences between time points (p<0.05).

4.3 Characteristics of Fatiguing Task

4.3.1 Torque Impulse (TQ_{IMP})

There was no two-way interaction effect for TQ_{IMP} ($p = 0.171$). There was a main effect for Condition ($F_{1,19} = 26.2$; $p < 0.001$; $\eta^2 = 0.58$). Post-hoc analyses indicated that, when collapsed across sex, LT (55820.78 ± 40685.08) had higher TQ_{IMP} than HT (17510.16 ± 12814.70; $p < 0.001$), depicted in Figure 5 below.

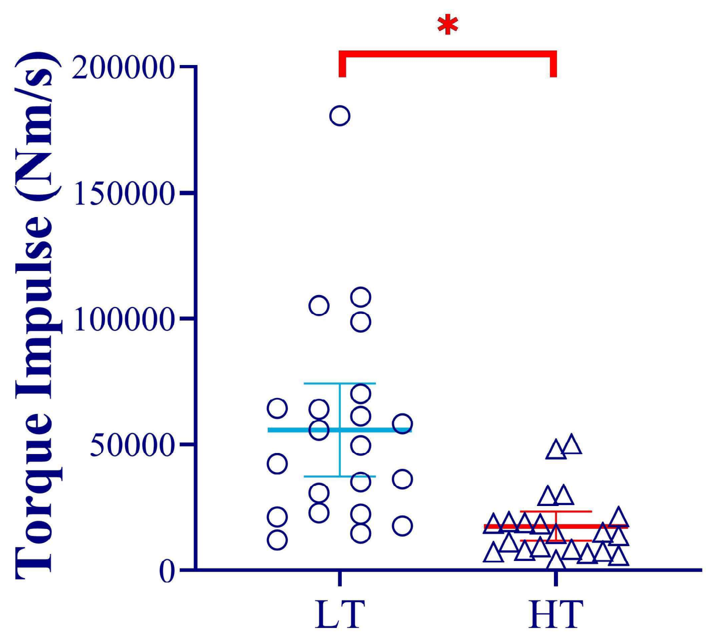

Figure 5. Individual and mean (±95% CIs) torque impulse resulting from low- (LT) and high-torque (HT) contractions.
*Denotes significant differences between conditions (p<0.05).

4.3.2 Repetitions Completed

There was a significant Condition × Sex interaction effect for repetitions completed ($F_{1,19} = 5.1$; $p = 0.036$; $\eta^2 = 0.21$). Post-hoc analyses indicated that more repetitions were completed at LT than HT in both males (LT: 38.0 ± 30.2 repetitions; HT: 7.5 ± 4.0 repetitions; $p = 0.006$) and females (LT: 79.9 ± 50.5 repetitions; HT: 12.1 ±

12.8 repetitions; $p = 0.001$). Further, females completed more repetitions than males during LT ($p = 0.031$), but not HT ($p = 0.275$). Differences in repetitions completed are depicted below in Figure 6.

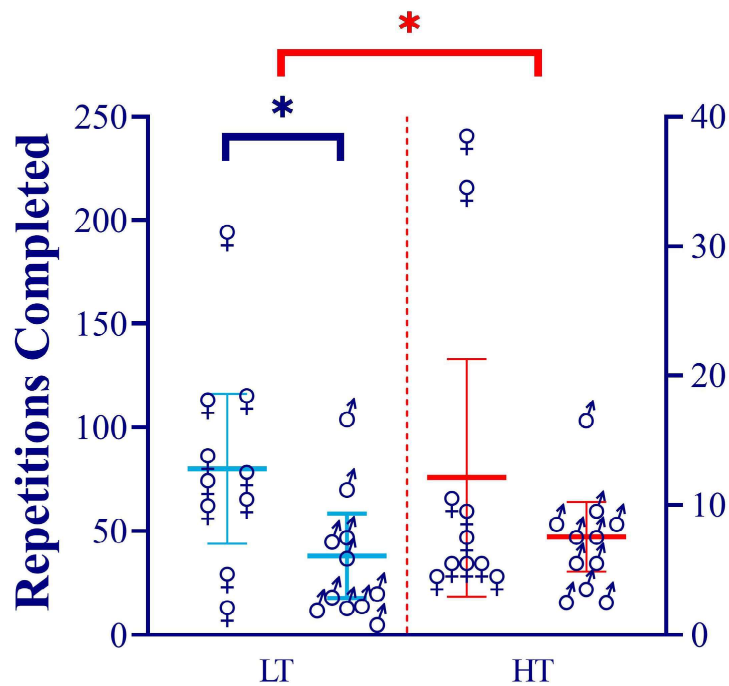

Figure 6. Mean (±95% CIs) repetitions completed during low- (LT) and high-torque (HT) fatiguing tasks.
*Denotes significant differences between conditions and sexes ($p<0.05$).

4.3.3 Vastus Lateralis (VL_{iEMG}) and Vastus Medialis (VM_{iEMG}) Integrated Electromyography

There was no three-way interaction effect for VL_{iEMG} or VM_{iEMG} ($p = 0.382$). There was a significant interaction effect for Condition × Muscle ($F_{1,19} = 6.8$; $p = 0.017$;

$\eta^2 = 0.26$). Post-hoc analyses indicated that, when collapsed across sex, both VL_{iEMG} and VM_{iEMG} were significantly greater in LT (VL: 28.3 ± 19.6 µV; VM: 43.3 ± 34.3 µV) than HT (VL: 7.9 ± 7.1 µV; VM: 11.4 ± 12.1 µV; $p < 0.001$ for both). VM_{iEMG} was significantly greater than VL_{iEMG} during both HT ($p = 0.040$) and LT ($p = 0.006$) contractions, as depicted below in Figure 7.

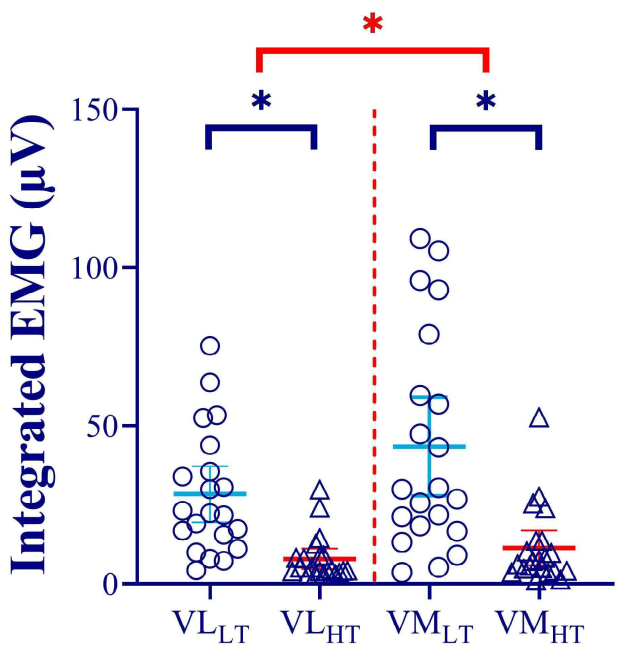

Figure 7. Individual and mean (±95% CIs) iEMG of the VL and VM resulting from low- (LT) and high-torque (HT) contractions.
*Denotes significant differences between conditions and timepoints (p<0.05).

CHAPTER V

DISCUSSION

The present study examined sex-differences in quadriceps fatigability and neuromuscular function following both high- and low-torque repeated, intermittent, isometric contractions. The main finding of the present investigation was a greater decrement in neuromuscular function following LT exercise, when compared to the HT exercise bout. While sex differences in exercise performance were observed, differences in neuromuscular function during and immediately following the exercise bout were minimal between males and females. Overall, females demonstrated greater fatigue resistance (i.e., repetitions completed) during low-intensity, but not high-intensity repeated, isometric contractions of the quadriceps. While both high- and low-intensity exercise elicited quadriceps fatigue in both sexes, the present data suggest that neuromuscular fatigue is more dependent on the task, rather than sex.

Fatigue resulting from an exercise bout is most commonly quantified by a measured decline in voluntary strength (Hunter, 2018). Following both high- and low-torque contractions, a decrease in MVIC strength was observed, confirming the presence of fatigue. Interestingly, maximum strength was slightly greater prior to low-intensity contractions compared to high-intensity baseline strength. However, strength was lower following contractions of low intensity, indicating a larger decline in maximal strength in the LT condition (Figure 1). Specifically, MVIC strength declined an average of 28.3% following high-intensity contractions, while a 41.3% decline was observed following low-intensity contractions. As expected, males had greater strength when compared to female participants, both before and after exercise. This observed sex difference in overall strength is well documented in the literature (Dearth et al., 2010; Hunter et al., 2006) and unsurprisingly. Despite this strength difference, males and females experienced nearly identical declines in maximum force following each exercise bout, as males MVIC strength declined by an average of 42.0% (LT) and 29.0% (HT), while females MVIC strength was reduced by 40.2% (LT) and 27.3% (HT). Overall, the present data suggest that minimal sex differences were observed in strength decline following either high- or low-intensity exercise, with low-intensity contractions eliciting greater muscular fatigue.

Despite MVIC strength being the gold-standard for measure of fatiguability, the underlying physiological changes cannot be understood from changes in strength alone. Thus, changes in PTT, VA, and EMG amplitude were assessed to better understand the underlying neuromuscular mechanisms responsible for declines in force production. Significant decreases were observed in PTT following both low- and high-intensity contractions, which is indicative of peripheral fatigue (Figure 2). While not significantly different, low-intensity (-53.2%) contractions did elicit slightly greater declines in PTT than the high-intensity condition (-42.6%; Figure 2). Thus, the similar declines in PTT denote comparable changes in twitch properties between these exercise intensities.

Similar to MVIC strength, a sex difference in PTT was present at baseline, where males (81.6 ± 21.0 Nm) exhibited significantly greater PTT than females (53.2 ± 12.7 Nm). However, this difference was eliminated following the fatiguing exercise bouts. This elimination of a sex difference is in agreement with previous work by Albert and colleagues who found that males had greater twitch torque than females before, but not after, ten 30 second isometric contractions of the elbow flexors and knee extensors (Albert et al., 2006). Further, recent work by Ha and colleagues supports our findings of greater PTT in males at baseline with similar declines between sexes following both sustained isometric contractions and repeated 30% MVIC isotonic contractions of the plantar flexors (Ha et al., 2022).

Voluntary activation, as assessed via the interpolated twitch technique, is a common measure of central fatigue. Similar to the changes in peripheral fatigue, VA declined similarly across sexes in both exercise conditions. However, the LT exercise bout caused a significantly greater decline in VA. Such changes are depicted in Figure 3 above. While no difference was observed at baseline between conditions, VA declined approximately 7.3% following low-intensity contractions, while remaining unchanged (+0.1%) after the high-intensity condition. Thus, the present data suggest that low-intensity contractions caused greater manifestations of central fatigue and were limited by central activation failure, as described previously by Kent-Braun and colleagues (Kent-Braun, 1999). Interestingly, while there was a significant decrease in EMG amplitude following fatigue, there was no difference between conditions. This similarity in muscle excitation, coupled with similarities in twitch torque, indicate the presence of elevated central fatigue following low-intensity contractions. In addition to an overall decline in EMG activity from baseline, the present data suggest that there were sex differences in muscle excitation. Males exhibited greater EMG amplitude than females during MVIC for both the VL and VM. Interestingly, while females exhibited no significant differences in excitation between muscles, there was a large effect size ($\eta^2 = 0.24$) for inter-muscle differences in males. Specifically, males VL_{AMP} was significantly lower, measuring approximately 52% the activity of their VM_{AMP} during maximal contractions. This contrasts with Myer et al, whom demonstrated an unbalanced medial to lateral quadriceps ratio in females, but not males, during a valgus maneuver similar to what may lead to anterior cruciate ligament rupture (Myer et al., 2005). It is possible these differential findings can be due to the task being analyzed, as fatigue, and the contributing muscle excitation, are very task dependent (Hunter, 2018).

The proposed rationale for the increased fatigue resistance of females pointed to increased proportions of Type I, fatigue-resistant muscle fibers in the vastus lateralis (Staron et al., 2000). Interestingly, the present data demonstrate similar reliance on the VL and VM during maximal contractions in females, but not males, during MVIC. Therefore, it can be hypothesized that differences in fiber type and/or neuromuscular control of the knee extensors may differ between sexes. Overall, our data suggests that exercise intensity, rather than sex, contributes to the divergent changes in neuromuscular properties examined in the present investigation. Specifically, these data suggests that when taken to volitional fatigue, lower intensity isometric exercise elicits greater central fatigue than that of higher intensity contractions. Aside from greater muscle excitation during MVIC in males, the only existing neuromuscular sex difference, baseline PTT, was eliminated following fatiguing exercise.

As expected, a greater number of total repetitions, and consequently, significantly greater VL_{iEMG} and VM_{iEMG}, were completed during the LT condition as compared to HT (Figure 6). VM_{iEMG} was significantly greater than that of the VL in both conditions. Additionally, females completed nearly double the repetitions than males during the LT, but not HT condition. This aligns with numerous previous investigations, which consistently observed that females displayed greater time to task failure when compared to males during sustained contractions (Ansdell et al., 2017, 2019; Clark et al., 2005; Hunter, Critchlow et al., 2004) or intermittent contractions (Hicks et al., 2001). Further, our findings suggest that a lack of sex differences in repetitions of higher intensity is consistent with previous findings suggesting that the female advantage in fatigue resistance is diminished with increasing contraction intensity (Hicks et al., 2001). Additionally, torque impulse was greater as a result of LT contractions compared to HT, indicating that more total work was completed during the LT fatiguing bout than the HT (Figure 5). This is in contrast with previous findings, demonstrating no difference in total work completed between 30% and 70% MVIC repeated, isometric contractions of the knee extensors to failure (Muddle et al., 2018). It is possible that this differential finding is a result of our participants completing a much greater number of contractions at 30% than that of Muddle et al. This is likely due to the plateau duration of Muddle et al. being over 20 seconds longer than the plateau utilized in this experiment. Additionally, our inclusion of females resulted in a greater number of repetitions completed when groups were collapsed, while Muddle et al. included only males in their study design. Finally, our contractions were time-matched between conditions. Each contraction, regardless of intensity, was 20 seconds long and inclined and declined at 10%/second. Therefore, our force plateaus were not equivalent in time. However, in the work by Muddle et al., contractions were matched for total work. Given the differing intensities, the plateaus were of much different length to result in the same total work. Our experimental design was selected to ensure similar pacing of contractions and to ensure enough contractions could be completed to compare the time-course of fatigue between differing intensities.

In order to understand the time-course and onset of fatigue, the first, middle, and last complete repetitions, as well as the incomplete repetition when failure was achieved, were analyzed. A similar technique for fatigue analysis has been used previously to assess the time-course of fatigue (Muddle et al., 2018). During all repetition timepoints, males had greater mean torque than females. Further, males' mean torque began declining significantly after the MID repetition. This differed from females, for which average torque did not statistically differ between at any timepoint during the fatiguing tasks. The FAIL rep of both conditions was the lowest of its respective condition, further confirming that participants reached volitional failure, producing force more than 5% below their target torque. Regardless of sex, fatigue during the high-torque contractions set in more rapidly, with a significant decline in average torque after the MID contractions. This is likely a result of the fewer number of repetitions able to be completed at such a high intensity and the more rapid onset of fatigue accumulation by the high intensity contractions. Surprisingly, the TQ_{CV}, a commonly used surrogate for force steadiness, was greater during low-torque contractions compared to high-torque. At the onset of measurable fatigue at MID, torque variation increased, reaching its peak at FAIL. As participants failed the task, they were unable to consistently produce steady force within 5% of their target during the contraction plateau. As such, EMG amplitude was greatest during the LAST and FAIL repetitions of either condition. This pattern of increasing EMG activity is consistent with prior literature (Jenkins et al., 2015). Further, HT elicited greater EMG amplitude of both the VL and VM than the LT condition, with

EMG amplitude at the completion of the LT condition failing to reach the level of the FIRST contraction in the HT condition. This contrasts previous research in which low-torque contractions (50% MVIC) completed until failure reached similar EMG amplitude than a 90% MVIC contraction completed a single time (Miller et al., 2020). The cited research explained a nonsignificant difference between EMG amplitudes with a moderate Cohen's *d*, suggesting there was a difference between values. Given the other fatigue data presented in their findings, it is important to note they point to EMG amplitude painting an incomplete picture of neural drive between conditions. Our present data suggest that EMG amplitude differences, when paired with greater declines in maximum force, changes in voluntary activation, and decreased force steadiness demonstrate the more complete picture of neural fatigue achieved within our LT condition. This contrasting finding in our data is likely due to the lower intensity of our low-torque condition, compared to the previously cited research using a moderate-torque threshold of 50% MVIC.

The present study investigated the potential sex differences in fatigability following high- and low-torque repeated, isometric contractions of the knee extensors to failure. We hypothesized that males would be stronger, although more fatigable, at both exercise intensities. Our findings demonstrate that while males were stronger, females were only more fatigue resistant during low-torque (30% MVIC) contractions, completing nearly twice the number of repetitions as their male counterparts. The only additional sex difference, baseline twitch torque, was eliminated following fatiguing exercise. Additionally, we hypothesized that muscle excitation would be greater during high torque contractions. Indeed, our data suggest this to be the case, with EMG amplitude during the final repetition of low-torque never reaching similar amplitude as during high-torque. Thus, it is unlikely that similar levels of motor unit recruitment were achieved during the two conditions. The present data suggest that neuromuscular fatigue appears to be dependent on the constraints of the task, rather than sex of the participant. Further research is needed to examine the differential mechanisms underlying fatigue at different intensities to prescribe more optimal training and nutritional strategies to combat fatigue, ensuring inclusion of both sexes as participants for a more comprehensive understanding of the complex physiological mechanisms.

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APPENDIX

Appendix A: Institutional Review Board Letter of Approval

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INSTITUTIONAL REVIEW BOARD
February 27, 2020

Principal Investigator:	Ryan Colquhoun, PhD		
IRB # and Title:	IRB PROTOCOL: 20-027 [1553670-2] Sex-Differences in Neuromuscular Properties during Fatiguing Exercise		
Status:	APPROVED	Review Type:	Full Committee Review
Approval Date:	February 17, 2020	Submission Type:	New Project
Initial Approval:	February 17, 2020	Expiration Date:	
Review Category:	Full Board		

This panel, operating under the authority of the DHHS Office for Human Research and Protection, assurance number FWA 00001602, and IRB Database #00000286, has reviewed the submitted materials for the following:

1. *Protection of the rights and the welfare of human subjects involved.*
2. *The methods used to secure and the appropriateness of informed consent.*
3. *The risk and potential benefits to the subject.*

The regulations require that the investigator not initiate any changes in the research without prior IRB approval, except where necessary to eliminate immediate hazards to the human subjects, and that **all problems involving risks and adverse events be reported to the IRB immediately!**

Subsequent supporting documents that have been approved will be stamped with an IRB approval and expiration date (if applicable) on every page. Copies of the supporting documents must be utilized with the current IRB approval stamp unless consent has been waived.

Notes:

Full Board Review and Approval for exercise training to include Dual Energy X-Ray Absorptiometry (DXA)

Informed Consent dated January 28, 2019

BIOGRAPHICAL SKETCH

Name of Author: Katie G. Kennedy

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Publications:

Keller, J.L., **Kennedy, K.G.** Men exhibit faster skeletal muscle tissue desaturation than women before and after a fatiguing handgrip. *Eur J Appl Physiol* (2021).

Keller, J. L., **Kennedy, K. G.**, Hill, E. C., Fleming, S. R., Colquhoun, R. J., & Schwarz, N. A. (2022). Handgrip exercise induces sex-specific mean arterial pressure and oxygenation responses but similar performance fatigability. *Clinical Physiology and Functional Imaging*.