

Extreme-intensity exercise: Exercise tolerance and recovery

by

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B.S., Kansas State University, 2015

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AN ABSTRACT OF A DISSERTATION

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Department of Kinesiology
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Abstract

Severe-intensity exercise describes specific exercise intensities where contraction-induced metabolic markers (e.g., inorganic phosphate, H^+ , pH) do not reach steady-state, but continue to change until task failure is reached. It has been found that the rates of change in these markers are intensity-dependent, but reach similar values at the limit of exercise tolerance (T_{lim}). Therefore, the amount of work done at T_{lim} is not different across severe-intensity work rates. However, we have previously shown evidence of a supra-severe-intensity domain (i.e., extreme-intensity exercise), where the amount of work performed at T_{lim} is significantly lower than during severe-intensity exercise. Further, the mechanisms limiting exercise tolerance reverse at significantly faster rates during recovery from extreme-intensity exercise compared to following severe-intensity exercise. Therefore, the overall aims of this dissertation were to examine the differences in exercise tolerance between severe- and extreme-intensity exercise as well as measure important neuromuscular recovery immediately following exercise cessation in order to elucidate what potential mechanistic differences may be contributing to the accelerated accumulation of fatigue. In our first investigation (Chapter 2), we demonstrated that maximal voluntary contraction (MVC) was significantly decreased following severe- and extreme-intensity exercise. MVC recovery was apparent in both men and women following severe-intensity exercise, with little to no recovery following extreme-intensity exercise. Further, peripheral fatigue, estimated by reductions in potentiated twitch force (Q_{pot}), did not develop to the same degree following extreme- compared to severe-intensity exercise and showed significant recovery within 90 s in men and 150 s in women. To further investigate sex differences in neuromuscular fatigue development and force recovery following extreme-intensity exercise, in our second investigation (Chapter 3), we found no differences in W'_{sev} , or W'_{ext} , between men and women. MVC and Q_{pot} forces recovered faster

following extreme-intensity exercise compared to following severe-intensity exercise, with women recovering to values not significantly different from baseline sooner than in men. Further, it was evident that men accumulated greater peripheral fatigue during submaximal exercise than women; however, there were no sex differences following near-maximal (90% MVC) exercise. In our final pilot investigation (Appendix A), we examined the potential effects of creatine monohydrate supplementation on extreme-intensity exercise tolerance. Although no statistical differences were found in MVC, Q_{pot} , W'_{sev} , or W'_{ext} , individuals showed large variability in responses to creatine supplementation, with creatine supplementation having profound effects on exercise tolerance in some, but not all, individuals. Collectively, this dissertation provides novel findings and improves our understanding of exercise intensity domain-dependent fatigue mechanisms and their contributions, especially during extreme-intensity exercise. Further, we provide evidence of differences in neuromuscular recovery between men and women, which are likely to have important implications regarding sex-dependent-mechanisms limiting exercise tolerance. Therefore, it is important to consider the differences between men and women regarding the mechanisms and level of fatigue and time course of recovery when developing exercise prescription (e.g., work rate intensity, recovery between exercise modalities) for specific populations.

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Preface

This dissertation represents three novel projects. Chapter 2 represents an original research article that has been submitted to the *Applied Physiology, Nutrition, and Metabolism* journal and is currently under the peer-review process. Chapter 3 represents a second original research article that is anticipating submission. Appendix A represents a preliminary research study with the results and future directions highlighted.

Chapter 1 - Introduction

Although muscle fatigue (defined as the temporary decline in maximal force or performance) is commonly experienced during exercise, the specific sources of fatigue during exercise develop from many sources (6, 11). Fatigue can originate at sites at or proximal to the neuromuscular junction, i.e., central fatigue (4, 10, 15) or distal to the neuromuscular junction, i.e., peripheral fatigue (3, 7, 9). The mechanisms limiting tolerance of exercise, however, are intensity-dependent, and therefore exercise-intensity domains have been used to describe expected responses to exercise (17-19, 24, 25). For example, during moderate- and heavy-intensity exercise, $\dot{V}O_2$, inorganic phosphate, and lactate reach steady state (14, 26). However, during severe-intensity exercise, each increase to a maximal level before task failure (14, 19). Critical torque/power/speed has been identified as the threshold separating heavy- and severe-intensity domains, thus also separating work rates where metabolic steady-state is attained from those where it is not (18, 19). In addition to critical torque, a second parameter of severe-intensity exercise is W' . W' represents the limited exercise tolerance within the severe-intensity domain (13). Interestingly, W' is not different across severe-intensity work rates, thus task failure of severe-intensity exercise is predictable. This also implies that mechanisms of fatigue are similar across severe-intensity work rates (13).

Hill et al. (2002) proposed that because severe-intensity exercise causes $\dot{V}O_2$ to increase to a maximum ($\dot{V}O_{2max}$), there would be a supra-severe intensity domain consisting of work rates that cause task failure before $\dot{V}O_{2max}$ is attainable and T_{lim} would be shorter than predicted by the severe-intensity power-duration relationship (12). Indeed, recent data from our laboratory has shown that dynamic knee-extension exercise $> 60\%$ one-repetition maximum (1RM) was significantly shorter than predicted by the severe-intensity power-duration relationship (1).

Interestingly, we also found that work rates $> 60\%$ 1RM also displayed a separate, smaller W' , providing novel insights of the extreme-intensity domain (1). We further showed that, although there were no differences across any exercise intensity in voluntary activation (%VA), both potentiated twitch force (Q_{pot} ; indicator of peripheral fatigue) and maximal voluntary contraction (MVC) remained significantly decreased at 90 s following task failure of severe-intensity exercise, but were not different from baseline values at 90 s of recovery following extreme-intensity exercise (1). This suggested that the mechanisms limiting extreme-intensity exercise tolerance were not only different from those limiting severe-intensity exercise, but were also quickly reversible following exercise cessation. However, it is important to note that there was ~ 90 s delay between task failure and the first post-exercise measurements due to transferring subjects to different equipment, therefore hiding force recovery responses occurring immediately following task failure.

It is well established that women have greater tolerance to exercise compared to men. Interestingly, this difference appears to be less dramatic, and in some cases non-existent, at higher intensity work rates (8, 16, 27). Specifically, Yoon et al. (2007) found that women were able to exercise longer at 20% MVC, but not at 80% MVC, compared to men (27). Maughan et al. (1986) also found women exercised longer than men at 50% and 70% MVC, but not at 80 and 90% MVC (16). Although CT appears to occur at a higher percentage of maximal force output relative to MVC in women compared to men, absolute amount of work (W'_{sev}) was not different between sexes (5). Therefore, combined with previous data showing exercise tolerance to be similar between men and women, this would predict that men and women may show similar W' for both severe- and extreme-intensity domains.

In addition to increased exercise tolerance at work rates < 70% MVC, women also show greater fatigue resistance during exercise (20, 21). Fatiguing mechanisms within the exercising muscle (at or distal to the neuromuscular junction, i.e., peripheral fatigue) are seen in both men and women at low- and high-intensity work rates; however, the contribution of peripheral fatigue varies at the limit of exercise tolerance (T_{lim}) with respect to the intensity of exercise and between sexes. For example, peripheral fatigue (as estimated by electrical stimulation) was shown to be similar between men and women following 60 s of sustained MVC, but was greater in men following submaximal fatiguing exercise consisting of 120 knee extensions at 20% MVC over 6 minutes (23). Further, previous research has found that men show a greater reduction in voluntary activation following intermittent MVCs compared to women, suggesting central fatigue has a greater contribution to sustained maximal exercise tolerance in men (23). Also, the mechanisms of fatigue are quickly reversed following higher intensities (1, 22), compared to lower intensities, in men, with much of the recovery happening in the initial minutes (< 3) following exercise cessation (2). Specifically, Q_{pot} and MVC forces reached values similar to baseline forces within 150 seconds following task failure of extreme-intensity exercise, but remained depressed throughout 150 seconds of recovery following severe-intensity exercise (1). It is currently unclear in women if the time course of recovery following severe- and extreme-intensity exercise to task failure would follow similar intensity-dependent responses.

Therefore, the aims of this dissertation were to investigate the differences in the development of peripheral and central fatigue between severe- and extreme-intensity exercise and the respective recovery immediately following task failure as well as to identify potential mechanisms limiting extreme-intensity exercise. Specifically, we used an isometric knee-extension exercise model and quantified maximal voluntary contraction (MVC) as well as

maximal muscle force (Q_{pot}) available at task failure and throughout the immediate recovery following severe- and extreme-intensity exercise. In Chapter 2, we tested the hypotheses that reductions in MVC, Q_{pot} , and %VA at task failure (T_{lim}) following extreme-intensity exercise would be less than following severe-intensity exercise, and that Q_{pot} and MVC following extreme-intensity exercise would show significant recovery within 2 minutes but remain depressed following severe-intensity exercise. We then investigated differences in responses to severe- and extreme-intensity exercise between men and women to identify potential sex-dependent mechanisms of fatigue in Chapter 3. Specifically, we hypothesized that both men and women would display a W'_{ext} that would be significantly less than W'_{sev} , MVC would be reduced to greater extent at task failure following severe- and extreme-intensity exercise in men compared to women, and peripheral fatigue, estimated by reduced potentiated twitch force, would be greater at task failure following severe-intensity exercise in men compared to women, with no sex difference following extreme-intensity exercise. Finally, we collected preliminary data to examine the potential effects of creatine supplementation on W'_{ext} in Appendix A. We hypothesized that creatine supplementation would increase W'_{sev} and W'_{ext} .

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Chapter 2 - Neuromuscular recovery from severe- and extreme-intensity exercise

Summary

We have shown that maximal voluntary contraction force (MVC), potentiated twitch force (Q_{pot}), and voluntary activation (%VA) recovered to baseline within 90s following extreme-intensity exercise. However, methodological limitations masked important recovery kinetics. The current study tested the hypotheses that reductions in MVC, Q_{pot} , and %VA at task failure (T_{lim}) following extreme-intensity exercise would be less than following severe-intensity exercise, and that Q_{pot} and MVC following extreme-intensity exercise would show significant recovery within 2 minutes but remain depressed following severe-intensity exercise. Twelve subjects (6 men) completed two severe-intensity (40 and 50%MVC) and two extreme-intensity (70 and 80%MVC) isometric knee-extension exercise bouts to task failure. Neuromuscular function was measured at baseline, T_{lim} , and through 150 s of recovery. MVC was reduced less following extreme-intensity exercise compared to following severe-intensity exercise in women. MVC was not different at task failure across intensities in men. MVC recovery was apparent in both sexes following severe-intensity exercise, with little to no recovery following extreme-intensity exercise. Q_{pot} was not different at task failure across intensities in women and returned to baseline values within 150 s during recovery following extreme-intensity exercise. Q_{pot} was reduced less following extreme-intensity compared to severe-intensity exercise in men and showed significant recovery within 90 s following all intensities. No differences in %VA were detected pre- to post-exercise, or across recovery, for any intensity in either sex. Together, these data reinforce that fatigue responses to

exercise are intensity domain-specific and suggest that peripheral factors may contribute to T_{lim} during extreme-intensity exercise but recover quickly.

Introduction

Severe-intensity exercise has been well described as a domain of work rates that are associated with progressive metabolic and neuromuscular responses (15, 31, 33), such as $\dot{V}O_2$, blood lactate, blood and intramuscular H^+ and inorganic phosphate, which do not reach steady-state, but increase until task failure is reached (15, 25). Exercise tolerance in the severe-intensity domain can be expressed as a hyperbolic power-duration relationship when plotting time as a function of work rate, where the asymptote is termed critical power (CP), and the curvature constant is termed W' . This has resulted in a widely accepted interpretation that the work done in the severe-intensity domain above CP (i.e., W') is independent of work rate (32, 33). There is further evidence suggesting that the physiological mechanisms responsible for exercise cessation are likely peripheral, as contraction-induced metabolites associated with decreases in force production (e.g., inorganic phosphate), are produced and are not different at task failure across severe-intensity work rates (11). The power-duration relationship of the severe-intensity domain, however, only remains accurate through constant-load exercises in which obtaining $\dot{V}O_{2max}$ is possible, therefore, the typical minimum time to task failure (T_{lim}) is greater than two minutes. Constant-load exercises that consist of an intensity that would cause task failure before $\dot{V}O_{2max}$ is able to be obtained would be defined as supra-severe-intensity exercise and has been dubbed the extreme-intensity domain (23). We have previously shown that T_{lim} during extreme-intensity exercise occurs earlier than predicted by the severe-intensity power-duration relationship (1), and is characterized by a separate, smaller W' (W'_{ext}). Although limited research exists regarding the physiological responses to extreme-intensity exercise, by utilizing the same interpretation of the severe-intensity domain, the W'_{ext} suggests that the mechanisms limiting extreme-intensity

exercise, although likely different from those seen during severe-intensity exercise, are common throughout the extreme-intensity domain, and currently remain unknown.

Previous studies have shown that much of the loss in force at T_{lim} remains unrestored in the first few minutes (< 2 min) following prolonged exercise (> 15 min) (6, 35). Previous data from our lab extended this finding, showing reductions in maximal voluntary contraction force (MVC), potentiated twitch force (Q_{pot} ; indicator of peripheral fatigue), and percent voluntary activation (%VA; indicator of central fatigue) were still evident 90 s into recovery following severe-intensity exercise compared to baseline values. However, no residual reductions in MVC, Q_{pot} , or %VA compared to baseline were found 90 s into recovery following extreme-intensity exercise (1) suggesting that by then the muscles were fully recovered. Therefore, it is likely that the mechanisms limiting exercise tolerance also show differences in the kinetics during recovery from fatigue, being much faster following extreme-intensity exercise compared to severe-intensity exercise. Procedural limitations in our previous study masked the condition of the muscle at T_{lim} and throughout early recovery (90 s) following task failure. First, there was a short (< 30 s) delay while transferring subjects from the exercise ergometer to the force transducer following task failure. Second, the protocol we utilized recommended discarding the first 2 neuromuscular measurements (at 30 and 60 s) due to incomplete potentiation (27). This resulted in our first data point being 90 s into recovery. From these results, it became clear that in order to determine the contributions of peripheral and central factors limiting extreme-intensity exercise tolerance, neuromuscular measurements would need to be made at task failure and throughout early recovery.

It is well established that the relative contributions to fatigue by peripheral and central factors are intensity-dependent (see refs: (14)). These differences may also be apparent with maximal exercise, including extreme-intensity exercise (1, 23). However, to date, no studies have

compared the relative neuromuscular contributions to fatigue in the context of severe- and extreme-intensity domains. Therefore, the purpose of this study was to examine neuromuscular conditions immediately following task failure and to investigate the immediate rate of recovery following severe- and extreme-intensity exercise. We hypothesized that 1) the changes in MVC, Q_{pot} , and %VA immediately following task failure from extreme-intensity exercise would be significantly less than following severe-intensity exercise in both men and women, and 2) Q_{pot} and MVC following extreme-intensity exercise would begin to recover within 2 minutes but remain depressed following severe-intensity exercise in both sexes. In order to make measurements at T_{lim} and early into recovery, we moved from an isotonic knee-extension ergometer to one incorporating isometric contractions, thus permitting us to measure the relevant neuromuscular responses immediately at task failure and early recovery. Finally, although the main purpose of this study was not to examine specific differences between men and women, we tested for a main effect of sex to determine if the groups should be analyzed separately.

Methods

Subjects: Six men (mean $\pm$ S.D.: 23 ± 3 yr; 87.5 ± 16.1 kg; 179.3 ± 2.3 cm) and six women (mean $\pm$ S.D.: 22 ± 1 yr; 58.3 ± 3.4 kg; 158.8 ± 4.2 cm) participated in this study. All participants were free from cardiovascular, pulmonary, and metabolic disease as determined by a medical history questionnaire. Prior to participation in this study, subjects were informed of all procedures, and associated potential risks and benefits. Written informed consent was obtained from all participants prior to participation. Subjects were instructed to refrain from vigorous exercise 24 hours, alcohol consumption 12 hours, and food and caffeine 2 hours prior to each session, as well as to maintain current exercise habits in order to avoid any training or detraining effect. All research components were reviewed and approved by the Institutional Review Board of Human Subjects (#8369) at Kansas State University, Manhattan, KS.

Experimental Design: Subjects visited the laboratory a minimum of 4 times, with at least 48 hours between sessions. On the first visit, subjects were familiarized with all testing procedures and equipment prior to testing. All exercise testing and measurements were performed on the right leg using a custom-built isometric knee extension ergometer and force transducer (LBG1, BLH Electronics, Waltham, MA, USA). Subjects were seated upright and the backrest was adjusted so that hip flexion angle was 105° and knee flexion angle was 90° . Force transducer position on the lower leg was adjusted for each subject such that a 90° angle of pull was maintained. The position of the force transducer and backrest setting were recorded and replicated for each subject and exercise sessions.

Constant-Load Tests: During each subsequent visit, subjects performed one of 4 intermittent isometric constant-load tests to T_{lim} at a target force of 40, 50, 70, or 80% MVC in random order

on separate visits. Based on our previous findings that intensities greater than $\sim 60\%$ MVC would elicit task failure in < 2 min (1) reflecting extreme-intensity exercise, intensities were chosen to ensure two severe- (40 and 50% MVC, $T_{lim} = 2 - 15$ min) and two extreme- (70 and 80% MVC, $T_{lim} < 2$ min) intensities would be tested. MVC was measured prior to each exercise test to examine day-to-day variability. Subjects performed all knee-extension exercise at a 60% duty cycle (3 s contraction; 2 s relaxation) at a rate of 12 contractions/min as per a pre-recorded audio cue. Target force was displayed as a line generated on the display. Subjects were required to reach and maintain target force for the entire 3 s of contraction as indicated by visual and verbal feedback. Subjects were verbally encouraged throughout the test. Task failure was defined as the first failure to reach and maintain 90-95% target force for $> 66\%$ of the required time. Upon task failure, the post-exercise neuromuscular assessment began at the subsequent audio cue.

Neuromuscular Function: Neuromuscular function testing was conducted similar to previous extensively used protocols (9, 13, 16, 22). Briefly, testing was performed on the right leg prior to and immediately following each constant load exercise test. Adhesive electrodes (4 x 6 cm) were used to electrically stimulate the knee extensor muscles of the right leg via the femoral nerve. The anode was attached to the gluteal fold. The cathode was positioned over the approximate location of the femoral nerve, and minor adjustments were made based on verbal feedback from the participants, who were instructed to report the greatest feeling of a knee-extension motion to remove activation of other thigh muscles. Maximal stimulation was assessed prior to each exercise bout. Stimulation intensity was initiated at 50 mA and was increased in 25 mA increments until the measured force and compound muscle action potential (M-wave) ceased to increase. The stimulator current was then increased an additional 30% to ensure the stimuli were supramaximal. This current averaged 575 mA across subjects, with a range of 400 – 800 mA. Force was sampled

at 1000 Hz and displayed on a computer screen (LabVIEW, National Instruments, Austin, TX, USA). The femoral nerve was stimulated using a high-voltage constant-current electrical stimulator (DS7AH, Digitimer, Welwyn Garden City, UK). Paired stimuli (doublets) were delivered at 400 V with 100 μ s square-wave pulse durations and a 10 ms pulse interval. Prior to each exercise test, subjects performed a series of 6, 3 s maximal voluntary contractions (MVCs), beginning every 30 s. Doublet muscle stimulations were delivered 5 s prior to each MVC, 1.5 s into the MVC, and 5 s after each MVC to obtain measurements of unpotentiated, superimposed, and potentiated doublet forces, respectively. MVC was determined as the greatest force attained prior to the superimposed muscle doublet stimulation. A series of 7 of these neuromuscular assessments was completed immediately upon task failure (T_{lim}) and for the next 3 min.

Data analysis: Maximal voluntary contraction (MVC) was calculated as the greatest force attained prior to the superimposed stimulation.

Potentiated twitch force (Q_{pot}) has been shown to increase after the first neuromuscular measurements, becoming maximal after the third neuromuscular measurement (27), likely due to incomplete potentiation. Therefore, the average of the last three of six Q_{pot} forces during baseline neuromuscular measurements was used as baseline Q_{pot} , as done previously (27). However, the post-exercise measurements were assumed to be fully potentiated as subjects were exerting maximal effort to reach target force at task failure. Therefore, individual neuromuscular measurements were analyzed as representing the current state of the muscle. In addition to investigating the change in absolute Q_{pot} , Q_{pot} was scaled relative to the decrease in force across exercise, i.e., baseline = 100%; force at end exercise = 0%.

Voluntary activation (%VA) was calculated using doublet interpolation corrected for when the superimposed stimulation did not occur during the MVC plateau force:

$$\%VA = [1 - (\text{force prior to superimposed doublet}/MVC) * (\text{superimposed doublet force}/Q_{pot})]$$

Statistical Analysis: A two-way ANOVA was used to test for day-to-day differences in the pre-exercise value of the MVC for potential training adaptations as well as between sexes (intensity x sex). Two-way ANOVAs with repeated measures were used to test for differences in MVC, Q_{pot} , and %VA 1) across work rates at each time point during recovery within men and women (work rate x time) and 2) at each time point during recovery between men and women within each work rate (time x sex). Differences were considered statistically significant when $p < 0.05$. Data were reported as means $\pm$ standard deviation (SD) unless otherwise noted.

Results

Resting isometric MVC force among all subjects was 79.0 ± 17.2 kg. There were no significant day-to-day differences in MVC ($p = 0.32$). Mean $\pm$ SD force and T_{lim} between sexes for each intensity are shown in Table 1. Women had a lower MVC and resistances at each relative work rate than men ($p = 0.002$). Women exercised longer at 40% MVC compared to men ($p < 0.001$), but no other sex differences in T_{lim} were present.

Neuromuscular Function:

Maximal voluntary contraction (MVC): When analyzed as the entire group ($n = 12$) MVC was significantly decreased at task failure compared to baseline following all exercise intensities. MVC at task failure was not decreased to the same degree following exercise at 80% MVC compared to exercise at 40 and 50% MVC ($p < 0.01$). MVC remained depressed throughout 150 s of recovery following each exercise intensity. MVC was significantly higher at 90 s of recovery following severe-intensity exercise (40 and 50% MVC) compared to at task failure ($p < 0.001$), and at 60 s of recovery following exercise at 70% MVC ($p = 0.004$), demonstrating significant recovery from fatigue by these time points. Maximal force following exercise at 80% MVC was not different from force at task failure until 150 s of recovery ($p = 0.004$), however, this is likely because MVC forces were not as decreased, suggesting overall less fatigue. Indeed, MVC at 150 s of recovery was significantly greater following 70 and 80% MVC compared to following exercise at 40% MVC ($p < 0.05$).

To examine MVC responses to exercise within each sex, MVC forces in both men and women at baseline, task failure, and up to 150 s into recovery are shown in Fig 2.1. Men had greater baseline MVC compared to women (Fig 2.1). MVC was significantly reduced in both men

and women following each work rate and remained significantly lower than baseline values throughout 150 s of recovery. Baseline force, force immediately following task failure, and force at 150 s of recovery in men and women are shown in Fig 2.2. Within men, no differences were found in MVC among intensities at task failure or after 150 s of recovery. Conversely, within women, exercise at 70 and 80% MVC did not decrease maximal force production to the same degree as exercise 40% MVC at task failure ($p < 0.003$) or after 150 s of recovery ($p < 0.03$).

Potentiated twitch force (Q_{pot}): When analyzed as the entire group ($n = 12$) absolute Q_{pot} was significantly decreased at task failure compared to baseline following all exercise intensities. Q_{pot} at task failure was not decreased to the same degree following exercise at 80% MVC compared to exercise at 50% MVC, with no other differences at task failure detected. Q_{pot} remained depressed throughout 150 s of recovery following each exercise intensity, except for at 150 s of recovery following exercise at 80% MVC ($p = 0.145$). Further, Q_{pot} following extreme-intensity exercise (70 and 80% MVC) was greater after 150 s of recovery compared to following severe-intensity exercise (40 and 50% MVC; $p > 0.01$).

To examine Q_{pot} responses to exercise within sex, absolute Q_{pot} forces in both men and women at baseline, task failure, and up to 150 s into recovery are shown in Fig 2.3, while Q_{pot} relative to the decrease in force caused by exercise are shown in Fig 2.4. Men showed higher baseline Q_{pot} compared to women. Q_{pot} at task failure was significantly reduced from baseline for both men and women at all four work rates, but no sex differences were detected at task failure following any work rate ($p = 0.97, 0.41, 0.15, 0.37$ after 40, 50, 70, and 80% MVC, respectively). Baseline force, force immediately following task failure, and force at 150 s of recovery in men and women are shown in Fig 2.5. Within men, exercise at 70% MVC did not decrease Q_{pot} to the same degree as exercise at 50% MVC at task failure ($p < 0.044$) or at 150 s of recovery following 40 or

50% MVC ($p < 0.04$). Within women, Q_{pot} was not different at task failure across work rates. Further, Q_{pot} following exercise at 80% MVC was not decreased to the same degree as following exercise at 40% or 50% MVC at 150 s of recovery ($p < 0.05$).

Voluntary activation (%VA): No differences were found at baseline within men ($93.5 \pm 2.2\%$, $p > 0.94$), women ($95.3 \pm 3.2\%$, $p > 0.99$), or between sexes ($p > 0.70$). The %VA was not different from baseline at task failure following any of the four work rates in either sex, nor was %VA different across all four work rates within men ($p > 0.08$; $82.8 \pm 11.0\%$, $87.3 \pm 6.6\%$, $90.4 \pm 12.1\%$, $92.7 \pm 3.2\%$ following exercise at 40, 50, 70, and 80% MVC, respectively), or within women ($p > 0.84$; $93.8 \pm 5.3\%$, $89.6 \pm 11.6\%$, $90.9 \pm 10.3\%$, and $91.2 \pm 3.6\%$ following exercise at 40, 50, 70, and 80% MVC, respectively). Further, there were no differences in %VA after 150 s of recovery within or between sexes across all four work rates.

Discussion

Major findings: Our hypotheses were partially confirmed by these data. In men, maximal force produced at task failure were not different across all intensities. However, women produced greater force (i.e., less decline) at task failure following extreme-intensity exercise (i.e., 70 and 80% MVC) compared to lower-intensity exercise (i.e., 40% MVC). MVC force recovery was apparent in both sexes following severe-intensity exercise. However, no recovery in maximal voluntary force was detected in women following exercise at 70% MVC or in either sex after exercise at 80% MVC (Fig 2.1). Q_{pot} (indicator of peripheral fatigue) was reduced less at task failure following extreme-intensity exercise (70 and 80% MVC) compared to severe-intensity exercise (40 and 50% MVC) in men. However, Q_{pot} was reduced to a similar degree across all four work rates in women. Although peripheral fatigue was still apparent in men following all exercise intensities at 150 s of recovery, there was significant recovery within 60 s (Figs 2.3 & 2.4). Women also showed a partial response in recovery following severe-intensity exercise, but reached forces that were not statistically different from baseline values after extreme-intensity exercise, implying full recovery (Fig 2.3). Lastly, no statistical differences in %VA (indicator of central fatigue) were detected following any of the four work rates in men or women, nor across recovery following any of the work rates.

Recovery kinetics: Although neuromuscular recovery following exercise has previously been reported (1, 10, 36), few studies have examined changes through the initial seconds/minutes immediately following exercise cessation. We previously have shown that recovery from fatigue occurs faster following task failure at intensities closer to MVC (1) compared to submaximal intensities (1, 6, 35). Therefore, we hypothesized that Q_{pot} and MVC would recover faster following extreme-intensity exercise compared to severe-intensity exercise. Consistent with this,

in women, Q_{pot} returned to baseline values within 2 minutes following 70% MVC and after one minute following 80% MVC, while Q_{pot} remained significantly reduced following 40 and 50% MVC (Fig 2.3); This suggests that peripheral fatigue development following extreme-intensity isometric exercise is fully recovered in women in < 2 minutes, while still apparent after severe-intensity exercise. The current data also suggest that men do not fully recover to baseline values within 150 s following extreme-intensity exercise (Fig 2.3); however this is inconsistent with previous data from our lab (1). It is likely that these differences are due to differences in mode of exercise, e.g., one- vs two-legged knee extension (24) or dynamic vs isometric contractions (5, 26). Indeed, Senefeld et al. (2018) found isometric exercise decreased Q_{pot} to a greater degree than dynamic exercise (36). Further, they found that a 60 s sustained, maximal isometric knee-extension contraction reduced Q_{pot} to $\sim 35\%$ of baseline force, and had recovered to $\sim 85\%$ of baseline force by 150 s in both men and women. Our current data support the finding that, although recovery from isometric exercise may be slower than from dynamic exercise, much of the force loss is recovered in the immediate minutes after exercise cessation. Our current data further characterize the recovery of force throughout the 150 s immediately following exercise (Figs 2.1 & 2.4) and is consistent with other data that shows much of the loss of MVC and Q_{pot} force (20, 21) and %VA (19, 21) (indicating peripheral and central fatigue, respectively), is recovered in the first 150 s following exercise cessation.

Our data also support the finding that recovery from higher intensity exercise (i.e., extreme-intensity exercise) occurs faster than from lower intensity exercise (i.e., $\leq$ severe-intensity exercise). Although this has been suggested (6, 35), the current study is the first to detail this finding in the context of exercise intensity domains. It is well accepted that physiological responses to exercise are intensity-domain dependent. Given the previous finding that the boundary between

severe- and extreme-intensity domains occurs ~60% MVC (1), previous studies have also showed profound differences in physiological responses during exercise. There is evidence of greater limitations to blood flow due to intramuscular pressures causing contraction-induced occlusion beginning ~50-60% MVC (7, 37). Wernbom et al., (2006) found vascular occlusion decreased exercise tolerance at 20 – 40% MVC, but not at 50% MVC, suggesting that by 50% MVC, contractions themselves would occlude muscle blood flow (37). Contraction-induced limitations to blood flow would directly impact O₂ delivery, thus providing a potential explanation as to why $\dot{V}O_{2max}$ may not be reached before task failure occurs (23). Limitations to O₂ delivery combined with the relatively high force requirements place a greater demand on alternative ATP resynthesis pathways, such as utilization of phosphocreatine. Indeed, phosphocreatine (PCr) breakdown has been shown to increase nonlinearly at higher intensities (8). In addition, PCr has a fast half-recovery time (~ 1 min) after maximal exercise (12), thus potentially providing an explanation for a faster recovery in force seen following extreme-intensity exercise (Figs 2.1 & 2.4).

Indicators of central fatigue development have been found at maximal and near-maximal work rates (10, 38). Although %VA was not significantly different in men or women in the current study, individual responses showed a wide range in central fatigue development across exercise intensities. Chartogne et al. (2020) found a negative correlation between central fatigue and peripheral fatigue development during 5-minute repeated MVCs (17). Further, it could be that a small contribution of central fatigue may be enough to cause a “critical combination” of fatiguing factors that limit exercise tolerance at extreme intensities (2, 11). This, combined with fatigue-producing metabolite and substrate conditions (e.g., intramuscular inorganic phosphate, and/or decreased PCr), may cause task failure to occur earlier than predicted by the severe-intensity power-duration relationship, but which is also quickly reversible (19-21).

Sex differences: Consistent with previous studies, men produced higher MVC (Fig 2.1) and $\dot{Q}_{pot}$ forces (Fig 2.2) compared to women (30, 36). In contrast, women were able to sustain exercise for longer at 40 and 50% MVC; however, sex differences in exercise tolerance were not evident at 70 and 80% MVC, presumably during extreme-intensity exercise. This is consistent with the study by Maughan et al. (1986), who showed no significant differences in exercise endurance at 80 and 90% MVC between men and women, while women exercised significantly longer than men at 50 and 70% MVC (29). Conversely, Ansdell et al. (2017) found that women did exercise longer than men at 50% MVC (4). It has been suggested that women's ability to exercise longer than men during severe-intensity exercise could be due to greater oxygen delivery and oxidative metabolism (3, 34), which could in turn be explained by women developing less absolute muscle occlusion force during contractions than men for the same %MVC task (7).

Our data show that the magnitude of peripheral fatigue development measured at task failure was dependent on exercise intensity in men, but not in women. Women have been shown to have faster recovery from exercise compared to men (3, 36). That these differences are less apparent after maximal exercise lends further support that blood flow delivery and/or intramuscular conditions common to both men and women (e.g., elevated H^+ , inorganic phosphate, and/or decreased phosphocreatine, ATP) contribute to the limited exercise tolerance of the extreme-domain compared to that predicted by the severe-intensity domain power-duration relationship (18, 28).

Experimental considerations: Several factors should be considered when interpreting the data from the current study. First, the boundary between the severe- and extreme-intensity domain has not yet been clearly defined. Although it is agreed that extreme-intensity exercise would result in task failure before $\dot{V}O_{2max}$ is reached (23), preliminary data from our lab showed inconsistent $\dot{V}O_2$

responses to maximal knee-extension exercise, precluding $\dot{V}O_2$ as a reliable demarcation. Therefore, work rates that resulted in task failure in under 2 minutes were considered extreme-intensity exercise. We previously showed that this occurred at $\sim 60\%$ MVC in men (1), and therefore work rates at 70 and 80% MVC were chosen to increase the likelihood of being in the extreme-intensity exercise domain, and 40 and 50% MVC to be most likely in the severe-intensity domain. However, it is possible that 70% MVC may have been severe-intensity exercise for some individuals and 50% MVC may have been extreme-intensity exercise for others.

This study used absolute percentages of MVC for comparisons. It is possible that women at 40 and 50% MVC were on the lower end of their relative power-duration relationship (i.e., closer to critical torque) compared to men, therefore able to exercise longer before W' was completely utilized (3). However, although women exercised longer, they also showed faster recovery following exercise. Future studies should match men and women for aerobic exercise capacity as well as MVC to better identify specific sex differences in the contributions of peripheral and central fatigue during and following extreme-intensity exercise.

Finally, the current study examined 12 subjects, consisting of 6 men and 6 women. The primary purposes of this study were not necessarily to examine differences due to sex. However, because responses to exercise in women are largely lacking in relation to men, we recruited both sexes. Initial analyses were made with grouped data, but it was immediately apparent that there are likely sex differences in the response to exercise as well. Therefore, we present data separated by sex. However, the low subject numbers may have hidden other important differences. Future study designs need to be done in such a way to elicit these differences between men and women.

Conclusions: That the physiological responses to exercise are intensity domain-dependent is well known. However, little is known about how the responses to extreme-intensity exercise compare with the other domains, specifically severe-intensity exercise. The current data showed that women were able to sustain severe-intensity exercise longer than men, but there were no differences in extreme-intensity exercise tolerance. It is also apparent that there are differences in the neuromuscular recovery characteristics immediately following exercise in these two intensity domains. Men and women both showed significant recovery following extreme-intensity exercise. However, while men showed evidence of residual peripheral fatigue 150 s into recovery, women appeared to be fully recovered from peripheral fatigue within 120 s after exercise cessation. These findings have important implications in understanding the potential mechanisms contributing to intensity-dependent exercise tolerance and time course of recovery. Therefore, practitioners need to consider exercise intensity and recovery characteristics specific to men and women when designing optimal loading for training and rehabilitation in both sexes.

	Resistance (N)		T _{lim} (s)	
	Men	Women	Men	Women
MVC	92.7 ± 11.4	65.4 ± 9.5 *		
80% MVC	73.8 ± 8.8	51.9 ± 7.9 *	62 ± 15	72 ± 18
70% MVC	64.2 ± 9.2	45.7 ± 7.8 *	86 ± 16	134 ± 25
50% MVC	47.0 ± 5.7	33.9 ± 3.6 *	148 ± 24	190 ± 35
40% MVC	37.2 ± 4.2	25.5 ± 3.3 *	240 ± 55	350 ± 113 *

Table 2.1: Times to task failure.

Mean ± SD resistance and time to task failure (T_{lim}) for all intensities. *Different from men (p < 0.05).

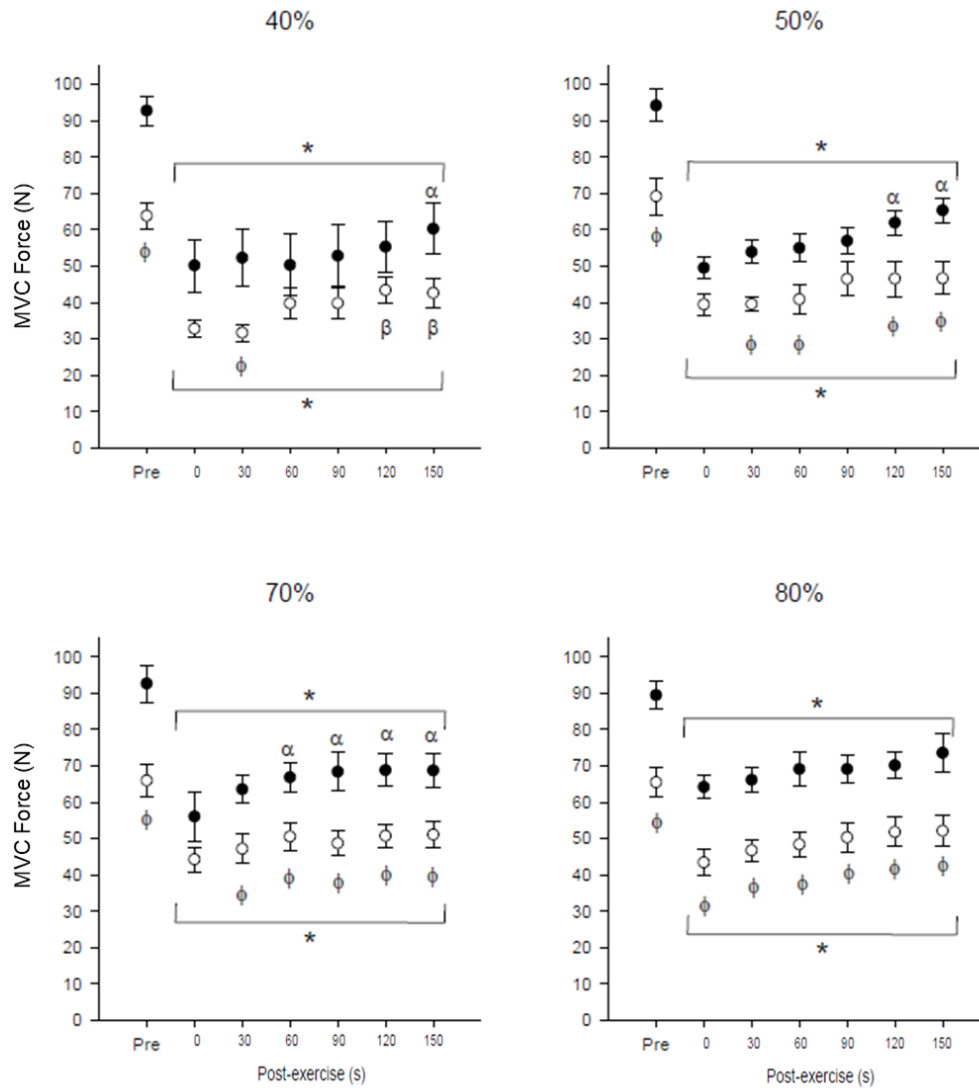


Figure 2.1: Change in maximal voluntary contraction force through recovery.

Absolute maximal voluntary contraction force (MVC) with Pre (baseline) and each Post-exercise measurement beginning immediately after task failure within each intensity. Men (●), Women (○).

* Significantly lower than Pre-exercise value. α significantly different from task failure (0 s) within men, β Significantly different from task failure (0 s) within women, Φ Significantly different from men, $p < 0.05$.

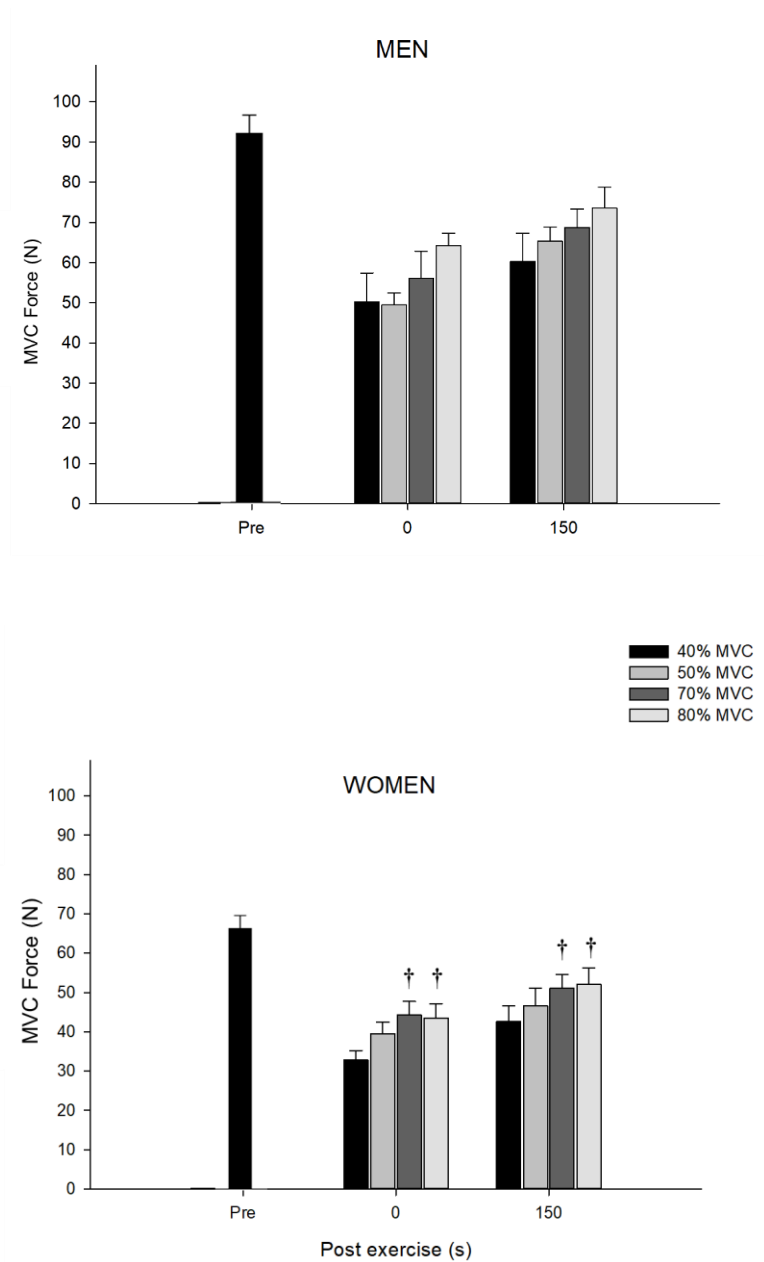


Figure 2.2: Change in maximal voluntary contraction force across exercise and recovery.

Absolute maximal voluntary contraction force (MVC) with Pre-exercise (baseline), immediately following task failure (0 s), and at 150 s of recovery in men and women. † Significantly greater than 40% MVC, $p < 0.05$.

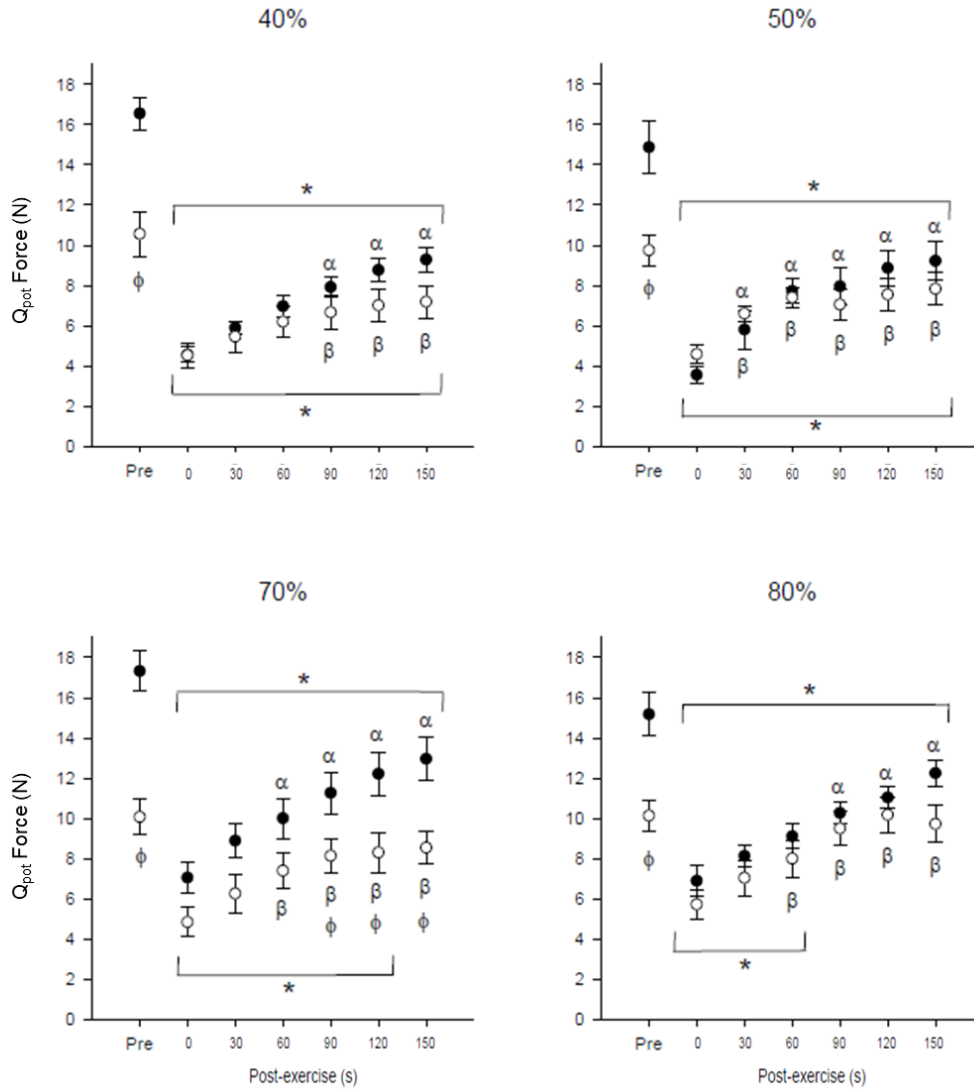


Figure 2.3: Change in potentiated twitch force through recovery.

Absolute potentiated twitch force (Q_{pot}) with Pre (baseline) and each Post-exercise measurement beginning immediately after task failure within each intensity. Men (●), Women (○). * Significantly lower than Pre-exercise value. α significantly different from task failure (0 s) within men, β Significantly different from task failure (0 s) within women, Φ Significantly different from men, $p < 0.05$.

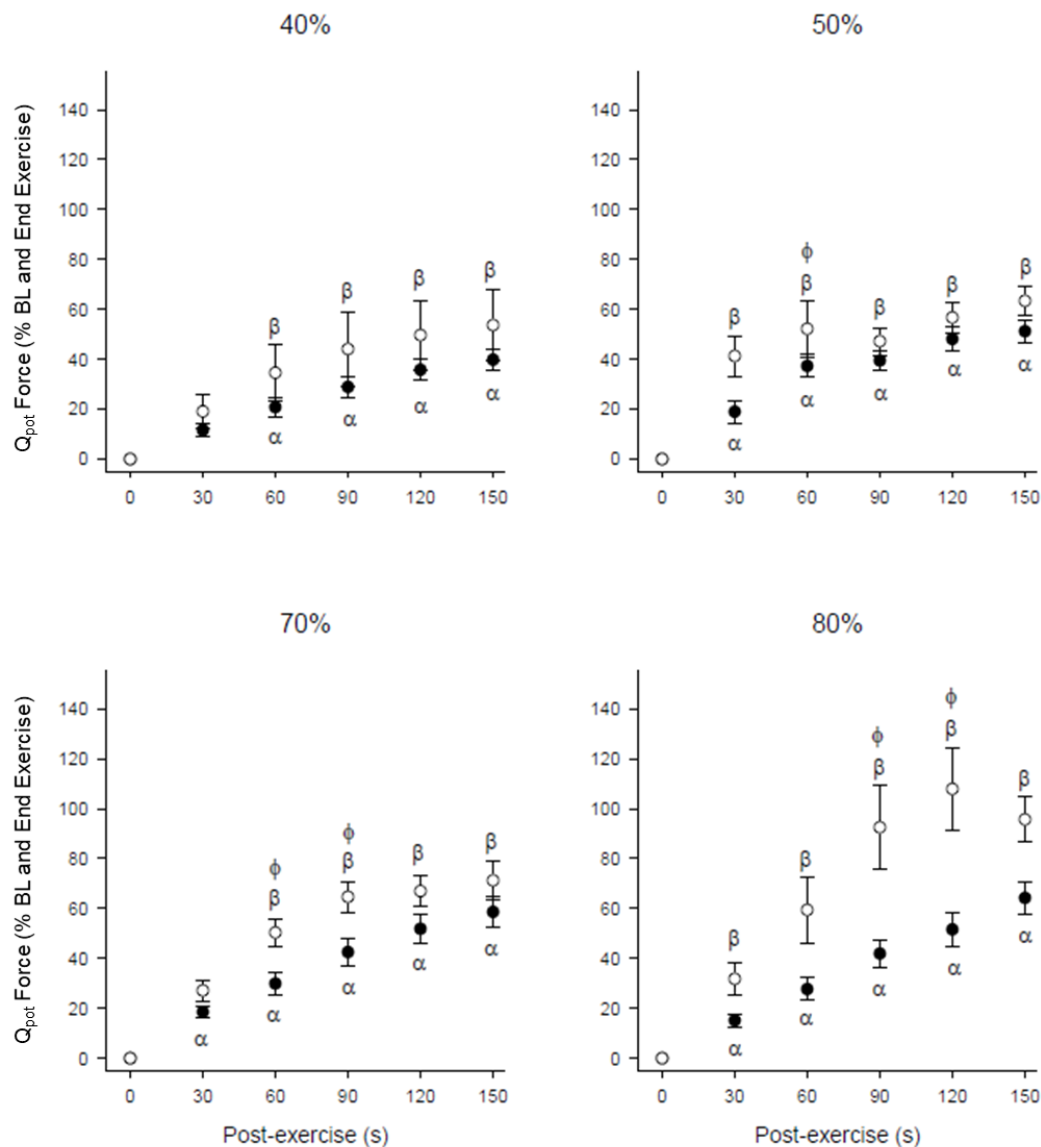


Figure 2.4: Recovery of potentiated twitch relative to the change in force across exercise.

Potentiated twitch force (Q_{pot}) relative to baseline and end-exercise to examine changes in recovery relative to amount of fatigue accumulated during each intensity beginning immediately after task failure. 100% represents baseline Q_{pot} forces, whereas 0% represents Q_{pot} at task failure. Men (●), Women (○). α significantly different from task failure (0 s) within men, β Significantly different from task failure (0 s) within women, Φ Significantly different from men, $p < 0.05$.

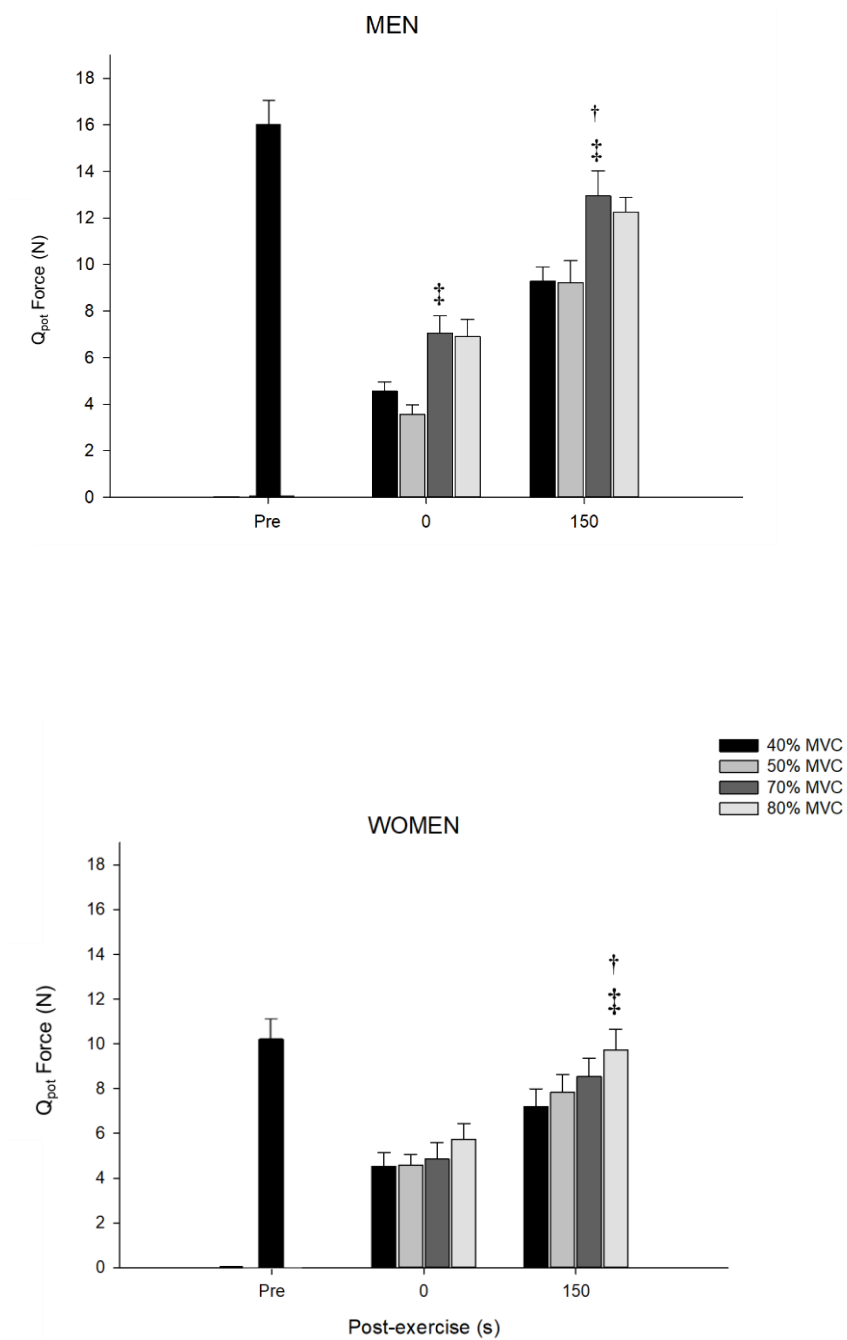


Figure 2.5: Change in potentiated twitch force across exercise and recovery.

Absolute potentiated twitch force (Q_{pot}) with Pre-exercise (baseline), immediately following task failure (0 s), and at 150 s of recovery in men and women. † Significantly greater than 40% MVC, ‡ Significantly greater than 50% MVC, $p < 0.05$.

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Chapter 3 - Effect of sex on the extreme-intensity power-duration relationship

Summary

We have shown that, akin to the severe-intensity power duration relationship (i.e., W'_{sev}), there exists a separate, smaller power-duration relationship of the extreme-intensity domain (W'_{ext}) in men. We have also shown evidence that there may be differences in contributions of central and peripheral fatigue between men and women during and immediately following extreme-intensity exercise. The current study tested the hypotheses that 1) the W'_{ext} would be significantly less than W'_{sev} in both sexes, but not different between men and women, 2) absolute MVC would be reduced to greater extent at end-exercise following severe- and extreme-intensity exercise in men compared to women but not when scaled relative to baseline, and 3) peripheral fatigue would be greater at task failure (T_{lim}) in men compared to women following severe-intensity exercise, with no sex difference following extreme-intensity exercise. Following familiarization, 7 men and 7 women completed three severe- (T_{lim} : 2-4 min, S1; 5-7 min, S2; 8-12 min, S3) and three extreme-intensity (70, 80, 90% MVC) isometric knee-extension bouts to task failure. Maximal voluntary contraction (MVC) and potentiated twitch force (Q_{pot}) were measured and compared at baseline, task failure, and 150 s of recovery. W'_{ext} was significantly smaller compared to W'_{sev} in men (2.4 ± 1.2 kJ vs 3.9 ± 1.3 kJ; $p = 0.03$) and in women (1.6 ± 0.8 kJ vs 2.9 ± 1.7 kJ; $p = 0.05$), however there were no sex differences in W'_{ext} or W'_{sev} . There were no sex differences in MVC at task failure following severe-intensity exercise. However, MVC was lower in women following extreme-intensity exercise compared to men, although there were no sex differences in MVC relative to baseline.

Further, there were no differences in MVC by the end of recovery compared to baseline in men or women following extreme-intensity exercise.

Q_{pot} was not different at task failure following severe- and extreme-intensity exercise between men and women, however, men showed lower Q_{pot} relative to baseline, suggesting greater peripheral fatigue development, with the exception of exercise at 90% MVC. These data provide evidence that important sex differences exist in the contributions of peripheral fatigue to task failure and in recovery from exercise which depend on exercise intensity. Therefore, practitioners need to consider exercise intensity and the time course of recovery when prescribing exercise to men and women.

Introduction

Metabolic responses to exercise are dependent on intensity of exercise and can therefore be characterized by separate intensity domains. Depending on the modality of exercise, the boundary between the heavy- and severe-intensity exercise domains has been termed critical torque (CT; or the analogous critical power or critical speed). The second parameter of the severe-intensity domain, W' , describes the amount of work performed during a constant-load, severe-intensity exercise bout to task failure (T_{lim}). Interestingly, this amount of work performed is not different across severe-intensity work rates (18, 20). Previous research in our lab (1) has shown evidence of an upper boundary of the severe-intensity domain, as the power-duration relationship was no longer accurate at predicting work capacity at work rates $> 60\%$ 1RM, compared to the lower boundary occurring at $\sim 25\%$ maximal voluntary contraction (MVC) during isometric knee-extension exercise. Further, the supra-severe-intensity work rates (i.e., extreme-intensity domain) displayed a linear relationship across extreme-intensity work rates, with a separate and smaller slope (W'_{ext}) than the W' of the severe-intensity domain (W'_{sev}). Therefore, the specific mechanisms causing fatigue during extreme-intensity exercise are likely different than the mechanisms limiting severe-intensity exercise (1).

It is well established that women have greater tolerance to exercise compared to men (12, 14, 17). Interestingly, this difference appears to be less dramatic, and in some cases non-existent, at higher intensity work rates (9, 17, 26). Specifically, Yoon et al. (2007) found that women were able to exercise longer at 20% MVC, but not at 80% MVC, compared to men (26). Maughan et al. (1986) also found women exercised longer than men at 50% and 70% MVC, but not at 80 or 90% MVC (17). Although CT appears to occur at a higher percentage of maximal force output relative to MVC in women compared to men, the absolute amount of work (W'_{sev}) was not different

between sexes (3). Therefore, combined with previous data showing exercise tolerances to be similar between men and women (9, 17, 26), these observations predict that men and women may show similar W' for both severe- and extreme-intensity domains.

In addition to increased exercise tolerance at work rates up to $\sim 50 - 70\%$ MVC, women show greater fatigue resistance during exercise (21, 22). Fatiguing mechanisms within the exercising muscle (at or distal to the neuromuscular junction, i.e., peripheral fatigue) are seen in both men and women at low- and high-intensity work rates; however, the contribution of peripheral fatigue varies at the limit of exercise tolerance (T_{lim}) with respect to the level of intensity and between sexes. For example, peripheral fatigue (as estimated by reduced forces relative to baseline MVC during electrical stimulation of resting muscle) was not different between men and women following 60 s of sustained MVC, but was greater in men following submaximal fatiguing exercise consisting of 120 knee extensions at 20% MVC over 6 minutes (24). Further, previous research has found that men show a greater reduction in voluntary activation following intermittent MVCs compared to women, suggesting central fatigue has a greater contribution to sustained maximal exercise tolerance in men (24). Also, the mechanisms of fatigue are quickly reversible following higher intensities, compared to lower intensities, in men (1, 23), with much of the recovery happening in the initial minutes (< 3) following exercise cessation (2). Specifically, Q_{pot} and MVC forces were not different from baseline after 150 seconds of recovery following task failure of extreme-intensity exercise, but remained depressed throughout 150 seconds of recovery following severe-intensity exercise (1). It is currently unclear if the time course of recovery following severe- and extreme-intensity exercise to task failure are different between men and women.

Therefore, the primary objectives of the current study were to compare the effect of sex on 1) the W' of both the severe- and extreme-intensity exercise domains and 2) neuromuscular

recovery characteristics immediately following exhaustive, isometric knee-extension exercise in both exercise intensity domains. We hypothesized that 1) the W'_{ext} would be significantly less than W'_{sev} in both sexes, but not different between men and women, 2) absolute MVC would be reduced to greater extent at end-exercise following severe- and extreme-intensity exercise in men compared to women but not when scaled relative to baseline, and 3) peripheral fatigue would be greater at task failure (estimated by reduced potentiated twitch force; Q_{pot}) in men compared to women following severe-intensity exercise, with no sex difference following extreme-intensity exercise.

Methods

Subjects: Seven healthy men (mean $\pm$ S.D.: 26 ± 4 yr; 81 ± 14 kg; 176 ± 6 cm) and seven healthy women (mean $\pm$ S.D.: 23 ± 3 yr; 67 ± 8 kg; 165 ± 5 cm) volunteered for this study. All participants were free from cardiovascular, pulmonary, and metabolic disease as determined by a medical history questionnaire. Prior to participation in this study, subjects were informed of all procedures, and associated potential risks and benefits. Written informed consent was obtained from all participants prior to participation. Subjects were instructed to refrain from vigorous exercise 24 hours, alcohol consumption 12 hours, and food and caffeine 2 hours prior to each session, as well as to maintain current exercise habits in order to avoid any potential training or detraining effect. All research components were reviewed and approved by the Institutional Review Board of Human Subjects (#10181) at Kansas State University, Manhattan, KS.

Experimental Design: Subjects visited the laboratory a minimum of 7 times, with at least 48 hours between sessions. On the first visit, subjects were familiarized with all testing procedures and equipment prior to testing. All exercise testing and measurements were performed on the right leg using a custom-built isometric knee extension ergometer and force transducer (LBG1, BLH Electronics, Waltham, MA, USA). Subjects were seated upright and the backrest was adjusted so that hip flexion angle was 105° and knee flexion angle was 90° . Force transducer position on the lower leg was adjusted for each subject such that a 90° angle of pull was maintained. The position of the force transducer and backrest setting were recorded and replicated for each subject and exercise sessions.

Constant-Load Tests: During each subsequent visit, subjects performed one of 6 intermittent isometric constant-load tests to T_{lim} . Target forces during each exercise test were chosen to elicit

3 severe- and 3 extreme-intensity work rates. Based on our previous finding that intensities greater than $\sim 60\%$ MVC would elicit task failure in < 2 minutes and could therefore be considered extreme-intensity work rates (1), and intensities that elicit T_{lim} within 2-15 minutes reflect severe-intensity exercise, severe-intensity work rates were selected to elicit T_{lim} between 9-15 minutes (S1), 5-8 minutes (S2), and 3-4 minutes (S3). Extreme-intensity work rates were performed at 70, 80, and 90% MVC. Exercise tests were performed in random order on separate visits. MVC was measured prior to each exercise test to examine day-to-day variability. Subjects performed all knee-extension exercise at a 60% duty cycle (3 s contraction; 2 s relaxation) at a rate of 12 contractions/min as per a pre-recorded audio cue. Target force was displayed as a line generated in the middle of the display to blind subjects to intensity. Subjects were required to reach and maintain target force for the entire 3 s of contraction as indicated by visual and verbal feedback. Subjects were verbally encouraged throughout the test. Task failure was defined as the first failure to reach and maintain target force and the post-exercise neuromuscular assessment began at the subsequent audio cue.

Neuromuscular Function: Neuromuscular function testing was conducted similar to previous protocols used in our laboratory (1, 6). Briefly, testing was performed on the right leg prior to and immediately following each constant load exercise test. Adhesive electrodes (4 x 6 cm) were used to electrically stimulate the knee extensor muscles of the right leg via the femoral nerve. The anode was attached to the gluteal fold. The cathode was positioned over the approximate location of the femoral nerve, and adjusted based on verbal feedback from the participants, who were instructed to report the greatest feeling of a knee-extension motion so as to remove activation of other thigh muscles. Maximal stimulation was then assessed prior to each exercise bout. Stimulation intensity was initiated at 50 mA and was increased in 25 mA increments until the measured force and

compound muscle action potential (M-wave) ceased to increase. The stimulator current was then increased an additional 30% to ensure the stimuli were supramaximal. Force was sampled at 1000 Hz and displayed on a computer screen (LabVIEW, National Instruments, Austin, TX, USA). The femoral nerve was stimulated using a high-voltage constant-current electrical stimulator (DS7AH, Digitimer, Welwyn Garden City, UK). Paired stimuli (doublets) were delivered at 400 V with 100 μ s square-wave pulse durations and a 10 ms pulse interval. Prior to each exercise test, subjects performed a series of 6, 3 s maximal voluntary contractions (MVCs), beginning every 30 s. Doublet muscle stimulations were delivered 5 s prior to each MVC, 1.5 s into the MVC, and 5 s after each MVC to obtain measurements of unpotentiated, superimposed, and potentiated doublet forces, respectively. MVC was determined as the greatest force attained prior to the superimposed muscle doublet stimulation. A total of 6 of these neuromuscular assessments was completed starting immediately upon task failure (T_{lim}) and every 30 seconds thereafter for the next 150 s.

Data analysis: Potentiated twitch force (Q_{pot}) has been shown to increase after the first neuromuscular measurements, becoming maximal after the third neuromuscular measurement (16), likely due to incomplete potentiation. Therefore, the average of the last three of six Q_{pot} forces during baseline neuromuscular measurements was used as baseline Q_{pot} , as done previously (16). However, the post-exercise measurements were assumed to be fully potentiated as subjects were exerting maximal effort to reach target force at task failure. Therefore, individual neuromuscular measurements were analyzed as representing the current state of the muscle.

Statistical Analysis: A two-way ANOVA was used to test for day-to-day differences in the pre-exercise value of the MVC for potential training adaptations as well as between sexes (intensity x sex). Two-way ANOVAs with repeated measures where appropriate were used to test for differences 1) among the work rates at each neuromuscular measurement within sex (work rate x

neuromuscular measurement) and 2) at each neuromuscular measurement between men and women within each work rate (neuromuscular measurement x sex). Differences were considered statistically significant when $p < 0.05$. Data were reported as means $\pm$ standard deviation (SD) unless otherwise noted.

Results

Isometric MVC forces are shown in Table 1. There were no significant day-to-day differences in MVC ($p = 0.42$). Women had a lower CT force compared to men (18.5 ± 2.8 N vs 26.8 ± 6.8 N, $p = 0.018$), however CT as %MVC was not different between sexes (32 ± 9 N vs 30 ± 10 N). Further, work rates as %MVC were not different between men and women for S1 ($40 \pm 9\%$ MVC vs $41 \pm 7\%$ MVC), S2 ($44 \pm 10\%$ MVC vs $45 \pm 8\%$ MVC), or S3 ($52 \pm 11\%$ MVC vs $52 \pm 9\%$ MVC). Mean $\pm$ SD force and T_{lim} between sexes for each intensity are shown in Table 1. Women had a lower MVC and resistances at each relative work rate than men ($p = 0.002$). Women had greater exercise tolerance during the lowest severe-intensity work rate (S1) compared to men ($p < 0.001$), however no other sex differences in T_{lim} were present.

W'sev and W'ext: Fig 3.1 shows the W'_{sev} and W'_{ext} in both men and women. The W'_{sev} was 3.9 ± 1.3 kJ and 2.9 ± 1.7 kJ in men and women, respectively. The W'_{ext} was significantly lower than W'_{sev} in both men and women (2.4 ± 1.2 kJ, $p = 0.03$ and 1.6 ± 0.8 kJ, $p = 0.05$; respectively), however, there were no differences detected in either W'_{sev} or W'_{ext} between men and women.

Neuromuscular Function:

Maximal voluntary contraction (MVC): Absolute MVC forces in both men and women at baseline, task failure, and up to 150 s into recovery are shown in Fig 3.2. Men had greater baseline MVC compared to women (Fig 3.2). MVC was significantly reduced in both men and women following each severe-intensity work rate, but men produced greater maximal contraction forces compared to women following both severe- and extreme-intensity exercises (Fig 3.2). In men, although MVC did not fully recover within 150 s to baseline values following severe-intensity exercise, men produced greater force at 150 s compared to at task failure. This significant force recovery

following severe-intensity exercise was not seen in women (Fig 3.2). Exercise at 70% and 80% MVC significantly reduced MVC at task failure in both men and women, but only in women following 90% MVC. Further, MVC force in men was not significantly different from baseline at end-recovery following each of the three extreme-intensity exercise bouts. MVC in women had not fully recovered to baseline at end-recovery following 70% MVC, but had recovered to baseline force by 90 s following 80% MVC and by 30 s following 90% MVC (Fig 3.2). MVC force at task failure and at 150 s of recovery relative to the force at baseline in men and women are shown in Fig 3.3, and the reductions in %MVC force are shown in Fig 3.4.

Within men, baseline MVC was not different prior to any of the exercise bouts. Further, there were no differences in maximal force produced at task failure following the three severe-intensity exercises. However, MVC decreased to less of a degree at task failure for the three extreme-intensity exercise bouts compared to the three severe-intensity exercise bouts ($p < 0.05$). Similarly, there were no differences in MVC at the end of 150 seconds of recovery among the three severe- ($p < 0.05$) or the three extreme-intensity exercise ($p < 0.05$). However, MVC forces were higher at end recovery following extreme- compared to severe-intensity exercise ($p < 0.05$).

Within women, baseline MVC was not different prior to any of the exercise bouts. There were no differences at task failure following the three severe-intensity bouts ($p > 0.90$) or after the three extreme-intensity bouts ($p > 0.18$). Across all intensities, MVC at task failure was not reduced to the same degree following 90% MVC compared to the three severe-intensity bouts ($p < 0.008$). MVC following 80% MVC was not different compared to MVC following S2 ($p = 0.05$), with no other differences detected at task failure across all 6 intensities.

Potentiated twitch force (Q_{pot}): Absolute Q_{pot} forces in both men and women at each measurement after exercise are shown in Fig 3.5. Men showed higher Q_{pot} forces compared to women at baseline (Fig 3.5). Q_{pot} at task failure was significantly reduced from baseline for both men and women at all work rates. In men, Q_{pot} did not recover to baseline values during the 150 s of recovery following any of the severe-intensity exercises. Further, although Q_{pot} displayed significant recovery within 90 and 120 s following 70 and 80% MVC, respectively, Q_{pot} remained depressed compared to baseline. However, Q_{pot} force at 90 s recovery was not significantly different from baseline following exercise at 90% MVC. Q_{pot} in women was also depressed throughout 150 s recovery following severe-intensity exercise, with no significant difference between force at 150 s of recovery following exercise at 70% MVC, and at 90 s of recovery following exercise at 80 and 90% MVC compared to baseline.

Baseline force, force immediately following task failure, and force at 150 s of recovery relative to baseline force in men and women are shown in Fig 3.6. Women displayed greater Q_{pot} forces at earlier time points into recovery compared to men (Fig 3.5), which were not different from baseline forces after 150 s of recovery following exercise at 70% MVC and after 90 s of recovery following exercise at 80% MVC, while Q_{pot} forces in men were still significantly depressed throughout the measured recovery (Figs 3.5 & 3.6). These sex differences in recovery were not seen following exercise at 90% MVC, however, as both men and women produced forces similar to baseline at 90 s following task failure.

Within men, baseline Q_{pot} was not different prior to any of exercise bouts. There were no differences at task failure across the three severe-intensity bouts ($p > 0.99$). Q_{pot} at task failure following 80 and 90% MVC was greater compared to forces at task failure following each severe-intensity exercise ($p < 0.001$). However, Q_{pot} at task failure was not different following exercise at

70% MVC compared to exercise following severe-intensity exercise ($p > 0.07$), indicating mechanisms limiting exercise tolerance may also not be different across those intensities. However, Q_{pot} at end recovery (150 s following task failure) was not different across severe-intensity exercise ($p > 0.99$) or across extreme-intensity exercise ($p > 0.37$), and Q_{pot} at end recovery following extreme-intensity exercises was significantly greater compared to at end recovery following severe-intensity exercises ($p < 0.006$). Therefore, although Q_{pot} was not different at task failure across exercise at S1, S2, S3, and 70% MVC, Q_{pot} showed faster recovery kinetics following exercise at 70% MVC compared to severe-intensity exercise.

Within women, baseline Q_{pot} was not different prior to any of the exercise bouts. There were no differences at task failure across the three severe-intensity bouts ($p > 0.74$), across the three extreme-intensity bouts ($p > 0.99$), or across all exercise intensities ($p > 0.27$). Q_{pot} at 150 s was not different across extreme-intensity exercise ($p > 0.93$).

Discussion

Major findings: There are several original findings of the current study. First, the current data support the existence of a W'_{ext} in men as previously shown (1), as well as show evidence for the first time of a W'_{ext} in women. In both men and women, this W'_{ext} was less than the W'_{sev} , but was not different between sexes. Second, severe-intensity exercise reduced maximal force production to absolute forces that were not different between men and women at task failure; however, women produced lower absolute maximal forces following extreme-intensity exercise (Fig 3.2). However, these differences in MVC were lost when expressed relative to baseline MVC (Fig 3.3). Further, MVC remained depressed following severe-intensity exercise throughout the 150 s of recovery compared to baseline in both men and women but showed significant recovery following extreme-intensity exercise, to where MVC was not statistically different from baseline within 150 s of recovery (Fig 3.2). Finally, severe- and extreme-intensity exercise reduced Q_{pot} to forces that were not different between men and women at task failure (Fig 3.5). As men displayed greater Q_{pot} forces prior to exercise, this indicated that men incurred greater amounts of peripheral fatigue during exercise. Indeed, when examined relative to baseline, men had greater reductions in Q_{pot} at task failure compared to women, with the exception of exercise at 90% MVC (Fig 3.6).

Hill et al. (2002) recognized the existence of the extreme-intensity domain and predicted that it would consist of work rates where task failure would be encountered before $\dot{V}O_{2\text{max}}$ could be attained (10). However, that the extreme-intensity domain displayed a W' (W'_{ext}) has only been shown recently (1). It was suggested that the transition between the severe- and extreme-intensity domains occurred $\sim 60\%$ MVC for dynamic knee-extension exercise. The current data suggest this transition may occur at a greater intensity relative to MVC, at $\sim 70\%$ MVC, for isometric contractions, in men and women (Fig 3.1). Additionally, the current data show evidence of a W'_{ext}

in women. It has been acknowledged that women show greater exercise tolerance compared to men at intensities up to $\sim 50\%$ MVC (17, 26). It has been suggested that these sex differences during isometric exercise are associated with inherent differences in anatomical and physiological mechanisms of the exercising muscle (e.g., greater percentages of type I skeletal muscle fibers, increased muscle capillarity, see Hunter 2016) (11). Women also typically show lower absolute maximal and relative forces, and thus a decreased contraction-induced ischemia compared to men (4). Indeed, women had a significantly lower MVC and relative work rates at all intensities (Table 1). It has been shown that contraction-induced ischemia can begin at work rates $> 20\%$ MVC with full occlusion at $\sim 60\%$ MVC independent of absolute force (4). A similar effect is seen on exercise tolerance, which is significantly reduced with blood flow occlusion at intensities up to 40% MVC, but with no further reduction seen for intensities $> 50\%$ MVC (19, 25). These data suggest a mechanistic link between contraction-induced ischemia and exercise tolerance as expressed by differences in W'_{sev} ($\sim 20 - 60\%$ MVC) and W_{ext} ($> 60\%$ MVC).

Our previous data in men (1) showed severe-intensity dynamic knee-extension exercise significantly decreased MVC and slowed its recovery, but were not different from baseline after ~ 90 s of recovery following extreme-intensity exercise. Our current data are consistent with this previous data (Fig 3.2), further showing MVC in men were not different from baseline within 120 s of recovery following exercise at 70% , within 90 s of recovery following exercise at 80% MVC, and with no significant decrease following exercise at 90% MVC. Recovery of MVC following severe-intensity exercise was also found in women, although MVC remained depressed throughout the 150 s of recovery following 70% MVC. This may be further evidence that the transition between severe- and extreme-intensity exercise occurs at a higher intensity relative to MVC in women compared to men.

Potentiated twitch force (Q_{pot}) was not different between men and women throughout the 150 s of recovery (Fig 3.5). However, because Q_{pot} was greater in men prior to exercise, but were not different from women at task failure, suggests that men accumulated greater peripheral fatigue at task failure, except for exercise at 90% MVC (Fig 3.6). These results at near-maximal intensity are consistent with those of Senefeld et al. (2017), who found no differences in Q_{pot} relative to baseline between men and women following a 60-second sustained MVC (24). Our data are also consistent with previous research that shows women to be more fatigue-resistant than men (13). A possible explanation may be the frequency of activation required to meet exercise requirements. For example, it was found that when using electrical stimulation to examine potential mechanisms of fatigue, high frequency (50 – 100 Hz) was required to reach maximal force, which was not sustainable for more than a few seconds (15) but was quickly reversible. High-frequency fatigue is thought to be, at least in part, the result of accumulation of K^+ in the T-tubules and interfiber spaces of muscle, disrupting action potential propagation along the plasmamembrane as shown by a reduction in amplitude and slowing of the waveform (15). In contrast, lower frequency stimulation (20 Hz) resulted in longer duration exercise, for repetitive contractions (5, 8) but a much longer period to recover (hours or days) (7, 15). Putative mechanisms for low-frequency fatigue are a reduced release of Ca^{2+} from the sarcoplasmic reticulum and/or muscle damage associated with structures associated with excitation-contraction coupling (see refs: (15)).

Experimental considerations: Although data during and following extreme-intensity exercise exist, little has been interpreted within the paradigms of exercise intensity domains. Therefore, it is unknown if the transition from severe- into extreme-intensity exercise occurs as a threshold, as seen for the separation between moderate- and heavy-intensity domains (lactate/gas exchange threshold) and heavy- to severe-intensity domains (critical power/torque), or a gradual transition,

with mechanisms limiting exercise tolerance contributing to a greater degree with increased intensity. In the current study, based on our previous observation (1) that the transition between intensity domains occurred at $\sim 60\%$ MVC, we chose work rates with the assumption that they would be within the extreme-intensity domain (70, 80, and 90% MVC). However, it is possible that the transition into the extreme-intensity domain may occur at a greater intensity, such that 70% MVC may represent severe-intensity exercise in some subjects.

Conclusions: We showed further evidence of a W'_{ext} in men and novel evidence of a W'_{ext} in women. Although the effect of sex on the intensity at which the transition from severe- to extreme-intensity exercise occurs remains to be precisely elucidated, it is clear that those mechanisms which are dependent on the exercise intensity domain are evident in both men and women. We also showed that while there was a similar time course for recovery of total maximal voluntary force between men and women, men developed greater peripheral fatigue compared to women. Therefore, it is likely that different mechanisms are contributing to limiting exercise tolerance. Future studies should focus on experimental designs which will elucidate those specific mechanisms to further our understanding of the sex-dependent responses to exercise, especially in order to appropriately design effective and targeted exercise training in men and women.

	Resistance (N)		T _{lim} (s)	
	Men	Women	Men	Women
MVC	90.9 ± 13.0	56.9 ± 8.0 *		
90% MVC	82.6 ± 14.1	49.7 ± 6.0 *	55.7 ± 25.3	66.4 ± 30.4
80% MVC	72.2 ± 10.3	44.8 ± 5.7 *	77.1 ± 25.8	86.4 ± 32.8
70% MVC	63.6 ± 9.2	39.8 ± 5.6 *	108.6 ± 40.7	122.9 ± 42.2
S3	45.8 ± 5.1	29.8 ± 3.1 *	210.7 ± 42.8	259.7 ± 53.6
S2	38.6 ± 5.8	26.5 ± 2.1 *	345.0 ± 121.1	383.6 ± 132.4
S1	35.3 ± 5.5	23.4 ± 2.0 *	519.3 ± 203.6	769.3 ± 291.5 *

Table 3.1: Times to task failure.

Mean ± SD resistance and time to task failure (T_{lim}) for all intensities. *Different from men (p < 0.05).

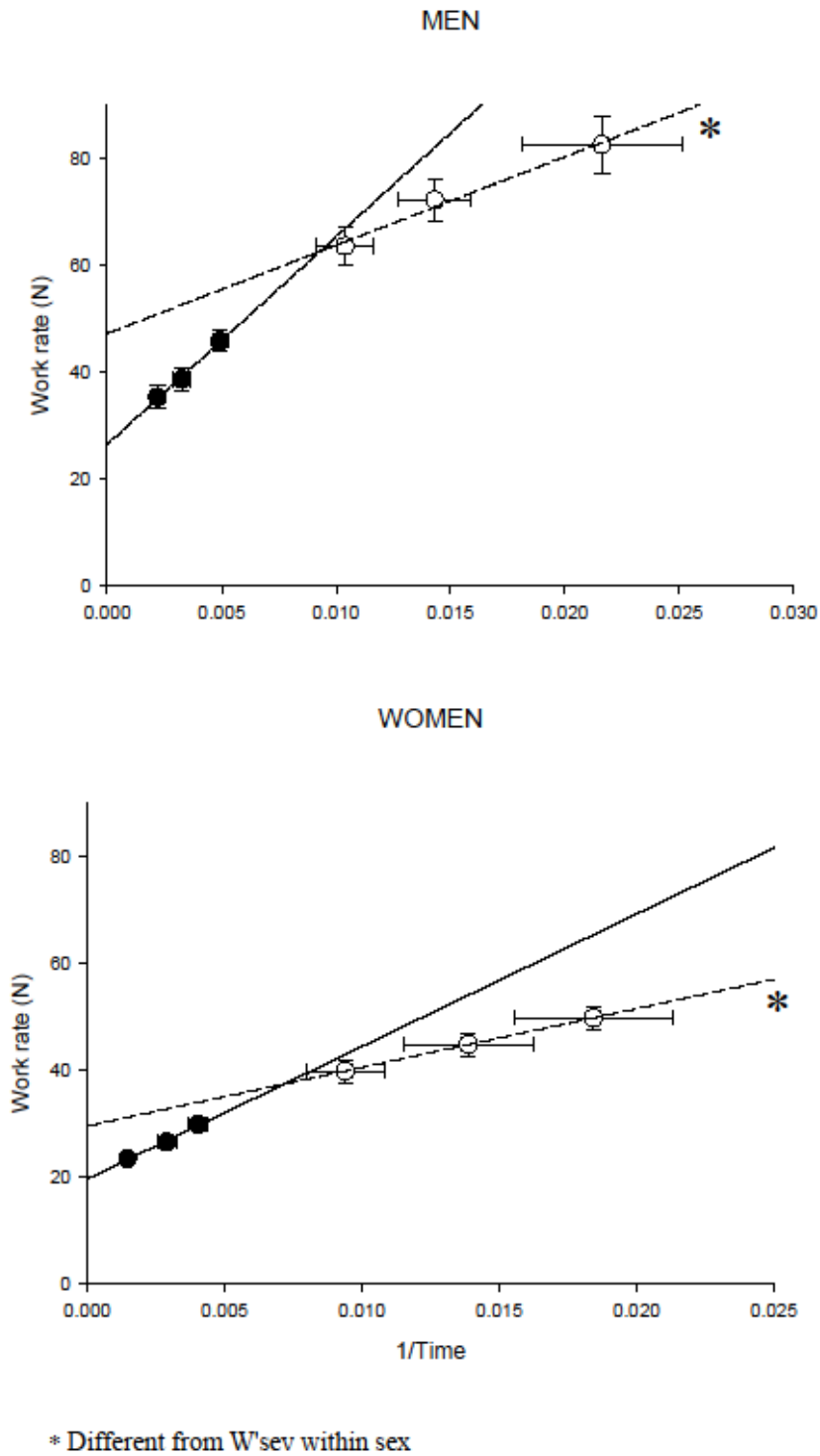


Figure 3.1: Difference between W'_{sev} and W'_{ext} .

Mean W'_{sev} (solid line) vs W'_{ext} (dashed line) in both men and women.

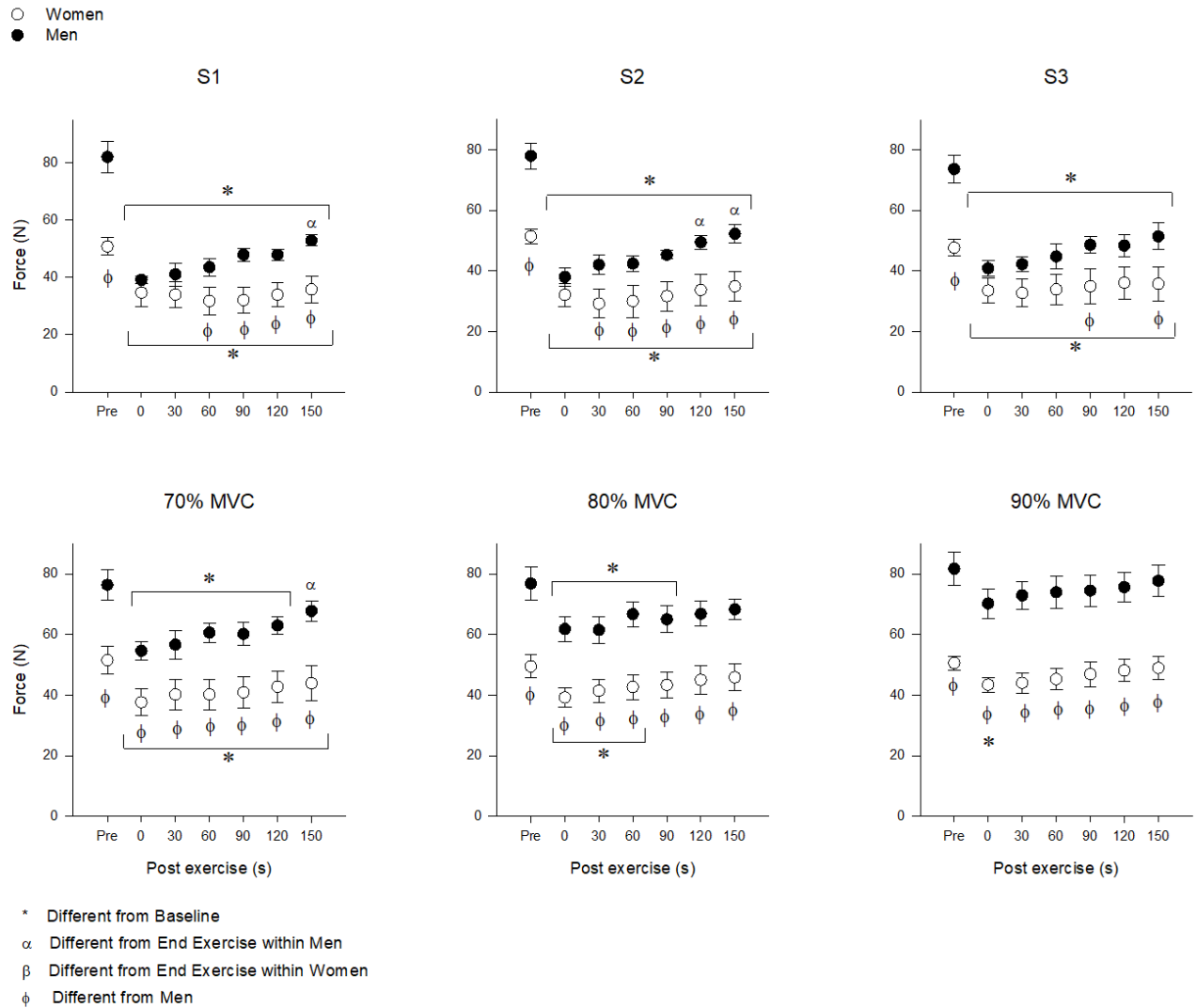


Figure 3.2: Change in maximal voluntary contraction force through recovery.

Maximal voluntary contraction force (MVC) at baseline, task failure, and during 150 s of recovery in absolute force in both men and women.

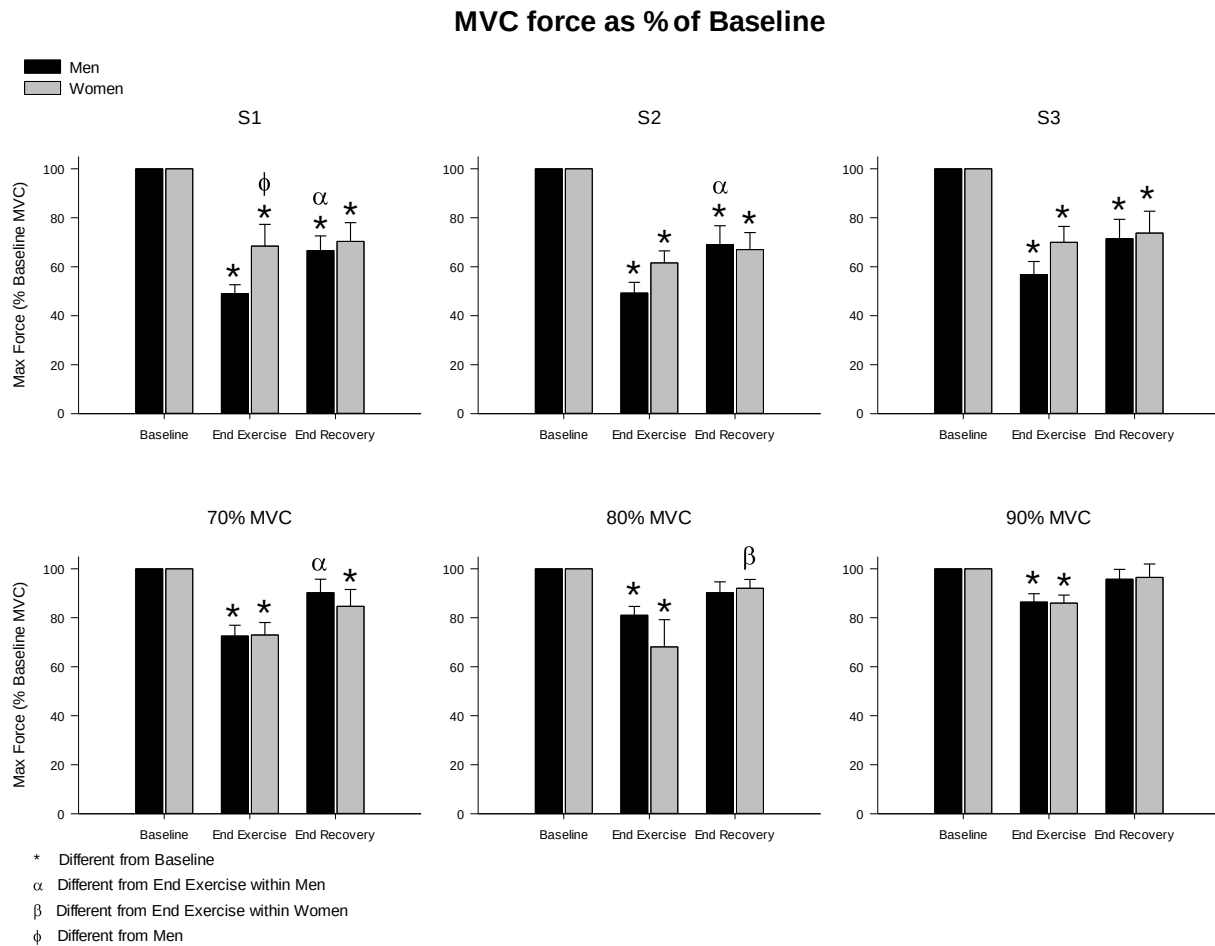


Figure 3.3: Change in maximal voluntary contraction force relative to baseline across exercise and recovery.

Maximal voluntary contraction force (MVC) relative to force at baseline at end exercise and end recovery in both men and women.

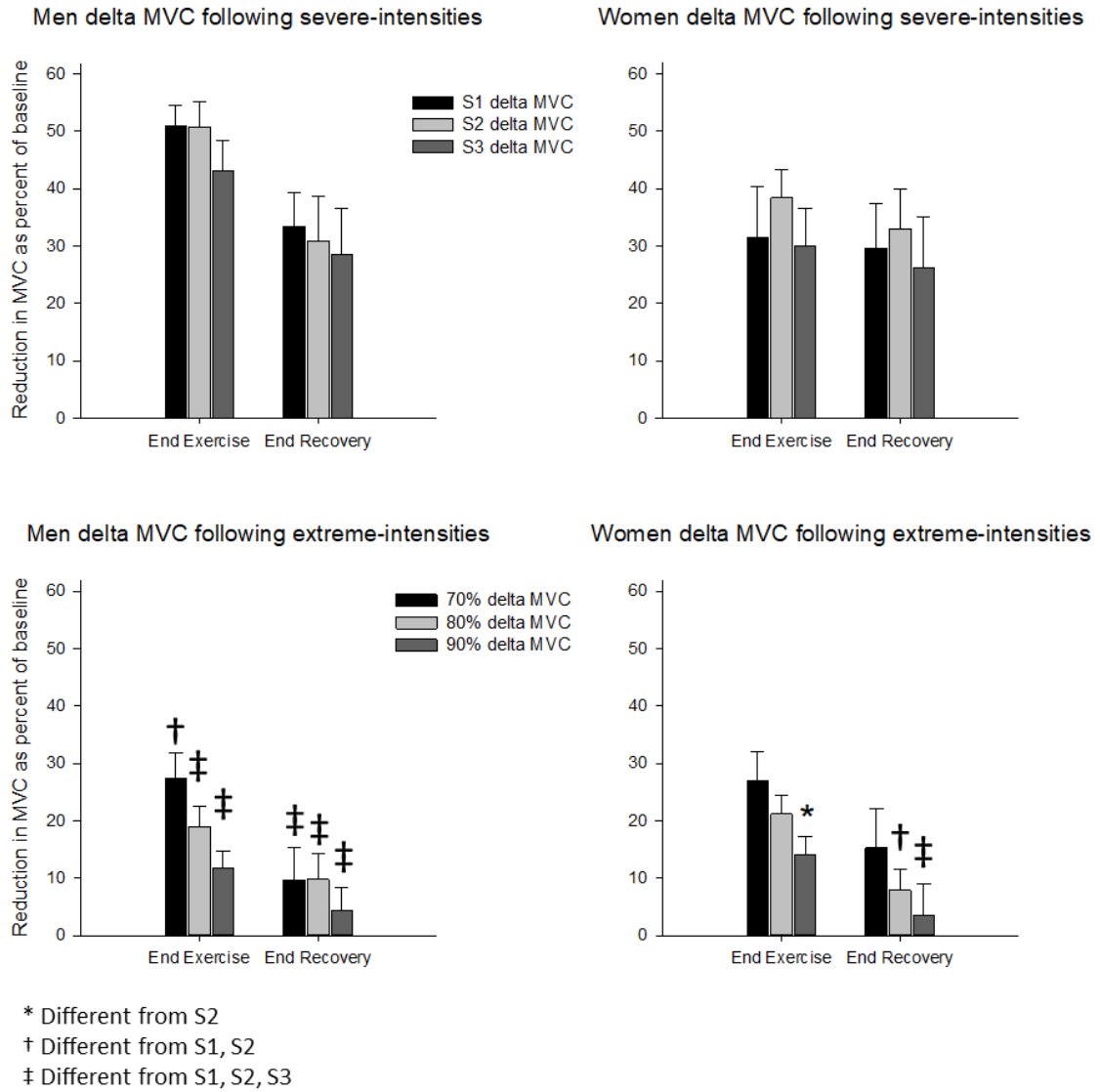


Figure 3.4: Differences in maximal voluntary contraction force across intensities.

Reduction in MVC relative to baseline at end exercise and end recovery across exercise intensities within men and within women. See Figs 3.2 & 3.3 for differences between End Exercise and End Recovery.

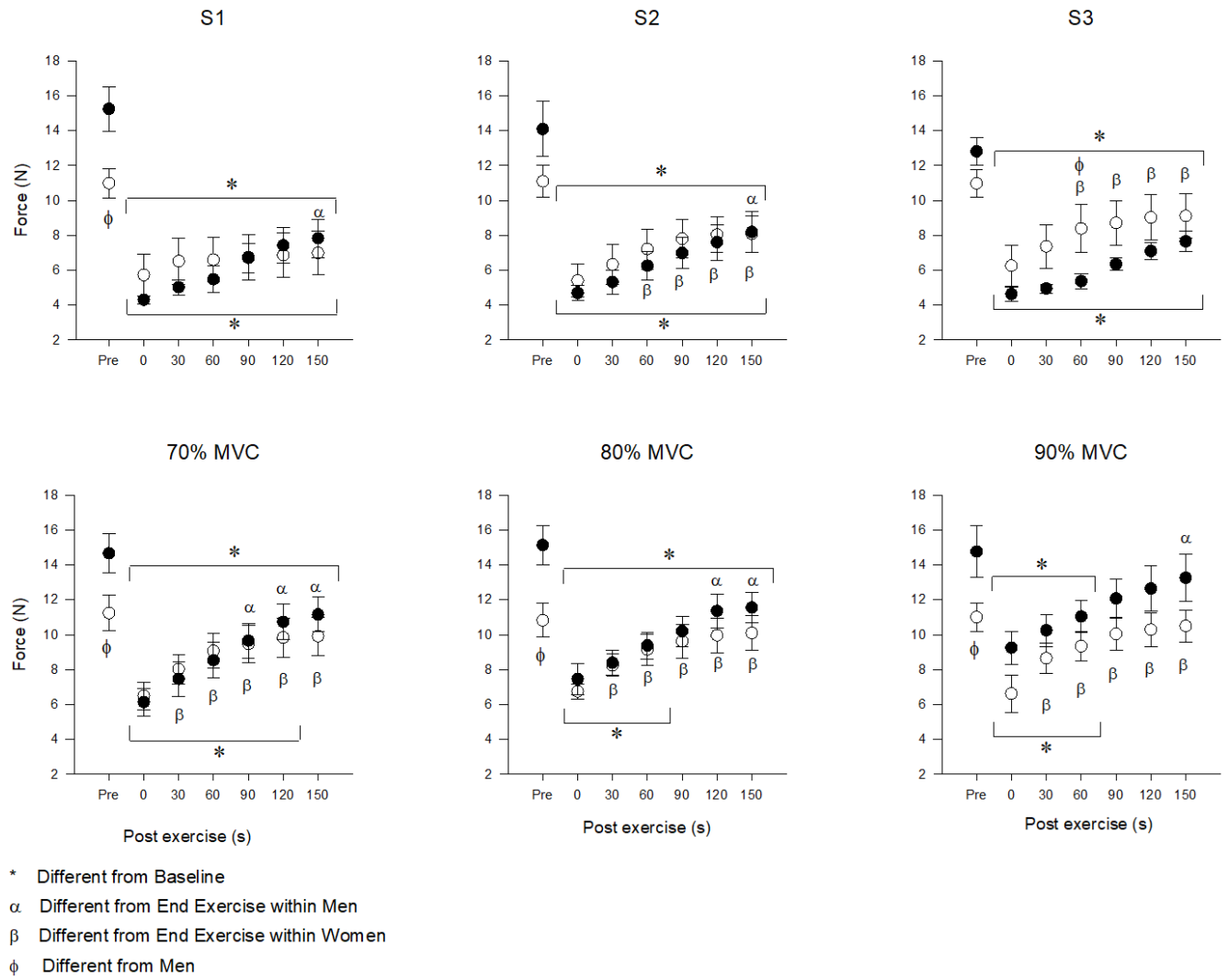


Figure 3.5: Change in potentiated twitch force through recovery.

Potentiated twitch force (Q_{pot}) at baseline, task failure, and during 150 s of recovery in absolute force in both men and women.

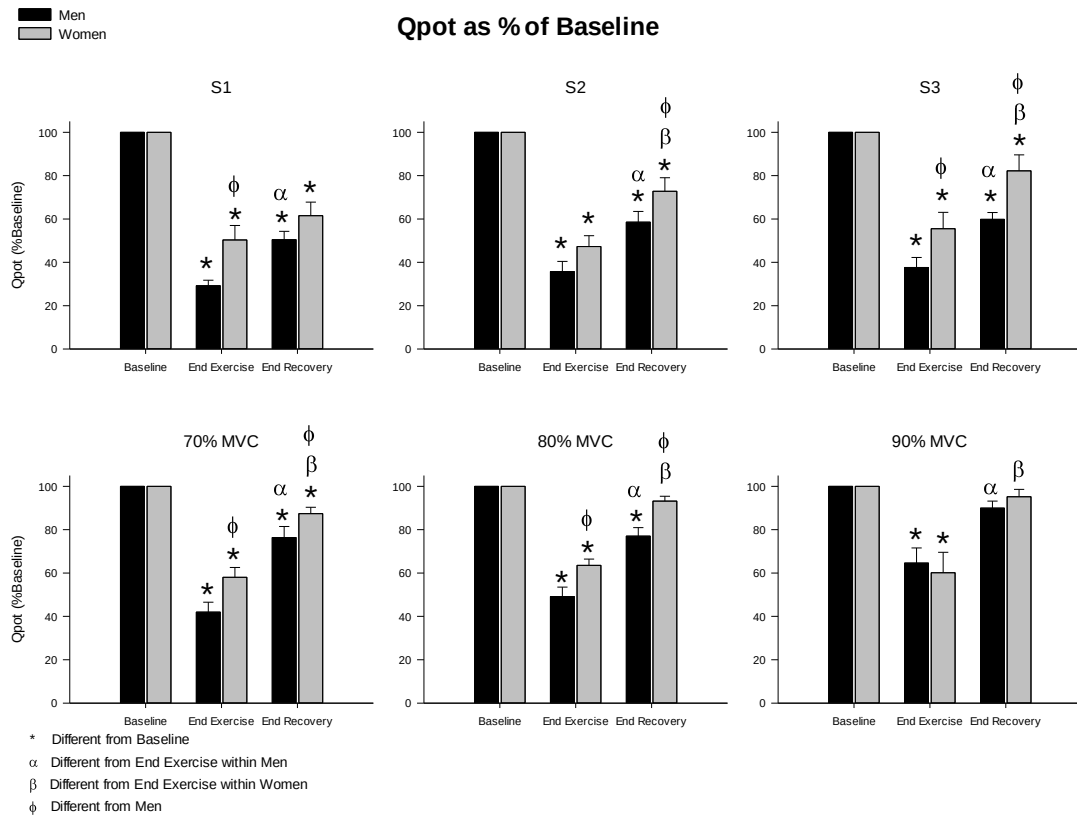


Figure 3.6: Change in potentiated twitch force relative to baseline across exercise and recovery.

Potentiated twitch force (Q_{pot}) relative to force at baseline at end exercise and end of recovery in both men and women.

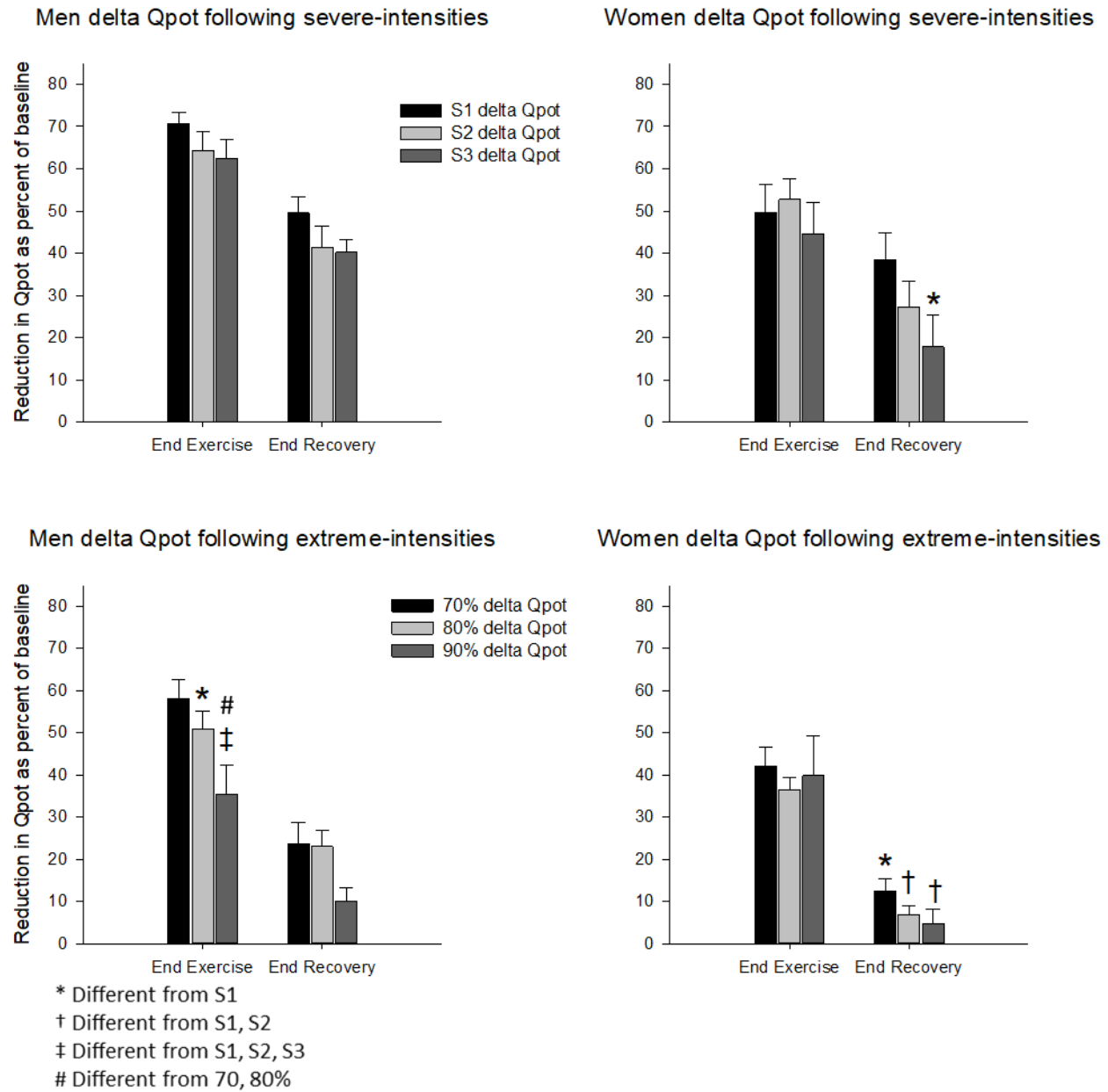


Figure 3.7: Differences in potentiated twitch force across intensities.

Reduction in Q_{pot} relative to baseline at end exercise and end recovery across exercise intensities within men and within women. See Figs 3.5 & 3.6 for differences between End Exercise and End Recovery.

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Chapter 4 - Conclusions

The overall aims of this dissertation were to compare neuromuscular fatigue brought on by severe- and extreme-intensity exercise and the force recovery in the first 150 s immediately following task failure. We demonstrated that extreme-intensity exercise consistently decreased maximal voluntary contraction (MVC) and twitch force (Q_{pot}) to less of a degree at task failure compared to severe-intensity exercises (Chapter 2 & 3), suggesting less peripheral fatigue is developed during extreme-intensity to task failure compared to severe-intensity exercise. We subsequently provided evidence that MVC and Q_{pot} had a faster time course in recovery following extreme-intensity exercise compared to severe-intensity exercise (Chapters 2 & 3). Together, these data support that there are differences in the neuromuscular fatigue development and the recovery characteristics immediately following severe- versus extreme-intensity exercise, suggesting that different mechanisms of fatigue are limiting exercise tolerance in the two intensity domains. Further, we showed that there are not only intensity-dependent differences in neuromuscular response to exercise, but that these responses are also different in men and women (Chapter 3). Specifically, both men and women displayed a W'_{ext} that was significantly less than W'_{sev} . Absolute MVC force was not different between men and women following extreme-intensity exercise. However, these differences were not evident when expressed relative to baseline MVC, suggesting men developed greater overall fatigue. Further, MVC after 150 s of recovery following extreme-intensity exercise was not different from baseline, suggesting the mechanisms limiting extreme-intensity exercise are quickly reversible. Men also displayed a greater development of peripheral fatigue compared to women (estimated by decreased potentiated twitch force; Q_{pot}).

following extreme-intensity exercise, further reinforcing that the mechanisms limiting severe- and extreme-intensity exercise likely differ between men and women.

Additionally, we investigated the potential impact of creatine supplementation on W'_{sev} and W'_{ext} (Appendix A). We found no difference in W'_{sev} or W'_{ext} with compared to without creatine supplementation. However, the small sample size may be masking potential differences, as our data were not consistent with previous data showing creatine supplementation increases W'_{sev} . Therefore, we recommend further investigation into the effect of creatine supplementation on extreme-intensity exercise tolerance.

Although the transition from severe- to extreme-intensity exercise has yet to be precisely elucidated, these data repeatedly show that there are intensity- and sex-dependent mechanisms limiting severe- and extreme-intensity exercise in men and women. These findings have important implications in understanding the mechanisms contributing to exercise tolerance and time course of recovery through the wide range of intensities that are specific to men and women. However, it is important to consider that these mechanisms would be present not only during exercise, but also during everyday tasks which require intense skeletal muscle forces. Therefore, these data support that in future studies, exercise intensity should be controlled for to appropriately investigate the specific fatiguing mechanisms and the subsequent time course of recovery from fatigue. This will have a direct benefit when designing optimal loading and recovery periods for training and rehabilitation that are specific to men and women.

Appendix A - Preliminary data: Effect of creatine supplementation on extreme-intensity exercise

Summary

Previous data have shown that creatine supplementation increases maximal exercise tolerance. Further, creatine supplementation increased the power-duration relationship of the severe-intensity exercise domain. However, it is currently unknown how creatine supplementation effects the power-duration relationship of the extreme-intensity exercise domain. Six subjects completed three severe- and three extreme-intensity exercise bouts following placebo and creatine supplementation. Maximal voluntary contraction (MVC), critical torque (CT), W'_{sev} , and W'_{ext} were not different following creatine supplementation compared to the placebo condition. However, it is likely that the small sample size was not statistically powered and could be masking potential differences. Therefore, we recommend further investigation into the effect of creatine supplementation on extreme-intensity exercise tolerance.

Introduction

Physiological responses to exercise are intensity-domain specific (3, 4, 12). During severe-intensity exercise, metabolic markers (e.g., lactate, H^+ , inorganic phosphate) continue to increase without reaching steady-state until task failure (T_{lim}) is reached (4). Consistently, $\dot{V}O_2$ continues to increase to $\dot{V}O_{2max}$ (12), and therefore, exercises must be at intensities which allow $\dot{V}O_{2max}$ to be reached. The lower boundary of severe-intensity exercise has been dubbed critical torque (CT; or critical power / speed, dependent on exercise modality). A second parameter of severe-intensity exercise is W'_{sev} which represents a work capacity consistent across severe-intensity work rates. Given that the work capacity is constant, exercise tolerance during severe-intensity exercise is work rate-dependent and predictable. However, the upper boundary of severe-intensity exercise is much less understood, but which has been predicted to separate severe-intensity exercise from work rates that reach task failure before $\dot{V}O_{2max}$ is attainable (i.e., extreme-intensity exercise) (9).

Extreme-intensity exercise elicits task failure sooner than would be predicted by the severe-intensity domain power-duration relationship (1), suggesting a change in either fatiguing mechanisms or increased rate of accumulation of fatigue. Increased resting stores of phosphocreatine (PCr) via oral ingestion of dietary creatine has shown to increase exercise tolerance during maximal cycling (2, 5) and weightlifting (7, 15). Further, Miura et al. (1999) found that creatine supplementation increased W'_{sev} , with no effect on critical power (11). Although previous studies have examined the effects of creatine supplementation on maximal exercise tolerance, it is currently unknown how creatine supplementation specifically affects the W'_{ext} in the context of extreme-intensity exercise.

Therefore, this preliminary study examined the effects of creatine monohydrate supplementation on the power-duration relationship of the extreme-intensity domain (W'_{ext}) compared to that of the severe-intensity domain (W'_{sev}). We hypothesized that the W'_{sev} and W'_{ext} would be greater following creatine supplementation compared to control.

Methods

Subjects: Six subjects (mean $\pm$ S.D.: 27 ± 4 yr; 74.0 ± 15.0 kg; 172.0 ± 8.3 cm), 4 men and 2 women, participated in this study. All participants were free from cardiovascular, pulmonary, and metabolic disease as determined by a medical history questionnaire. Prior to participation in this study, subjects were informed of all procedures, and associated potential risks and benefits. Written informed consent was obtained from all participants prior to participation. Subjects were instructed to refrain from vigorous exercise 24 hours, alcohol consumption 12 hours, and food and caffeine 2 hours prior to each session. Subjects were instructed to maintain current exercise habits throughout the study in order to avoid any training or detraining effect. All research components were reviewed and approved by the Institutional Review Board of Human Subjects (#10181) at Kansas State University, Manhattan, KS.

Experimental Design: On the first visit to the laboratory, subjects were fully familiarized with the testing equipment and procedures. All tests were performed on a custom-built, knee-extension ergometer and force transducer (LBG1, BLH Electronics, Waltham, MA, USA). Subjects were seated upright so that hip-flexion angle was 105° and knee-flexion angle was 90° . Force transducer height was adjusted for each subject such that a 90° angle of pull was maintained. The height of the force transducer and backrest setting was recorded and replicated for each subject and exercise sessions. Real-time force was displayed on a monitor ~ 1 m from the subject. Following familiarization, subjects were given either creatine monohydrate or a placebo. A loading period of $4 \times 5 \text{ g} \cdot \text{day}^{-1}$ for 5 days followed by $5 \text{ g} \cdot \text{day}^{-1}$ has been shown to effectively increase, and maintain the increased levels of resting muscle creatine (8, 10) and this loading was used for both conditions. Subjects then completed a total of 12 exercise tests, 3 severe-intensity and 3 extreme-intensity exercise tests after each condition. Exercise tests consisted of 3 work rates to elicit T_{lim} between

2-5 minutes (S3), 6-9 minutes (S2), and 10-15 minutes (S1), and 70, 80, and 90% MVC (assumed to be extreme-intensity exercise (1) and were performed in random order with a minimum of 48 hours between tests to avoid a training effect. Target force was fixed and subjects were instructed to reach and maintain target force at a 60% duty cycle (3 s contraction, 2 s relaxation) as per audio cue. Task failure was defined as failure to reach and/or maintain target force after one contraction.

Since creatine has a washout period of ~ 28 days (6), we utilized a single-blind study to minimize time between conditions and maintain participant adherence. Subjects were unaware of the current condition, but were given the placebo for condition one. This allowed for a one-week “washout” period before loading of the second condition (creatine monohydrate) to begin. In order to maintain operational validity, researchers were blinded to exercise time and were not given results of exercise time until after all conditions had been completed. This avoided potential bias of increasing encouragement during the second (creatine loading) condition.

Statistical Analysis: Critical torque, MVC, W'_{sev} , and W'_{ext} were compared across placebo and creatine supplementation conditions using paired T-tests.

Results

There were no significant day-to-day differences in MVC within each condition. Mean $\pm$ SD maximal voluntary contraction (MVC), critical power (CP), W'_{sev} , and W'_{ext} are shown in Table 1 for both creatine and placebo conditions. Creatine did not significantly increase MVC ($p = 0.50$), critical torque ($p = 0.38$), W'_{sev} ($p = 0.17$), or W'_{ext} ($p = 0.19$). W'_{sev} and W'_{ext} following both placebo and creatine supplementation conditions are shown in Fig A.1.

Discussion

The current preliminary data are the first to test for effects of creatine supplementation on W'_{ext} . Contrary to our hypothesis, there was no significant effect of creatine supplementation on W'_{sev} or W'_{ext} . However, subjects showed a varying response to creatine supplementation in terms of MVC, W'_{sev} , and W'_{ext} . As such, we discuss potential external factors that could have impacted the current data.

The effects of creatine supplementation on exercise have been repeatedly examined with varying results. Although our primary findings are not consistent with our hypothesis, whether creatine supplementation has a positive (5, 7, 14, 15) or null effect (6, 13, 14, 16, 17) on maximal, constant-load exercise appears to be equivocal. For example, Urbasni et al. (1999) showed a 4.2% increase in maximal knee-extension torque concomitant with an 11% increase in exercise tolerance of sustained isometric force at 67% MVC (15). Conversely, it has been shown that creatine supplementation has had no effect on maximal contraction force (14, 16, 17) or exercise tolerance (6, 13).

The variability in effect of creatine supplementation in the current data may be due to current training status. Subjects were recruited to be physically active but not specifically exercise trained. It has been shown that part of the variability in response to creatine loading is due to current training status. Subjects were also instructed to maintain current training habits in order to avoid (de)training effects across the length of the study. It has been previously shown that creatine supplementation concurrent with exercise training increases exercise performance (8). Therefore, it is possible that subjects with a greater response to creatine supplementation may have had increased exercise volume compared to those who had a minimal / negative response. Future

studies should further investigate the possibility of training load during creatine supplementation and its effects on exercise tolerance.

Conclusions: The current data show no significant effect of creatine supplementation on W'_{sev} or W'_{ext} . However, individual responses in MVC, CT, W'_{sev} , and W'_{ext} to creatine supplementation were quite variable. It is likely that the current data were not adequately powered to show potential differences between placebo and creatine supplementation conditions. Further investigation into the effects of creatine supplementation on the severe- and extreme-intensity power-duration relationship should be closely examined to elucidate potential mechanisms limiting extreme-intensity exercise tolerance.

Placebo					Creatine				
Subject	MVC (N)	CT (N)	W'sev(kJ)	W'ext (kJ)	Subject	MVC (N)	CT (N)	W'sev(kJ)	W'ext (kJ)
AA01	114	18	6.5	1.2	AA01	120	25	5.1	6.2
SH02	82	35	3.3	0.7	SH02	74	33	4.6	2.1
DB03	70	27	4.6	3.4	DB03	70	22	9.5	2.9
ZA04	85	18	5.7	3.3	ZA04	70	20	4.7	1.7
LH05	50	19	1.7	2.7	LH05	63	21	2.4	0.8
CD06	63	21	2.2	0.6	CD06	60	22	3.5	0.8
AVG	77.3	23.3	4.0	2.0	AVG	76.2	23.8	5.0	2.4
SD	20.1	6.3	1.7	1.2	SD	20.2	4.5	2.2	1.8

Table A.1: Subject characteristics.

Maximal voluntary contraction (MVC), critical torque (CT), W'_{sev} , and W'_{ext} for each subject for both placebo and creatine supplementation conditions. No statistical differences were detected between conditions.

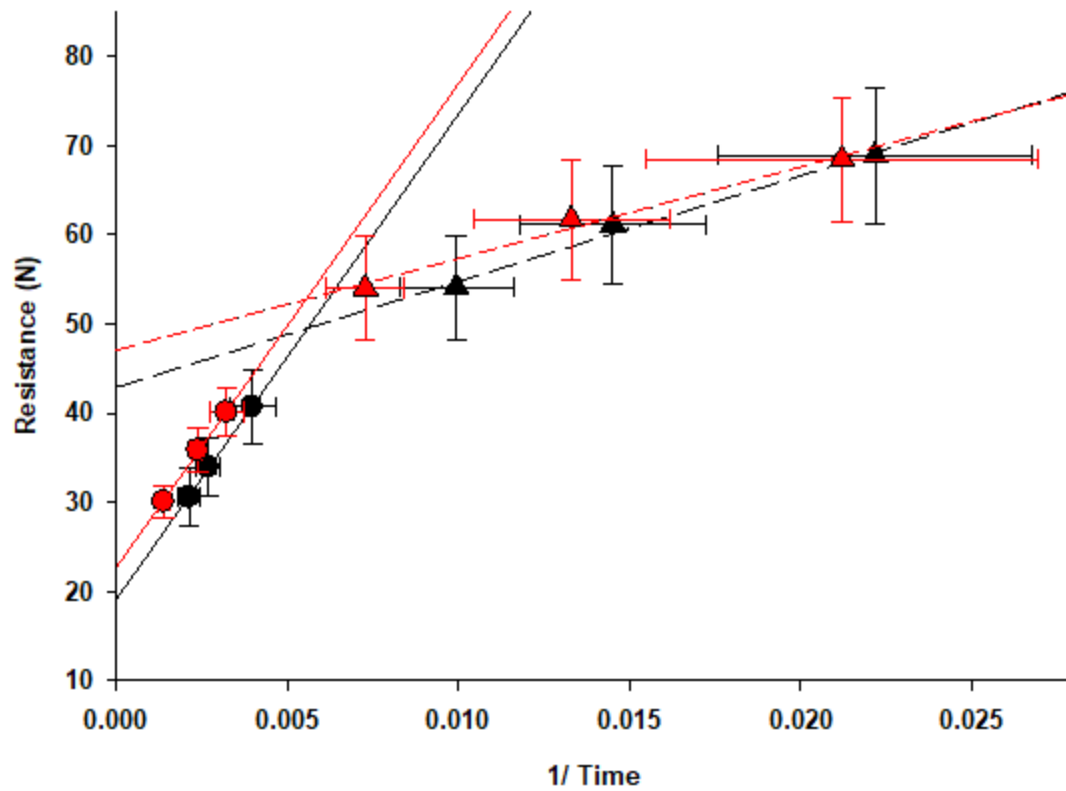


Figure A.1: W'_{sev} and W'_{ext} following placebo and creatine supplementation.

W'_{sev} (solid lines) and W'_{ext} (dashed lines) following placebo (black symbols, lines) and creatine supplementation (red symbols, lines). No statistical differences between conditions were detected.

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Appendix B - Curriculum Vitae

Andrew M. Alexander, ABD, MS

CURRICULUM VITAE

KANSAS STATE UNIVERSITY

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EDUCATION

Kansas State University

Ph.D. in Kinesiology

Emphasis: Exercise Physiology

Expected Graduation Date: 2021

Kansas State University

M.S. in Kinesiology, Magna cum laude

2017

Thesis: "Exercise Tolerance through Severe and Extreme Intensity Domains"

Emphasis: Exercise Physiology

Kansas State University

B.S. in Kinesiology, Magna cum laude

2015

Emphasis: Exercise Physiology

RESEARCH INTERESTS

The goal of my research is to increase our understanding of physiological mechanisms in health and disease to improve the quality of life, symptoms, and functional capacity in individuals suffering from cardiovascular and metabolic diseases. My interest in neuromuscular responses to exercise and the accompanying fatigue development, as well as my extensive training in integrative physiology, provide the general foundation of my previous and current research projects, which are specifically designed to examine the different physiological mechanisms during heavy-, severe-, and extreme-intensity exercise. My long-term goals are to pursue a career at an R1 University to further research investigations and disseminate current physiological understandings to future undergraduate and graduate level students.

PUBLICATIONS

ORIGINAL RESEARCH

Shane M. Hammer, Stephen T. Hammond, Sharon K. Parr, **Andrew M. Alexander**, Vanessa-Rose G. Turpin, Zachary J. White, Kaylin D. Didier, Joshua R. Smith, Thomas J. Barstow, Carl J. Ade. "Influence of muscular contraction on vascular conductance during exercise above versus below critical power" *Respiratory Physiology and Neurobiology*, 2021

Shane M. Hammer, **Andrew M. Alexander**, Kaylin D. Didier, Lillie M. Huckaby, Thomas J. Barstow. "Influence of blood flow occlusion on muscular recruitment and fatigue during maximal-effort small muscle-mass exercise" *Journal of Physiology*, 2020

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Kaylin D. Didier, Shane M. Hammer, **Andrew M. Alexander**, Jacob T. Caldwell, Shelbi L. Sutterfield, Joshua R. Smith, Carl J. Ade, Thomas J. Barstow. “Microvascular blood flow during vascular occlusion tests assessed by diffuse correlation spectroscopy” *Experimental Physiology*, 2019

Andrew M. Alexander, Shelbi L. Sutterfield, Karly N. Kriss, Kaylin D. Didier, Shane M. Hammer, Jacob T. Caldwell, Alex C. Dzewaltowski, Carl J. Ade, Thomas J. Barstow. “Prediction of emergency capsule egress performance” *Aerospace Medicine and Human Performance*, 2019

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Joshua R. Smith, Ryan M. Broxterman, Shane M. Hammer, **Andrew M. Alexander**, Kaylin D. Didier, Stephanie P. Kurti, Thomas J. Barstow, and Craig A. Harms. “Sex differences in the cardiovascular consequences of the inspiratory muscle metaboreflex” *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, 2016

MANUSCRIPTS IN REVIEW

Andrew M. Alexander, Shane M. Hammer, Kaylin D. Didier, Lillie M. Huckaby, Thomas J. Barstow. “Neuromuscular recovery from severe- and extreme-intensity exercise in men and women” In review

Kaylin D. Didier, Shane M. Hammer, **Andrew M. Alexander**, Korynne S. Rollins, Thomas J. Barstow. “The acute effects of passive heating on endothelial function, skeletal muscle oxygen delivery, and expression of serum HSP90 α ” In review

MANUSCRIPTS IN PREPARATION

Andrew M. Alexander, Thomas J. Barstow. “Sex differences in the power-duration relationship of the extreme-intensity domain” In progress

Andrew M. Alexander, Korynne S. Rollins, Thomas J. Barstow. “Effect of creatine monohydrate on extreme- and severe-intensity power-duration relationship” In progress

PRESENTED RESEARCH ABSTRACTS

Andrew M. Alexander, Shane M. Hammer, Kaylin D. Didier, Lillie M. Huckaby, Thomas J. Barstow. “Effect of extreme-intensity exercise on muscle force between men and women” American College of Sports Medicine. May 2020

Shane M. Hammer, **Andrew M. Alexander**, Kaylin D. Didier, Lillie M. Huckaby, Thomas J. Barstow. “Limb blood flow and muscle oxygenation responses to rhythmic exercise below and above critical force” American College of Sports Medicine. May 2020

, Kaylin D. Didier, **Andrew M. Alexander**, Shane M. Hammer, Thomas J. Barstow. “The effect of acute passive heating on microvascular oxygen delivery, exercise tolerance, and recovery” American College of Sports Medicine. May 2020

Andrew M. Alexander, Shane M. Hammer, Kaylin D. Didier, Lillie M. Huckaby, Camryn N. Webster, Thomas J. Barstow. “Sex differences in recovery from extreme and severe intensity exercise” Presented: American College of Sports Medicine. Orlando, FL. May 2019

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Shane M. Hammer, Jacob T. Caldwell, Kaylin D. Didier, **Andrew M. Alexander**, Carl J. Ade, Thomas J. Barstow. "Perfusive and diffusive microvascular oxygen delivery during simulated hypovolemia and dynamic forearm exercise" Presented: American College of Sports Medicine. Minneapolis, MN. June 2018

Kaylin D. Didier, Shane M. Hammer, **Andrew M. Alexander**, Kelsey J. Phelps, John M. Gonzalez, Thomas J. Barstow. "Near-infrared spectroscopy derived total [Heme] vs. assay derived total [Heme]" Presented: Experimental Biology. San Diego, CA. April 2018

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Shane M. Hammer, **Andrew M. Alexander**, Kaylin D. Didier, Joshua R. Smith, Jacob T. Caldwell, Shelbi L. Sutterfield, Carl J. Ade, Thomas J. Barstow. "Simultaneous measurement of perfusive and diffusive oxygen transport during incremental forearm exercise" Presented: American College of Sports Medicine. Denver, CO. June 2017

Joshua R. Smith, Ryan M. Broxterman, Shane M. Hammer, **Andrew M. Alexander**, Kaylin D. Didier, Thomas J. Barstow, Stephanie P. Kurti, and Craig A. Harms. "Cardiovascular consequences of the inspiratory muscle metaboreflex: effects of age and sex" Presented: American College of Sports Medicine. Denver, CO. June 2017

Kaylin D. Didier, Shane M. Hammer, **Andrew M. Alexander**, Jacob T. Caldwell, Shelbi L. Sutterfield, Carl J. Ade, Thomas J. Barstow. “Microvascular blood flow during post-occlusive reactive hyperemia assessed by diffuse correlation spectroscopy” Presented: American College of Sports Medicine. Denver, CO. June 2017

Andrew M. Alexander, Shane M. Hammer, Kaylin D. Didier, Dryden R. Baumfalk, Thomas J. Barstow. “Muscle recruitment patterns above critical power” Presented: Experimental Biology. Chicago, IL. April 2017

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Joshua R. Smith, Kaylin D. Didier, Shane M. Hammer, **Andrew M. Alexander**, Stephanie P. Kurti, Thomas J. Barstow, Craig A. Harms. “Contribution of prostaglandins to the inspiratory muscle metaboreflex-induced cardiovascular consequences” Presented: Experimental Biology. Chicago, IL. April 2017

Andrew M. Alexander, Joshua R. Smith, Stephanie P. Kurti, Sam R. Emerson, Thomas J. Barstow, Craig A. Harms. “Sex differences in gas exchange threshold pre- and post-puberty” Presented: American College of Sports Medicine. Boston, MA. June 2016

Kaylin D. Didier, Samuel L. Wilcox, Ryan M. Broxterman, Shane M. Hammer, **Andrew M. Alexander**, and Thomas J. Barstow. “Relationship between muscle activation and VO₂ during incremental ramp exercise” *Presented: American College of Sports Medicine. Boston, MA. June 2016*

Joshua R. Smith, Ryan M. Broxterman, Shane M. Hammer, **Andrew M. Alexander**, Kaylin D. Didier, Thomas J. Barstow, Stephanie P. Kurti, and Craig A. Harms. “Sex differences in the inspiratory muscle metaboreflex” *Presented: American College of Sports Medicine. Boston, MA. June 2016*

Joshua R. Smith, Ryan M. Broxterman, Shane M. Hammer, **Andrew M. Alexander**, Kaylin D. Didier, Thomas J. Barstow, Stephanie P. Kurti, and Craig A. Harms. “Effect of aging on the inspiratory muscle metaboreflex” *Presented: Experimental Biology. San Diego, CA. April 2016*

INVITED PRESENTATIONS

1. “Supra-severe intensity exercise: Exercise tolerance and recovery” *University of Utah, 2021*
2. “Supra-severe intensity exercise: Exercise tolerance and recovery” *Mayo Clinic, 2021*

TEACHING EXPERIENCE

Kansas State University, Manhattan, KS, USA

- | | |
|---|-----------------|
| 1. KIN 310 Research Methods Lab (Graduate Teaching Assistant) | F2020 – S2021 |
| 2. KIN 360 Anatomy and Physiology (Graduate Teaching Assistant) | S2020 – S2021 |
| 3. KIN 607 Muscle Physiology (Online-course creator / Instructor) | S2020 – Sum2020 |

- | | |
|---|---------------|
| 4. KIN 336 Exercise Physiology Lab (Graduate Teaching Assistant) | S2020 |
| 5. KIN 101 Introduction to Weightlifting (Instructor) | F2016 – S2020 |
| 6. KIN 101 Strength Training for Fitness (Instructor) | F2016 – S2020 |
| 7. KIN 605 Pathophysiology (Guest Lecturer) – Multiple Sclerosis review | F2018 |

REQUESTED ACADEMIC MENTOR

1. KIN 220 Behavioral Bases of Physical Activity
2. KIN 310 Research Methods
3. KIN 360 Anatomy and Physiology Lab
4. KIN 335 Exercise Physiology
5. KIN 336 Exercise Physiology Lab
6. KIN 601 Cardiorespiratory Physiology
7. KIN 603 Cardiovascular Physiology
8. KIN 605 Pathophysiology
9. KIN 607 Muscle Physiology
10. KIN 609 Environmental Physiology

KINESIOLOGY DEPARTMENT APPOINTED HEAD ACADEMIC MENTOR

- | | |
|--------------------------------|-------------|
| 1. KIN 335 Exercise Physiology | 2018 - 2020 |
|--------------------------------|-------------|

PROFESSIONAL SERVICE

PROFESSIONAL MEMBERSHIP

- | | |
|--|----------------|
| 1. American College of Sports Medicine (<i>Member</i>) | 2015 - Present |
| 2. American Physiological Society (<i>Member</i>) | 2015 - Present |

MANUSCRIPT REVIEWER:

1. American Journal of Applied Physiology
2. Journal of Applied Physiology
3. Frontiers in Physiology

RESEARCH GRANTS

College of Human Ecology Dissertation Research Grant (\$996)	2019
Arts, Humanities, and Social Sciences Small Research Grant (\$1,000)	2019
Annual Graduate Student Council Research Travel Grant (\$750 x5)	2016 - 2020
Annual College of Health and Human Resources Grant (\$500 x3)	2018 - 2020
Annual College of Human Ecology Research Travel Grant (\$500 x2)	2016 - 2017