

AN EXAMINATION OF SEX-RELATED DIFFERENCES IN
CENTRAL AND PERIPHERAL FATIGUE

by

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Muscle fatigue is classically defined as an exercise-induced decline in maximal voluntary muscle force or power. The development of muscle fatigue can occur within the muscle (peripheral fatigue), or within the Central Nervous System (CNS; central fatigue). Greater resistance to fatigue has been demonstrated in men compared with women. The purpose of the study was to examine sex-related differences in the site of muscle fatigue, using assessments of central and peripheral fatigue, as well as inhibitory sensory feedback. We hypothesized that force, EMG and M-wave amplitude would decrease with fatigue and, would not recover during occlusion, and would recover after blood flow was returned. We also hypothesized that these fatigue measures would be significantly larger in men than in women. MVC, EMG, M-Wave amplitude, and M-Wave latency data were analyzed. From the analyzed data, we were unable to find a significant difference between males and females for MVC, EMG, M-Wave amplitudes and M-Wave latency.

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I. Introduction

Muscle fatigue is classically defined as an exercise-induced decline in maximal voluntary muscle force or power (Gandevia, 2001). It develops in men and women soon after the onset of physical activity and is often assessed as a reduction in maximal voluntary contraction (MVC) force. The development of muscle fatigue can occur within the muscle (peripheral fatigue), or within the Central Nervous System (CNS; central fatigue). Typically these two types of fatigue are considered as separate systems, however, recent investigations have shown a potential for feedback from the peripheral system to the central system, which contributes to fatigue development (Amann et al., 2009).

During continual maximal or submaximal contractions, the inability to maintain the task will eventually occur. This failure is thought to occur as a result of several physiological processes, including inhibitory feedback loops within the neuromuscular system, which act as a protective mechanism. If there is no inhibitory feedback from the muscle, contraction will continue until a point of deformation or cell death (Amann et al., 2009). This particular feedback mechanism may explain discrepancies in muscular fatigue across different populations and could provide insight into the high levels of fatigue associated with diseases such as multiple sclerosis (Tesio et al., 2006).

Greater resistance to fatigue has been demonstrated in men compared with women (Hick et al., 2001, Russ et al., 2008, Hunter et al., 2009, Clark et al., 2005, Yoon et al., 2009). Several studies have suggested that differences in muscle mass, strength, and peripheral nervous system excitability do not provide a consistent pattern with regards to sex difference (Russ et al., 2008, Fulco et al., 1999, Russ et al., 2003, Wust et

al.,2007). The purpose of the study was to examine sex-related differences in the site of muscle fatigue, using assessments of central and peripheral fatigue, as well as inhibitory sensory feedback.

II. Background

Peripheral Fatigue

Peripheral fatigue is a reduction in force or power resulting from exercise-induced changes within the neuromuscular junction or myocyte. Within the cell membrane (sarcolemma) of a muscle fiber, there are multiple ion channels and pumps that function together to maintain a negative resting potential and allow for the generation of an action potential. Once an action potential is propagated through the neuromuscular junction and reaches the sarcolemma, it then travels to indentations within the membrane known as transverse-tubules (t-tubules). Once the action potential passes down the t-tubular membrane, the electrical signal is converted into a chemical one with the release of calcium from the sarcoplasmic reticulum (Hopkins et al.,2006). Upon release, calcium travels down its concentration gradient into the cytoplasm where it initiates the second portion of excitation-contraction coupling.

Muscle contraction is a result of a strong bond that occurs between two proteins; actin and myosin. Actin and myosin are aligned in an alternating parallel fashion within the sarcomere. At rest, myosin-binding sites are blocked by another filamentous regulatory protein known as tropomyosin. Actin is also prevented from binding with myosin due to a troponin complex composed of multiple subunits (Hopkins et al.,2006). Once calcium is released from the sarcoplasmic reticulum, it binds with one of the subunits on the troponin complex exposing the myosin-binding sites located on the actin chain.

Adenosine di-phosphate (ADP) and inorganic phosphate that are released from the

myosin once bound to actin cause the head to pivot which in turn moves the filament closer to the center of the sarcomere and produces a contraction. (Hopkins et al.,2006). After a contraction, the muscle requires a period of time to re-sequester calcium ions into the sarcoplasmic reticulum. If an action potential is generated when calcium remains in the cytoplasm, a muscle can reach tetanus or constant contraction. As calcium is forming myosin cross-bridges and releasing ADP, other metabolites build up within the myocyte. With an increased level of these metabolites within the muscle, there is a reduction of electrical conduction from the muscle membrane to the tubules that prevent the opening of the sarcoplasmic reticulum (Mellar et al.,2010). Peripheral fatigue also involves impairment of calcium release from sarcoplasmic reticulum (excitation-contraction uncoupling) and of the reuptake of calcium into the sarcoplasmic reticulum, which impairs myosin and actin cross-bridge cycling (Mellar et al.,2010). The release of ATP as energy for cross-bridge cycling within myofilaments is decreased causing bioenergetics failure due to impairment of the oxidative phosphorylation and/or glycolysis.

Peripheral fatigue is also dependent on fiber types. Striated muscle contains three fiber types. Type I fibers have a high capacity for oxidative phosphorylation as well as a high capillary density which follows with a high resistance to fatigue (Hopkins et al.,2006). Another muscle type is the Type II fibers. Type IIa fibers use oxidative phosphorylation and glycolysis. Type IIa fibers also have a high capillary density and fatigue slower (Mellar et al.,2010). Type IIb fibers depend mostly on glycolysis and have a low capillary density, therefore they fatigue quickly. This may be due to the reduction of blood to these particular fibers which prevent metabolites

from being 'washed-out' causing the peripheral system to signal for bioenergetic failure (Mellar et al.,2010).

One method of assessing peripheral fatigue is through electrical stimulation of the motor nerve. Stimulation of the nerve produces an involuntary contraction that eliminates the role of the CNS. Electrical stimulation is delivered to a motor neuron regularly over a period of time with rest intervals and the overall decline of force represents the peripheral fatigue (Davis et al.,2010). The electrical response of the muscle to this stimulation can also be recorded with electromyography (EMG). The EMG response is known as the M-wave and represents neuromuscular transmission (Davis et al.,2010). Therefore, in the presence of peripheral fatigue, the amplitude of the M-wave also declines (Davis et al.,2010).

Central Fatigue

The second primary type of muscle fatigue is that which arises from the central nervous system and is referred to as central fatigue. Central fatigue can develop from the cerebral cortex or at the level of the spinal cord. Most healthy individuals can voluntarily activate muscles near maximally (Gandevia 2001). During fatiguing tasks, neuronal firing rates decline as fatigue develops (Davis et al.,2010). A reduction in discharge frequency from spinal neurons, with some neurons ceasing to fire, contributes to the fatigue-induced reduction in force (Gandevia 2001). The decline of motor unit firing rate is important in order to match the slowing of the contracting muscle during fatigue. If firing rate were to remain the same, tetanic force within the muscle would be

maximized due to excess neurotransmission (Gandevia 2001). Although central fatigue is more complex, it has been referred to as having a minor role in task failure and its contribution can vary depending on the task and/or muscle (Bigland-Ritchie 1986). Central fatigue occurs through a reduced ability to activate motor neurons and can occur at different sites in the CNS. Central fatigue coming from the cerebral cortex can be due to impaired descending drive or simply reduced motivation to perform a certain task (Davis et al.,2010). At the level of the spinal cord, impaired alpha motor neuron firing or suboptimal recruitment rate can reduce muscle force (Gandevia ,2001; Davis et al.,2010). Fatigue from impaired alpha motor neuron firing will alter the EMG (Davis et al.,2010) signal. A reduced amplitude of EMG signals at failure to complete a task indicates either loss of recruitment or synergistic activation of multiple muscles (Gandevia 2001). Reductions in central drive can also occur as a result of increased inhibitory input to the CNS (Davis et al.,2010).

Sensory Feedback

Despite being commonly described as separate mechanisms of fatigue, central and peripheral fatigue have recently been suggested to be connected through feedback loops (Amann et al., 2009). Group III and IV sensory afferent fibers carry information pertaining to the metabolic state of the muscle. Their receptors are activated by decreases in pH and increases in metabolic byproducts within the muscle (Amann et al.,2009). By blocking the afferent feedback from Group III and IV sensory neurons, Amann et al.,(2009) showed that these neurons provide inhibitory feedback to reduce

central motor drive during fatigue. They suggest that this inhibitory feedback is protective, decreasing central motor drive to limit peripheral fatigue development (Amann et al., 2009). However, we do not yet know whether differences in this feedback loop can explain differences in fatigue across groups or conditions.

Sex Differences in Fatigue

Recent studies have established sex differences in fatigability of human skeletal muscle (Clark et al., 2005, Hunter et al., 2001, Russ and Kent-Braun 2003, Hicks et al., 2001).

These findings indicate that women are generally less fatigable than men during sustained isometric contractions. Yoon and colleagues (2007) found that women are more fatigue resistant than men during low-force fatiguing contractions. However, these analyses also concluded that fatigue is location, task and force dependent. Different fatigue resistance between men and women occurs with different muscles, different tasks and different force levels (Clark et al., 2003, Hunter et al., 2004). Studies that have examined muscle mass, strength and peripheral nervous system excitability have found no consistent explanation for sex related differences (Hicks et al., 2001). Sex differences in inhibitory feedback during fatigue has not been investigated.

The purpose of the study was to examine sex-related differences in the site of muscle fatigue, using assessments of central and peripheral fatigue, as well as inhibitory sensory feedback. We hypothesized that force, EMG and M-wave amplitude would decrease with fatigue and, would not recover during occlusion, and would recover after blood flow was returned. We also hypothesized that these fatigue measures would be significantly larger in men than in women.

III. Methods

Participants

Twenty young adults (13 females and 7 males) ages 18-30 years old were recruited for this study. All subjects had no known neurological or cardiovascular disorders and were fully aware of the protocol. Prior to participation in this research, each subject provided informed consent.

General Procedures

Subjects reported to the study on one visit where voluntary and stimulated data were collected. After assessing maximal voluntary contraction (MVC) force, baseline assessments of M-waves were obtained. Participants then completed the fatigue task, as described below.

Force

The subject's right foot was strapped to a custom-built device that allowed for the measurement of isometric force during ankle dorsiflexion. To assess MVC, subjects were asked to pull against the strap fastened around their foot as hard as possible for 4-5 seconds. This procedure was repeated two additional times with approximately two minutes of rest between each pull. The MVC was established as the highest of the three trials. Additional trials were completed if at least two trials were not within 10% of one another. All force data was amplified (PM-1000,

Dataq, Inc., Akron, OH), sampled at 25k Hz (USB-6363, National Instruments, Austin, TX) and stored for off-line analysis.

Electromyography

Surface electromyography (EMG) was recorded with 1-cm diameter sensors (Grass Astromed, Warwick, RI) placed 2 cm apart and taped over the tibialis anterior muscle. A ground electrode was placed on the side of the knee. The EMG signal was amplified and filtered between 10-1000 Hz (P511, Grass Astromed, Warwick, RI) and sampled at 25k Hz.

Stimulation

Stimulating electrodes measuring 0.5 cm in diameter and separated by 1.5 cm were placed over the surface of the skin above the peroneal nerve on the lateral aspect of the knee. Short (200ms) pulses of current were delivered to the peroneal nerve via the electrode in order to induce stimulation (DS7A, Digitimer, Hertfordshire, UK). The stimulation began with a lower intensity and was manually increased until there was no further increase in the electrical and mechanical response. The stimulus intensity was then set 10% above this intensity, to ensure supramaximal stimulation. Three responses were recorded and averaged to represent baseline M-wave. An additional stimulus was applied within 2 seconds following an MVC to establish the baseline potentiated M-wave response.

Fatigue Protocol

Before the fatigue protocol began, a large blood pressure cuff was positioned around the thigh and connected to a rapid inflator (E20, Hokanson ,

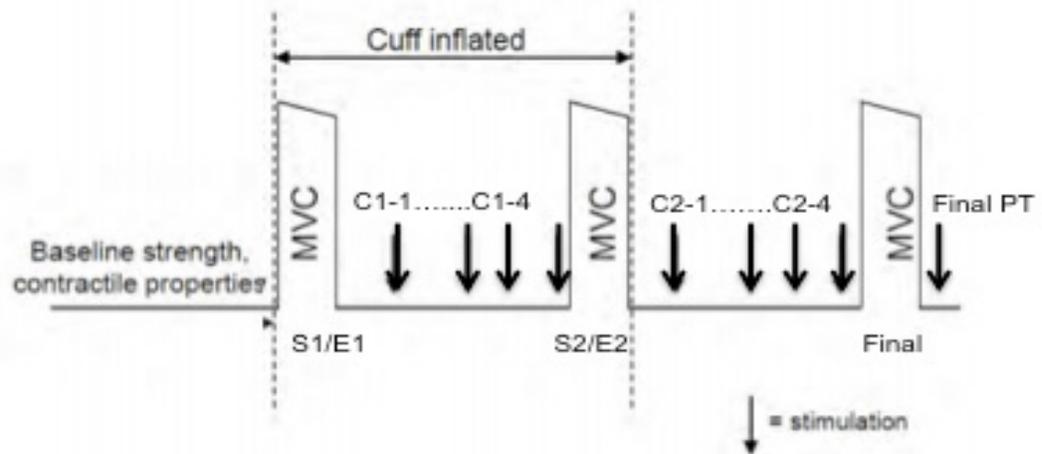
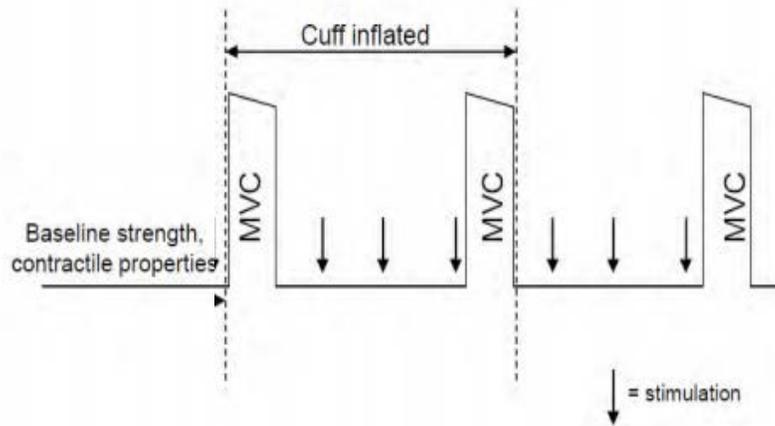


Figure 1 – The fatigue protocol. Each arrow indicates a stimulation. S1/E1 indicated by the first MVC. S2/E2 the second MVC. Final contraction is represented by the third and final MVC. C1-1 is the first stimulation directly after the first contraction. C2-1 is the stimulation directly after the second contraction. Final PT is directly after the final MVC.

Bellevue, WA). The fatiguing protocol, is illustrated in Figure 1.

The subject was provided with visual feedback on the computer screen in order to display the necessary target (100% MVC) to achieve each time they were ask to perform dorsiflexion. The subject was asked to perform two contractions to their maximal ability while the cuff was inflated to 220 mmHg. Each contraction lasted 20 seconds. One final maximum contraction was performed for five seconds after the cuff was deflated. There were three minutes of rest between each contraction.



Electrical stimulation from the electrodes placed over the peroneal nerve were delivered

during the 3 minute rest periods. Four electrical stimulations were delivered to induce M-waves; one directly after the contraction, one prior to one minute of rest, then two minutes of rest and one final stimulation before the third minute of rest prior to the next maximal contraction.

IV. Data Analysis

The data collected during and prior to the fatiguing protocol was examined using custom written programs in MatLab (MathWorks, Natick, MA) software. Custom written programs were used to analyze voluntary as well as stimulated contractile characteristics.

Force

For the 20-second contractions, the average force over the first and final five seconds of the contraction were calculated, ignoring the ramp up and ramp down during force development and relaxation. Fatigue was expressed as the relative decline in force over the contraction. Mean force was also calculated over the 5 seconds of the final contraction.

Voluntary EMG

The root mean squared (RMS) amplitude of the raw EMG signal was calculated over the first and final 5 seconds of the 20-second contractions using MatLab. The RMS amplitude was also calculated over the 5 seconds of the final MVC contraction.

M-Wave

The peak-to-peak amplitude of the M-wave was calculated in Matlab, through manual selection of time points before and after the M-wave response. The maximum and minimum values were then automatically determined and used to calculate the peak-to-peak amplitude. The three measures at baseline were averaged, to give one baseline value for each subject.

The latency of the M-wave was also calculated in Matlab. The stimulus artifact and beginning of the M-wave response were manually selected and the time between these points was calculated.

Statistical Analyses

Baseline values were compared between men and women using independent-samples t-tests. Two factor (sex, time) repeated measures ANOVAs were used to examine differences in each measure between men and women and throughout the fatigue protocol. Post-hoc pair-wise comparisons with Bonferonni corrections were used to explore significant main effects of time and significant interactions.

V. Results

Participant Characteristics

Table 1 illustrates baseline measures for men and women. There was no significant difference between men and women for baseline measures of MVC ($p=0.72$), EMG ($p=0.44$), or M-wave amplitude ($p=0.40$) or latency ($p=0.37$). Fatigue during the first 20-second contraction is expressed as the decline in MVC from the first to the last five seconds of the contraction. Fatigue, presented as percent of MVC declined, was not significantly different between males and females ($p=0.35$).

Table 1 – Participant Characteristics

	MVC (N)	EMG (mV)	M-Wave Amp (mV)	M-Wave Latency (ms)	Fatigue (% Decline)
Men	159.0 ± 66.5	2.06 ± 0.98	2.58 ± 1.01	4.11 ± 1.54	14.7 ± 16.8
Women	148 ± 51.1	1.69 ± 0.608	3.03 ± 1.18	5.39 ± 3.50	7.43 ± 14.8

MVC

Figure 2 displays the MVC over each contraction as a percentage of baseline MVC for both men and women. There was no significant difference between men and women ($p=0.38$), however there was a significant effect of time ($p=0.001$). Posthoc analysis revealed that force was significantly lower at the end of the 20-second fatiguing contraction than at the beginning ($p=0.04$). With the cuff inflated, the force at the start of the second contraction was lower than the start of the first contraction ($p=0.02$), but was similar between the end of the first contraction and

the start of the second contraction ($p= 0.70$). After the cuff was released, the MVC was similar to the start of the first contraction ($p= 0.18$), indicating recovery.

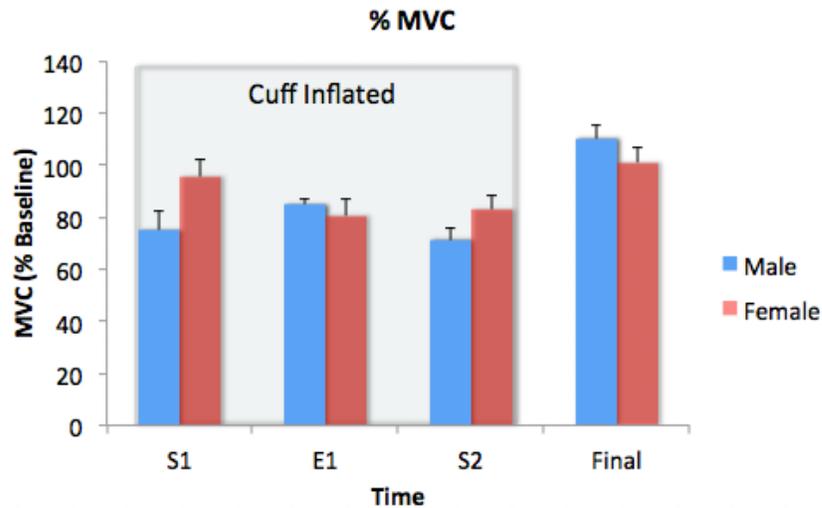


Figure 2 - Percent of baseline MVC per contraction over time for males and females. Shaded area indicates contractions that took place during occlusion. S1=start of the first contraction; E1=end of the first contraction; S2=start of the second contraction; Final=final 5-second MVC.

EMG

Figure 3 illustrates the percent of baseline EMG occurring during each contraction over time. There was no significant difference in EMG amplitude between men and women ($p=0.60$) and no significant changes were observed over time ($p=0.11$).

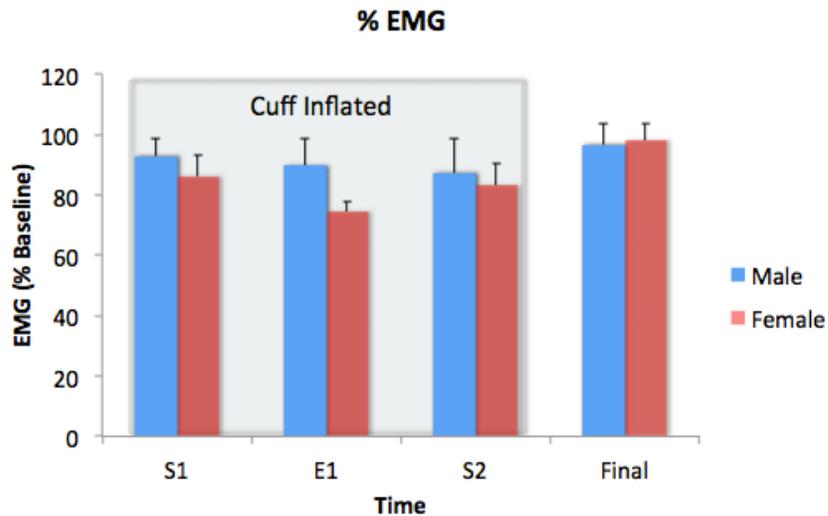


Figure 3 - Percent of baseline EMG amplitude for males and females. Shaded area indicates contractions that occurred during occlusion. S1=start of the first contraction; E1=end of the first contraction; S2=start of the second contraction; Final=final.

M-Wave Amplitudes

M-Wave amplitudes as a percentage of baseline amplitudes are shown in Figure 3. Un-potentiated baseline twitch data was used to determine M-wave amplitude percentages per stimulation over time. There was no significant difference between men and women ($p=0.70$), however there was a significant effect of time ($p=0.003$). Analysis revealed amplitudes were significantly lower at the start of the post-occlusion contraction than at the beginning of the fatiguing contraction ($p=0.03$). The end of the fatiguing contraction was also significantly lower than the beginning of the second contraction ($p=0.001$), but was similar between the beginning and end of the contractions with the cuff inflated ($p=0.50$). The end of the first contraction was also

significantly lower than the start of the second contraction ($p= 0.014$). the M-wave amplitude after the final contraction was similar to the first M-wave ($p=0.210$), showing recovery.

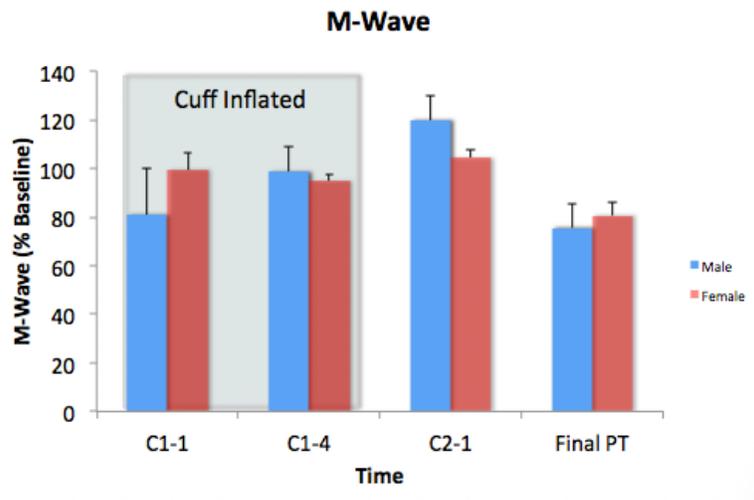


Figure 3 - Percent of baseline M-wave amplitude over the course of occluded and final contractions. Data are shown for males and females. Shaded area indicates occluded contractions. C1-1 = first stimulated contraction after first voluntary contraction. C1-4 = last stimulated contraction after first voluntary contraction. C2-1= first stimulated contraction after second voluntary contraction (during recovery), Final PT = final potentiated stimulated twitch.

M-Wave Latency

Figure 4 shows the percent of baseline M-Wave latency for males and females. There was no significance between sexes ($p = 0.60$). There was also no significant difference over time ($p = 0.11$).

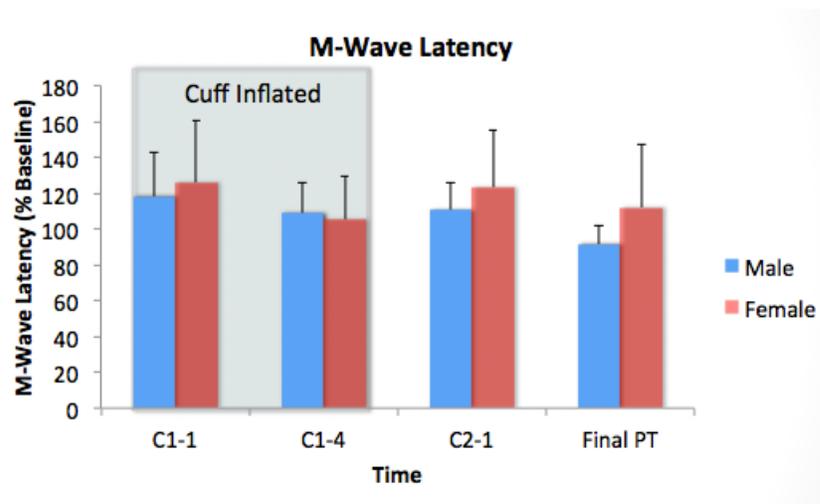


Figure 5 - M-Wave latency as a percentage of baseline latency. Males and females are compared over three occluded stimulations (shaded area) and one final stimulation. C1-1 = first stimulated contraction after first voluntary contraction. C1-4 = last stimulated contraction after first voluntary contraction. C2-1 = first stimulated contraction after second voluntary contraction (during recovery), Final PT = final potentiated stimulated twitch.

VI. Discussion

The purpose of the study was to examine sex-related differences in the site of muscle fatigue, using assessments of central and peripheral fatigue, as well as inhibitory sensory feedback. MVC, EMG, M-Wave amplitude, and M-Wave latency data were analyzed. From the analyzed data, we were unable to find a significant difference between males and females for MVC, EMG, M-Wave amplitudes and M-Wave latency. Force was reduced by fatigue and did not recover when blood flow was occluded. This is consistent with previous findings (Bigland-Ritichie et al.,1986), and suggests a role for inhibitory feedback from peripheral sensory receptors in limiting force production during fatigue.

Men and women showed a similar trend in decline in force with fatigue, which did not recover when blood flow was occluded (Figure 1). Both men and women recovered to baseline force levels when blood flow was returned, suggesting that inhibitory peripheral feedback is limiting force production in both sexes during fatigue. Such feedback has been suggested to prevent muscle damage from continued activation and metabolite accumulation (Amann et al.,2009).

Several studies have reported lower levels of muscle fatigue in women than in men (Hicks, et al, 2001). Although there was a trend for higher fatigue in men in this study, the difference did not reach statistical significance, likely due to variability in the amount of fatigue across subjects. However, similar levels of fatigue between men and women have also been reported in some cases (Hunter et al.,2009). Particularly, when matched for strength, men and women show no differences in fatigue, suggesting the mechanisms contributing to a sex differences for fatigability have something to do with

relative strength (Hunter et al.,2009). Our lack of difference in fatigue between sexes is consistent with this report, as baseline strength was similar between our women and men.

A possible explanation for sex differences in fatigue, when not matched for strength, could be the higher intramuscular pressures creating greater occlusion of blood flow in men than in women during static contractions (Hunter et al.,2009). These characteristics would result in a faster accumulation of metabolites within the muscle and a lack of oxygen resulting in a higher fatigue rate (Hicks et al.,2001). In our protocol, blood flow was externally occluded in all participants, eliminating this potential source of variability, to further isolate the impact of peripheral changes.

Men contain more Type II muscle fibers and have a greater muscle mass than women (Russ et al.,2003) thus producing larger maximum forces during contraction. Higher forces typically generate a higher metabolic demand therefore reducing the availability of oxygen (Russ et al.,2003). The reduced availability of oxygen forces a heavier reliance on anaerobic metabolic pathways for males (Russ et al.,2003), creating an excess of metabolic by-products which have been shown to directly correlate with fatigue (Kent-Braun et al.,1999, Bergstrom et al.,1988), and creating less fatigue resistance in men than in women. Women use oxidative metabolism decreasing their reliance on glycolytic pathways (Kent-Braun et al.,2002). This oxidative advantage women have relative to men that may produce differences in fatigue resistance is eliminated during occlusion (Russ et al.,2003). This suggests an oxidative advantage for women could be due to higher oxygen delivery or more use of oxidative phosphorylation (Russ et al.,2003). We did not find women to have an oxidative

advantage when comparing normal and ischemic conditions. Similar fatigue during ischemia between men and women in our study suggests similar levels of inhibitory feedback. Future investigations should quantify specific metabolites (H^+ , P_i , $H_2PO_4^-$) to indicate a similarity or difference in men/women metabolic build-up.

EMG

EMG amplitude was similar between sexes and did not change significantly over time during the fatigue protocol (Figure 2). Although just a trend, muscle EMG remained below 100% during occlusion and returned to values closer to 100% after reperfusion occurred. Other findings have indicated a potential increase in EMG amplitude during fatigue with submaximal contractions due to the progressive increase in motor unit activity (Clark et al., 2005). However such an increase in EMG amplitude has only been shown during submaximal contractions as new motor units can be recruited. During maximal contractions, full recruitment of the muscle will eliminate the potential for an increase in amplitude.

Generally, EMG amplitude will decrease with fatigue during maximal contractions (Clark et al., 2005). With the findings of Bigland-Ritchie (1986) expressing a decline in motor unit firing rates with fatigue, we would expect to see a decline in EMG over the fatiguing process. It is possible that the 20-second contraction was not long enough to detect a significant drop in EMG amplitude. The EMG-force relationship suggests that EMG amplitude levels off at ~85% MVC (Christie et al., 2009). Although we observed a significant decline in force with the fatiguing contraction, subjects were still producing more than 80% of MVC, which would result in small changes in EMG amplitude, as we observed.

M-Wave

Neither the M-wave latency, nor the amplitude was impacted by the fatiguing protocol. These results suggest that the motor neuron conduction and neuromuscular transmission were not affected by fatigue in men or women, which is consistent with previous studies involving brief fatiguing protocols (Bigland-Ritchie et al.,1982).

As shown in Figure 3, M-wave amplitudes increase significantly in both men and women during localized ischemia. This increase in amplitudes may be due to increased motoneuron excitability during peripheral occlusion (Zakutansky et al.,2005). Zakutansky and colleagues found acute ischemia to increase motor neuron excitability by increasing resting membrane potential which brings the motor neurons closer to threshold in young, healthy individuals. The motor neurons are therefore more responsive to input, creating higher M-wave amplitudes during acute ischemia. (Lin et al., 2002).

Once the cuff was deflated and reperfusion occurred, there was a significant decrease in M-wave amplitudes during the final stimulation. Wang and colleagues found that reperfusion causes significant microvascular alterations, these alterations include endothelial dysfunction, poor capillary perfusion and vasoconstriction in skeletal muscle (Wang et al.,2005). It is therefore possible that the significant decrease in M-wave amplitudes during the final stimulation could be the result of an inflammatory response to temporary damage on muscle fibers from reperfusion.

Limitations

A limitation in our present study was there were not an equal number of male and female subjects. Age was also limited to 18-30 years. Subjects were informed of the protocol prior to completing it, which may have resulted in below maximum initial contractions. There was also no measure of specific metabolites within the muscle during fatigue, this would have allowed for a more exact examination of the inhibitory pathway, which is stimulated by metabolic by-products.

Conclusions

The purpose of the study was to examine sex-related differences in the site of muscle fatigue, using assessments of central and peripheral fatigue, as well as inhibitory sensory feedback. Force was reduced between occluded contractions and failed to recover while the cuff was inflated. This indicates the importance of peripheral feedback during fatigue for both men and women and suggests that a potential oxidative advantage for women is eliminated during a time of high oxidative stress. Without this advantage similar feedback mechanisms must be present during occlusion. While measuring EMG, the inhibitory signal was not sufficient enough to detect a change in EMG amplitude. In the future, more sensitive measures such as motor unit recordings would be a good alternative for more precise data.

Further studies of these metabolic by-products and feedback mechanisms could potentially lead to solutions in a clinical setting where high-levels of fatigue is an issue. Examining more specifically the role of metabolic by-products in inhibitory feedback could offer insights into potential interventions to prevent fatigue in those more likely to experience fatigue-related issues.

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