UNIVERSITY OF OKLAHOMA

GRADUATE COLLEGE

# EFFECTS OF EXERCISE INDUCED MUSCLE DAMAGE ON CRITICAL TORQUE AND MITOCHONDRIAL FUNCTION

A THESIS

SUBMITTED TO THE GRADUATE FACULTY

in partial fulfillment of the requirements for the

Degree of

MASTER OF SCIENCE

By

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Norman, Oklahoma
2016

EFFECTS OF EXERCISE INDUCED MUSCLE DAMAGE ON CRITICAL TORQUE AND MITOCHONDRIAL FUNCTION

A THESIS APPROVED FOR THE
DEPARTMENT OF HEALTH AND EXERCISE SCIENCE

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## ACKNOWLEDGEMENTS

Dr. Black, thank you for taking a chance on a guy in Canada you did not know very much about. Thank you for being very flexible and finding the best way to motivate me. I appreciate everything you have taught me about research, work ethic and professionalism. Our combination of perseverance, patience, and a sprinkle of chaos has been an invaluable growing experience.

Dr. Ade, I have greatly appreciated all your guidance throughout my time at the University of Oklahoma. Your teaching style has taught me how to critically evaluate research, and focus on understanding not just the theory, but also the application.

Dr. Campbell, I have a great deal of respect for the way you conduct yourself amongst the faculty. I appreciate how you are interested not only in the research we conduct, but also our lives outside of the lab.

Thank you to all of my participants for giving up their time to complete a physically strenuous protocol. Your amazing effort made this research very exciting to conduct. None of this would be possible without you.

Thank you for everyone who assisted me in collecting and analyzing data. As you know, a thesis is a lot of work, and your assistance really helped me bring all of this together.

To all my lab mates, peers, and friends outside of the department, thank you for all your support. No one accomplishes anything alone, and I really appreciate the two years we spent together.

To Kristina, thank you for being able to stand my stress, and doing all the little things you can to help out in any way possible, such as ironing my shirt. I would have been lost, and rather wrinkled without you.

Finally, thank you to my mom, dad, sister, and friends in Canada and across the United States. Despite our distance, you were always there to lend moral support and provide me with the motivation I needed to finish this chapter in my life.

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## ABSTRACT

The primary aim of this study was to examine the effects of exercise induced muscle damage on critical torque and impulse above end test torque. A secondary purpose was to determine whether mitochondrial function played any role in observed changes. A total of 12 participants performed resting mitochondrial tests, MVC level tests, and a 5-minute all-out isometric knee extension test for critical torque both before and 48-hours following exercise induced muscle damage via electrical stimulation and eccentric isokinetic knee extension. Surface EMG was collected during the critical torque tests to ensure full effort was given. The muscle damage protocol was successful in seven of the participants. Of those seven, one was excluded for mitochondrial function analysis due to being an outlier. The primary findings were that exercise induced muscle damage 1) results in a reduced critical torque, 2) a reduced impulse above end test torque and 3) did not alter mitochondrial function in the working muscle. These findings could indicate that although oxidative capacity plays a large role in determining critical torque, there is more at play due to the lack of change in mitochondrial function. The drop in impulse above end power indicates the importance of muscular work capacity.

# CHAPTER I
# INTRODUCTION

Exercise tolerance can be a large determinant of performance in sport, and the resolution of its physiological basis is therefore a significant goal in exercise physiology. Exercise intensity can be separated into multiple domains based upon the energy demand of the activity [1]. The first domain is the moderate-intensity domain, which encompasses exercise below lactate threshold. Exercise in the heavy domain occurs above lactate threshold however despite an initial upward drift past expected values, physiological processes such as ventilation, pH, and $VO_2$ will still reach a steady state [2]. The final domain is the severe-intensity domain where physiological parameters will not reach a steady state, and $VO_2$ will progressively increasing until volitional fatigue is reached (49). The "threshold" or transition between the heavy intensity domain and the severe intensity domain has been termed "critical power" [3]. Critical power (CP) represents the upper limit of exercise intensity for prolonged aerobic exercise, and, theoretically, this power output could be sustained indefinitely [4]. Any work performed above CP will tap into a finite energy store termed W'. W' represents a fixed amount of work and as such exhaustion or exercise termination will depend on the rate at which this work is used or depleted during a bout of exercise (e.g. W' will be depleted slower and thus exhaustion will occur later at an intensity slightly above CP compared to an intensity that is well above CP) [5].

In any sport played at intensity sufficient to spend significant time in the severe domain, CP will become an important factor in determining exercise tolerance. CP has been shown to be generalizable to multiple exercise modalities such as cycling [6], running [7] and rowing [8]. CP has also been reliably determined using multiple

different exercise protocols. The criterion protocol involves multiple continuous exercise bouts at various intensities, presumably over CP in which exhaustion occurs within 3-15 minutes. Power output is then plotted against time-to-exhaustion ($T_{lim}$), resulting in a hyperbolic relationship in which the asymptote represents CP [9]. A single-bout 3-minute sprint protocol, which reaches a steady state in the last 30 seconds, has also been shown to yield a reliable measure of CP [10]. When isometric contractions are performed a similar relationship is observed, however because isometric exercise lacks a displacement CP is renamed as critical torque (CT). Recently a single-bout 5-minute maximal isometric knee extension protocol was validated as it was shown to produce CT values similar to a more traditional multiple bout protocol [11]. This protocol will be employed in the presented study.

It is well accepted that strength training improves performance not only in strength sports, but also in endurance sports such as running and cycling [12, 13]. Strength training improves movement economy and movement patterns through changes in motor-unit recruitment [14]. Such training tends to involve a large eccentric component which often results in exercise-induced muscle damage (EIMD) [15]. EIMD results in alteration to skeletal muscle structure and function [16] which leads to decreased force production and physical performance as well as delayed on-set muscle soreness (DOMS). EIMD and its associated force loss have been shown to reduce movement economy, or the amount of energy necessary to perform a task in relation to the work accomplished, in running conditions [17]. This means an individual has to use more energy for the exact running task following EIMD. Damage has also been shown to reduce maximal oxygen consumption ($VO_{2peak}$) during cycling exercise [18] and

during running [19]. The reductions have been shown to persist for up to 7-10 days [19]. However, the mechanisms by which these effects occur remain unclear. Reduced performance has been suggested to be linked to central factors such as inflammatory cytokines in brain areas responsible for fatigue, pain perception, and motivation which could result in an earlier onset of centrally mediated volitional fatigue [20]. Conversely, some effects of EIMD are clearly related to peripheral factors, as disruption of sarcomeres will impair the formation of cross-bridges and damage to the sarcoplasmic reticulum leads to impairments in excitation-contraction coupling (REF).

The there is also evidence EIMD impairs oxidative metabolism on the cellular level, although this is not universally supported. A recent study found that severe EIMD caused by neuromuscular electrostimulation (NMES) resulted in intramuscular acidosis at rest and impairment of mitochondrial function during exercise [21]—suggesting that in addition to sarcomere and sarcoplasmic reticulum damage that eccentric exercise may also damage mitochondria. Conversely, following 30 minutes of eccentric cycling, no impairments in oxidative metabolism were observed [22] and a study employing $P^{31}$-magnetic resonance spectroscopy found that reduced exercise tolerance was not a result of an increased use of anaerobic metabolism [20]. Thus it remains somewhat unclear as to whether oxidative metabolism is or is not affected by EIMD—and whether impairment in oxidative metabolism might underlie the observed decreases in $VO_{2\ peak}$ and aerobic exercise performance.

While CP remains mechanistically unresolved, oxygen availability has been shown to play a key role. The inspiration of hyperoxic gas was shown to increase CP and delay time-to-exhaustion [5] while inspiration of hypoxic gases decreases CP and

time-to-exhaustion [23] during cycling exercise. Additionally, Broxterman et al. [24] recently demonstrated that when blood flow to the exercising limbs was occluded that CP fell precipitously. These findings clearly highlight an important role the aerobic metabolism in determining CP. Therefore, if EIMD results in compromised oxidative function it could also adversely affect CP and this reduction in CP could account for the reduced exercise tolerance observed following EIMD [18, 19].

Thus the **Purpose** this study was: 1) to determine whether EIMD in the knee extensors affects the work-time relationship and its associated parameters of CT and Impulse Above End Test Torque (IAT, an analogue to W') as determined during isometric knee extensions and 2) to determine whether EIMD alters mitochondrial function (oxidative capacity) of the quadriceps muscles.

**Research Questions:**

1) Does eccentric exercise resulting in EIMD result in a decrease of CT and IAT'?

2) If CT is decreased, is this decrease due to impaired oxidative capacity?

**Null Hypotheses**

1. There will be no change in critical torque 48-hours following a bout of eccentric exercise that results in EIMD
2. There will be no change in IAT 48-hours following a bout of eccentric exercise that results in EIMD
3. There will be no change in NIRS assessed mitochondrial function 48-hours following a bout of eccentric exercise that results in EIMD

**Research Hypothesis:**

1. There will be a decrease in critical torque 48-hours following a bout of eccentric exercise that results in EIMD
2. There will be a decrease in W' 48-hours following a bout of eccentric exercise that results in EIMD
3. There will be a decrease in NIRS assessed mitochondrial function 48-hours following a bout of eccentric exercise that results in EIMD

**Delimitations:**

1. The results will only be able to be generalized to healthy individuals in the age range of 18-40
2. The results will only be able to be generalized to the knee extensor muscles

**Limitations:**

1. The sample will not be random; it will be a convenience sample
2. Participants will be asked to refrain from heavy lower body exercises outside of laboratory setting throughout the protocol

**Assumptions:**

1. Participants will give a maximal effort during CF testing
2. Participants will provide accurate medical history
3. Participants will give a maximal effort during muscle damage protocol
4. Reliability and validity of protocol was properly established by prior research

**Operational Definitions:**

1. *Critical power/critical torque:* The power output which can be sustained theoretically indefinitely; the upper limit to wholly aerobic work demarcating the heavy and severe intensity domains [4]
2. *Lactate Threshold*: The point at which lactate entry into the blood exceeds its removal [25]
3. *W'/ Impulse Above Critical Torque:* The finite work capacity one is able to perform above CP; a combination of anaerobic metabolism and intramuscular oxygen stores [26]
4. *Exercise Intolerance:* The point at which one can no longer perform a exercise at a given intensity [3]
5. $VO_2$*:* The amount of oxygen utilized by the body [27]
6. $VO_{2\ Peak}$*:* Maximal ability of the body to use oxygen [18]
7. *Exercise-Induced Muscle Damage:* Damage to muscle structure brought upon by exercise training, especially eccentric muscle contractions [15]

# CHAPTER II
# REVIEW OF LITERATURE

The proposed problem is to identify whether or not EIMD attenuates CF as determined by an isometric handgrip test. To gather background information on the subjects of EIMD and CF, a systematic review of literature was conducted (refer to table at the conclusion of this chapter). Online academic databases were scanned for pertinent articles. Articles were excluded primarily for non-relevant interventions such as diet, or if the research examined a specific 'non-healthy' population (i.e. chronic diseases).

## Critical Power

The evidence for an inversely proportional relationship between duration of high intensity exercise and power output began to be established in 1927 by A.V. Hill, when Hill first plotted world records for male and female swimming and running time vs. average speed [28]. Hill observed a 'power-duration' relationship which is best described by a hyperbolic function, whereas power increases, time to exhaustion ($T_{lim}$) is shortened. As power output decreases, $T_{lim}$ approaches an asymptote that signifies a rate muscles can perform at theoretically indefinitely, termed 'critical power'. This power represents the limit of wholly aerobic energy output [4]. Work done above critical power (CP) has a finite capacity which is termed W'. This relationship can be transformed into a linear formula which reads $P=(W'/t)+P_{LL}$, with W' as the slope and $P_{LL}$ as the intercept [6].

CP has been demonstrated to lie between the lactate threshold and VO2Max [23]. The exercise intensity between CP and lactate threshold has been deemed the 'heavy domain', where lactate accumulation and VO2 slow component will be present, however will attain a steady state. Intensities supra-CP are deemed 'severe', where VO2 will approach or exceed maximum levels and result in a predictable exhaustion [3].

To determine CP, Monod and Scherrer developed a protocol involving multiple dynamic exercise tests to local muscular exhaustion. Tests at various constant power-outputs were performed to $T_{lim}$. When force was plotted against $T_{lim}$, a hyperbolic relationship emerged. A linear relationship also existed between the total work done at each rate and the $T_{lim}$. The slope of this relationship is deemed critical power [6].

Monod's and Scherrer's findings were extended to total body exercise by Moritani et. al [9]. Moritani used an electrically braked cycle ergometer to determine VO2 peak during a ramp protocol, as well as CP using 3 dynamic work tests in similar fashion to Monod and Scherrer. Moritani found a linear relationship between total work and $T_{lim}$ in whole body exercise just as in localized exercise, making it possible to calculate $T_{lim}$ based on power output [9].

In the same study, Moritani concluded that CP was oxygen dependent. Conducting the multiple exhaustive trials at different levels of inspired $O_2$, it was found that hypoxic conditions decreased the slope of the relationship predictably (CP), while the intercept (W') remained unchanged [23]. The concept of CP being $O_2$ dependent was further reinforced in hyperoxic conditions, which where shown to increase CP estimates. Levels of PCr were found to decrease less rapidly, which resulted in extended $T_{lim}$ per power output [5].

Determining CP with the methods described thus far would take anywhere from 3 to 7 or more laboratory visits and tests, which could prove to be inconvenient when coupled with other manipulations. The need for a test protocol that estimates the heavy-severe exercise domain boundary more efficiently arose. Vanhatalo et. al. [10] observed the critical power formula P=W'/t+CP, and hypothesized that if W' was fully depleted (W'=0), P=CP. Having already established that a 3-minute all-out cycling test produced a repeatable power profile that reaches a steady state in the final 30-60s in an earlier study, it was tested whether this final power level was different from CP. When tested against the traditional multi-bout method, the end power during the 3-minute all-out test was no different from critical power. The work performed above end power was also not significantly different from W'. This was the first study to provide a method of determining the two parameters of the power-duration relationship in one laboratory visit [10].

Constantini et. al. [29] established the validity of a single session furthermore by combining a ramp protocol followed by a 3-minute all-out test. The combinations of these two tests allowed determinations of all exercise intensity boundaries in one laboratory visit. Furthermore, this study found that a familiarization trial for the 3-minute all-out test was not necessary, making determination of CP even easier. A similar combination of ramp test and sprint protocol was conducted by Murgatroyd et. al., using the ramp to indicate lactate threshold and Vo2 max, and the sprint to determine CP, reached the same conclusion [30].

With external validity always a concern with research, it is necessary to ensure laboratory-based concepts can be applied to the real world. One study tested the

multiple- bout test to determine CP in a velodrome. Three all-out tests of different duration were compared with CP determined in a lab setting, and were found to have very high agreeability[31]. Another study investigated the validity of CP tests performed on a rowing ergometer, both in all-out fashion and multiple constant work rates to exhaustion. End power was found to be highly correlated with CP, displaying the 3-minute all-out tests validity for various exercise modalities [8].

While W' is still not well understood, there is evidence that CP is a very consistent measure. As CP demarcates the limit of completely aerobic exercise, any preceding exercise has been proven to not impact it. In addition, since exercise below CP should be wholly aerobic and sustainable in nature, power outputs at this level should not, and have been proven to not, affect W'. Research studies have shown that exercise preceding a 3-minute all-out test above critical power deplete W', while have no effect on CP [26], as well as full out sprints prior to a 3-minute all-out test do not affect CP, regardless of recovery time [32].

The application for all-out critical power tests has recently been further extended to different contraction modalities and techniques. As opposed to the isotonic contractions that have been covered in this chapter thus far, a recent study utilized isokinetic cycling at two different rotations per minute (rpm). Trials were set at 100 and 60 rpm, and found that both models had high agreeability with each other as well as other CP protocols in terms of end power (CP) and work above end power (W')[33]. Isometric knee extension exercise has also been studied in an attempt to validate the torque-duration relationship. The protocol involved multiple tests with varying MVC percentages to failure compared against 60 isometric MVCs for 5 minutes (3s

contraction, 2 s relaxation), and found that this 5-minute MVC test appropriately predicted critical torque [11].

Most recently, Tschekovsky et. al. have began research on single-bout critical force (CF) tests using the forearm. The repeatability and validity of the critical force estimate from a maximal effort rhythmic isometric handgrip exercise test, as well as whether this would be a good indicator of CP was examined. These trials consisted of maximal effort rhythmic isometric handgrip exercises. Participants then completed two additional visits to exhaustion at 10% above CF, or 10% under CF capped at 20 min. The forearm grip protocol resulted in the same pattern of force decay to a level force as demonstrated in other exercise protocols. This plateau in force had good repeatability, and accurately predicted TTE for work supra-CF [34].

The research presented displays that this indefinite energy level can be applied to multiple modalities. Therefore choosing CF as our model will allow for more measurements due to its isometric nature. The consistency of CF and CP measurements makes it a very suitable method for assessment, and will allow reliable conclusions to be drawn from the proposed intervention.

**Exercise Induced Muscle Damage**

Exercise induced muscle damage (EIMD) is a phenomenon that anyone physically active has experienced at some point in their lives. It has been well established that eccentric contractions injury muscle more severely than concentric and isometric contractions. Armstrong et. al. investigated the effect of running on incline, flat, and decline planes in rats [15]. Decline running is primarily eccentric in nature,

while incline is concentric, with flat running being a mix of both. Armstrong et. al. assessed markers of muscle damage after putting rats through a running protocol. These markers include plasma creatine kinase (CK) and lactate dehydrogenase (LDH) levels, glucose-6-phosphate dehydrogenase (G-6-PDase), and histological observations. CK and LDH are usually located inside the muscle, so elevated plasma levels indicate damage of muscle cell's structure [35, 36]. G-6-PDase activity has been shown to be associated with the inflammation and repair process of skeletal muscles [37]. Armstrong et. al.'s results from 1983 clearly display greater muscle damage in downhill running than level. Immediately after exercise, plasma LDH and CK levels were significantly higher in declined runners than other running conditions, with a secondary elevation 1.5-2 days later. This secondary elevation was absent in the other conditions. Significant increases in G-6-PDase activity were observed in downhill runners and to a lesser extend in uphill runners, with no increases in level runners. Downhill runners also exhibited greater muscle disruption in the histological analysis [15]. Eccentric exercise has been shown to have the same effect in humans as it does in rats. Davies et. al. employed a box stepping protocol, with one leg performing the eccentric portion, and the other the concentric. Their results indicated that long lasting muscle weakness was observed in the eccentric leg, with minimal weakness observed in the concentric leg. It has been proposed that eccentric contractions cause more damage due to their recruitment of fewer motor units per given force [38, 39].

EIMD has been suggested to affect type 2 fibers more than type 1 fibers. In rabbit models, cyclic eccentric contractions cause similar changes to muscle as in humans. It was also found that type 2 fibers were selectively damaged [40]. The extent

to which EIMD injuries the musculature also depends on multiple factors. Warren et. al. investigated whether EIMD is larger in a single high stress contraction, or several contractions accumulated. Using rat soleus, muscles were eccentrically contracted between 0 and 10 times, and found that cumulative contractions result in significantly higher muscle damage [41]. It has also been shown that extending the duration of lengthening increases the damage. One study reported that the extent of injuries 3 days post EIMD increased with duration of the eccentric contraction up to 5 minutes in mice, however extending the lengthening beyond 5 minutes yielded no more damage. It was suggested that this lack of extra damage was due to loss of peak force. The same study varied peak force with the same lengthening velocity, and found muscle damage was positively correlated with peak force [42]. Talbot et. al. concluded that initial muscle length impacted EIMD [43]. Brooks & Faulkner found in 2001 that contraction velocity plays a minimal role in EIMD if muscle strain is not significant enough, and that muscle strain is a much better determinant of damage [44]. All these studies combined go to show there are many factors that play roles in determining the severity of EIMD per protocol.

Muscle damage causes multiple performance impacts. One study examined running economy before and after EIMD measured oxygen consumption, ventilation, respiratory exchange ratios (RER), heart rate, blood lactate, and rating of perceived exertion (RPE) at different percentages of Vo2Peak. Increases in heart rate, ventilation, RPE, RER, and blood lactate were observed following EIMD. There was also a reduction in stride frequency, stride length, and range of motion in the ankle and knee joints. This effect persisted for 3 days after EIMD, suggesting that damage reduces

exercise economy [17]. VO2 peak and ventilatory threshold have been shown to be reduced following eccentric exercise in cycling protocols [18]. Another study looking at time-trial performance found similar results, with EIMD causing a decreased power output, distance covered and VO2 [45]. In isometric maximum voluntary contractions, following EIMD, absolute strength has displayed detriments, while rate of fatigue was decreased. The authors suggested this might be due to a selective damage of type 2 fibers, resulting in increased reliance on fatigue resistant type 1 fibers [46].

P-MRS studies have indicated that there is an increased level of resting inorganic phosphate post EIMD, which suggests a higher resting muscle metabolism [47]. These higher resting inorganic phosphate levels may be responsible for a reduced exercise tolerance in damaged muscles, as damaged and undamaged muscles both reach the same absolute level of inorganic phosphate at exhaustion, and temporally there is not a greater depletion of PCr after damage [20]. This lack of a faster decrease in PCr levels discounts higher contributions of nonoxidative energy [20]. Using near infrared spectroscopy (NIRS), it has also been shown that EIMD slows deoxyhemoglobin kinetics, slowing the extraction of oxygen from the blood during the onset of exercise. The VO2 kinetics are preserved, however, by an increase in blood flow to the damaged muscle [27]. Studies on mice have found that eccentric exercise impairs mitochondrial function, making them more susceptible to mitochondrial permeability transition pores (MPTP). These pores can result in a lesser production of ATP, and cell death [48]. As mitochondria are the sight of aerobic metabolism, this may serve to explain some of the metabolic changes presented above. Research in humans has yielded contradictory advice. Walsh et. al. found that high intensity eccentric exercise did not reduce muscle

oxidative function, and that muscle oxygen utilization and transport are unchanged at rest [22]. Foure et. al. [21] recently found results conflicting with those of Walsh et. al [22]. Using isometric neuromuscular electrostimulaton (NMES) to induce damage larger than that of voluntary contractions, Foure et. al. [21] observed impaired mitochondrial function in exercising muscle, as well as elevated intramuscular acidosis in resting muscles. PCr recovery was slower, as well as reduced oxidative ATP indicated deficiency in mitochondria [21].

More research is required on this subject to further develop our understanding of muscle damage's impact on the metabolic properties of muscle. Due to CF being the limit to wholly aerobic exercise, a decrease in CF resulting from EIMD could very reasonably give evidence toward compromised metabolic processes. Such evidence would be helpful in understanding and fine tuning training and recovery programs for athletics, as well as stimulating further research.

**Near Infrared Spectroscopy**

Near Infrared Spectroscopy (NIRS) is a noninvasive method to determine muscle O2 saturation in the small vessels. Near infrared light penetrates the tissue and either gets absorbed by oxy- and deoxy-hemoglobin or scattered[49]. The near infrared light wavelengths (670 nm – 900 nm) provide a unique window where absorption properties of tissue can be measured as the oxygenated and deoxygenated molecules have its own absorption spectra[49]. Oxy and deoxyhemoglobin absorb 800 nm light equally; however at 760 nm the absorption is primarily deoxyhemoglobin. Monitoring these wavelengths therefore provide an index of deoxygenation. Scattering of the signal is measured directly by the device and accounted for[49].

During an extended bout of exercise, muscle will rely on the oxidative energy system. NIRS has been used to evaluate recovery of oxygenated hemoglobin, a measure that determines the balance of oxygen delivery to oxygen consumption. Measurements made under occlusion results in oxygen delivery and venous return to be cut out, and thus measuring only oxygen consumption. The rate of oxygen consumption under these conditions can be used to determine rate of PCr recovery[50]. After exercise, the PCr system is recovered via mitochondrial ATP production, and therefore is a measure of oxidative capacity. Nagasawa et al. (2003) compared time constants (Tc) for PCr recovery as determined by NIRS against the criterion method of P-MRS[51]. Following forearm exercise protocol, blood flow to the forearm was occluded every 20 seconds for ten seconds at a time up to 180 seconds, and every 30 seconds up to 600 seconds. During occlusion, oxygen consumption was determined using NIRS. This protocol was repeated twice, with the second time being 10 seconds offset from the first. This allowed having twice as many measures of oxygen consumption. Plotting the slopes of oxygen consumption over time resulted in the ability to determine a Tc for the NIRS data. This NIRS determined Tc was found to be significantly correlated with measures made by the P-MRS and thus a valid indicator of oxidative capacity[51]. Cross-validation of NIRS with P-MRS indexes of muscle oxidative capacity has proven NIRS to be valid for assessing mitochondrial function [50]. These findings have been shown to be independent of exercise intensity, and to have a high degree of reliability and reproducibility[52].

# CHAPTER III
# METHODOLOGY

## Participants

The University of Oklahoma's institutional review board for research on human subjects provided ethical approval for the experiment. Participants provided verbal and written informed consent. Once informed consent was obtained, participants were asked to complete a health and physical activity readiness questionnaires (PARQ) prior to any testing. Twelve participants volunteered (females=4, males=8) for and completed the study. Of those 12, only 8 participants demonstrated a >5% reduction in maximal voluntary strength (MVC) of the quadriceps from pre-damage to 48-hours post-damage. The 4 participants who did not demonstrate a reduction in MVC were judged to have not experienced EIMD and were therefore excluded from analysis. A sample of 8 was sufficient to detect an effect of 0.42 SD at an alpha level of 0.05, a power of 0.80, and assuming a correlation between repeated measures of CT of 0.95 [53].

Participants were required to arrive at the laboratory in a rested state, having performed no heavy exercise in the last 24 hours, and to have refrained from food and beverage in the previous 3 hours. Participants were also asked to refrain from the use of anti-inflammatories and/or any other pain medications for the duration of the study and to refrain from any therapeutic modality (ice, massage, etc.) following the eccentric exercise protocol. Compliance with these instructions was confirmed at the beginning of each testing session. All trials were performed at roughly the same time of day (within 2 hours).

Due to participants being volunteers, a non-probability sampling technique was necessary and recruitment occurred in the Norman, OK area by fliers, mass-email and

word of mouth. Males and female participants were used due to evidence they experience a similar magnitude of EIMD following eccentric exercise [54, 55]. All participants had not participated in resistance training with their quadriceps for the previous 6 months.

**Experimental Design**

A repeated measures design was used whereby each participant was assessed prior to and 48-hours post muscle damage. Following 2 familiarization sessions, critical torque of the knee extensors was assessed using a previously validated [11] 5-minute isometric knee extension exercise protocol where participants performed a series of maximal voluntary contractions for 3 seconds followed by 2 seconds of rest (60 total contractions). Electromyography (EMG) was collected from the contracting quadriceps during the CT test. Mitochondrial function was assessed prior to the CT test using NIRS as described previously [50].

*Visit 1 & 2 (45-60 minutes each) – Familiarization* The first two visits were to familiarize subjects to location and protocol. The participant was seated on a KinCom isokinetic dynamometer in the proper positioning, and with their hip placed at approximately a 90 degree angle. KinCom setting were noted for each participant to allow consistency between trials. Straps were placed across their chest to secure them to the seat. The ankle of their dominant leg was secured to the dynamometer lever such that their knee rests at an angle of 70 degrees below horizontal. Electrodes were placed on the bellies of the vastus medialis and vastus lateralis muscles. The participants then performed three maximal voluntary isometric contractions of the quadriceps. Following

the three MVCs, participants were familiarized to electrical muscle stimulation. Participants then conducted a familiarization to the critical torque assessment, and to the cuff inflations to be utilized for the near-infrared spectroscopy assessment.

*Visit 3 (60-75 minutes) – Baseline Mitochondrial Function and Critical Torque Assessment* Participants arrived to the lab, and assumed a resting supine position on the bench for 15 minutes. Blood pressure was taken prior to any testing. The NIRS probe was then placed on the belly of the vastus medialis muscle. Near-infrared spectroscopy assessment of mitochondrial function was then performed twice. The participants were then seated in the KinCom, and EMG electrodes were placed on their vastus lateralis muscle belly. The participants were then instructed to perform three sets of MVCs. Following a three minute break, the participants performed the critical torque assessment.

*Visit 4 (30-45 minutes) – Eccentric Exercise* Upon arrival, participants were asked to perform a muscle soreness assessment. They were then seated and properly secured into the KinCom. The participants then performed three sets of MVCs. The current to be used during the muscle damage protocol was then determined followed by the eccentric exercise protocol. Upon completion of the protocol, muscle soreness was reassessed.

*Visit 5 (60-75 minutes) - Mitochondrial Function and Critical Torque Assessment Following EIMD* Participants arrived to the lab roughly 48-hours after visit 4, and muscle soreness was assessed. They then assumed a resting supine position on the bench for 15 minutes. Blood pressure was taken prior to any testing. The NIRS probe was then placed on the belly of the vastus medialis muscle. Near-infrared spectroscopy assessment of mitochondrial function was then performed twice. The participants were

then seated in the KinCom, and EMG electrodes were placed on their vastus lateralis muscle belly. The participants were then instructed to perform three sets of MVCs. Following a three minute break, the participants performed the critical torque assessment.

**Experimental Procedures**

**Current Determination**

Participants were seated in the KinCom as previously described. Electrodes were placed on the vastus medialis and vastus lateralis muscles. Isometric contractions were evoked using 100 Hz electrical stimulation at the highest stimulation amplitude each participant could tolerate.

**Maximal voluntary isometric contraction of the quadriceps**

The participant was seated on the KinCom in the proper position described previously. The participant was asked to perform a maximum voluntary contraction using their dominant quadriceps muscle group. Participants were asked to contract their quadriceps as forcefully as possible such that their ankle "kicks" against the pad on the dynamometer lever. Each contraction lasted 3 seconds, three total contractions were performed, and 3 minutes of rest separated each contraction.

**Familiarization to critical torque assessment**

A 2 minute rest period was followed by a 2-minute exercise protocol where participants performed a series of MVC's with their dominant quadriceps. Each MVC

lasted 3 seconds, followed by a 2 second rest period—exercise continued in this manner for 2 minutes (12 total contractions will be performed). A metronome as well as verbal queuing was provided to assist participants in becoming familiar with the contraction cadence. Visual feedback of the torque produced during the MVC was provided to the participants. The critical torque testing protocol involved performing contractions in this manner for 5 minutes. Only 2 minutes of exercise were performed during this familiarization session in an effort to limit fatigue, but allow participants to learn the contraction cadence.

**Familiarization to near-infrared spectroscopy assessment of mitochondrial function**

Following a 5 minute rest period, participants were familiarized to the procedures for determining their mitochondrial function. Participants lied in a supine position on a padded table. The ankle of their dominant leg was placed on a raised, padded brace such that their lower leg and knee and slighted elevated from the table. A blood pressure cuff was placed around their thigh, approximately 10-15 cm distal to their inguinal ligament. The cuff was attached to a rapid cuff inflation/deflation pneumatic system. The cuff was inflated to ~250-280 mmHg (consistent with previous studies) to occlude blood flow distal to the cuff. The cuff was inflated for 30 seconds, released, and then participants will rest for 3-5 minutes. The cuff was again inflated for 30 seconds, released and a recover period of 3-5 minutes was allowed. Next, a series of cuff inflations and deflations, each lasting 10 seconds was performed. This was done for 1 minute (3 inflations and 3 deflations). This procedure was performed to familiarize

participants to the location of the cuff placement, and to the sensations that occur during cuff inflation/deflation.

**Near-infrared spectroscopy assessment of mitochondrial function**

Participants were placed in a supine position on a padded table with their lower leg elevated as described above. The blood pressure cuff was placed around their upper thigh as described in the familiarization. The near infrared spectroscopy probe was then be placed over the belly of the vastus lateralis. Placement location was determined by use of anatomical landmarks, palpation, and 2D Doppler ultrasound of the site. After a 3-5 minute rest period the cuff was inflated to ~250-280 mmHg for 60 seconds. It was then released and participants rested for 3-5 minutes. The cuff was again inflated to ~250-280 mmHg for 60 seconds, released and followed by a 3-5 minute rest period. After the rest period the participant performed a brief (20 seconds) knee extension exercise protocol was performed to raise the metabolic rate in the quadriceps muscle group. Immediately following the exercise protocol the blood pressure cuff around the thigh was inflated to ~250-280 mmHg for 10 seconds, released, and a 10 second recovery period was given. A series of 10 second inflations and 10 second deflations continued for 5-6 minutes (for a total of 15-18 periods of inflation). Following the final deflation a 2-3 minute rest period was be provided.

**Critical torque assessment**

Participants were seated on the KinCom in the same manner as in maximal voluntary isometric contraction of the quadriceps. Surface electromyography electrodes

were placed over the belly of the vastus lateralis muscle. Position was determined by anatomical landmarks and palpation. The location of electrode placement was shaved to remove and hair and dead skin cells and then cleaned with alcohol. The near infrared spectroscopy probe was then be placed over the belly of the vastus lateralis. Placement location was determined by use of anatomical landmarks, palpation, and 2D Doppler ultrasound of the site. The NIRS probe and EMG electrodes were secured in place using surgical tape and elastic wraps. Next, participants performed a series of MVC's to the cadence of 3 seconds of contraction followed by 2 seconds of rest for a period of 5 minutes (60 total contractions) to determine their critical torque. Participants had the assistance of a metronome, as well as visual and verbal feedback to help them provide a maximal effort for each contraction.

**Muscle soreness assessment**

The participant performed a rating of their perceived muscle soreness/pain in their dominant quadriceps muscle group. Participants performed a single legged squat and then used a 10 cm visual analog scale (VAS) to rate the pain/soreness experienced in their quadriceps.

**Eccentric exercise protocol**

Participants performed an eccentric exercise designed to induce muscle damage. While seated on the KinCom, maximal isokinetic eccentric contractions of the knee extensors will be performed. Participants initially performed 4 sets of 10 contractions at 30 degrees per second with 3 minutes of rest provided between sets. Contractions were

evoked using 100 Hz electrical stimulation at the highest stimulation amplitude each participant could tolerate. Following the 4 sets, MVC was re-tested. If a ~40% decrease in MVC was not observed, additional sets of 10 contractions were performed, after which MVC was again assessed. Eccentric exercise proceeded in this manner until MVC declined ~30%.

**Analysis**

All tests were perfomend using SPSS version 19. Paired t-tests were conducted to identify differences between pre-EIMD and post-EIMD CF, IAT and NIRS. A one-way ANOVA was run on the VAS scale for pre, post, and 48-hours post eccentric exercise. A 2x10 repeated measures ANOVA was run on EMG RMS and median frequency. A level was set a priori at $p<0.05$.

*Critical Torque Calculation* The average torque was obtained from the plateau of each 3-second contraction. The data for the final 6 contractions was then averaged and taken as critical torque.

*Impulse Above End Test Torque* IAT was calculated as the area under the torque curve but above the level of critical torque using the trapezoid method.

*NIRS Calculation* NIRS data was converted into a text view. From each 10-second occlusion following isometric exercise, an 8 seconds of data was plotted as [HB] vs time to find the slope. All the slopes were then plotted against time to allow an exponential decay fit from which a time constant was calculated.

*EMG* The root mean square was averaged from the plateau of each 3-second contraction. Median frequency was calculated from the raw EMG signal during the plateau. Data was averaged over 6 consecutive contractions at a time.

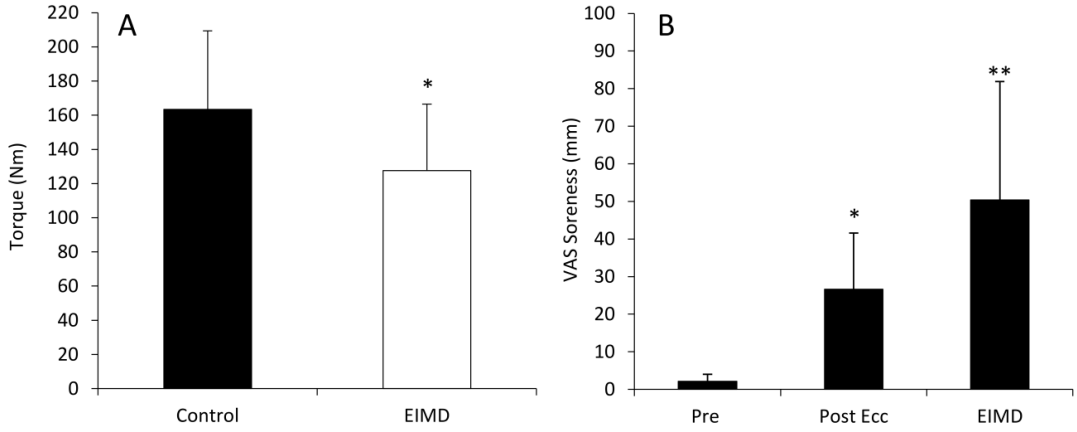
# CHAPTER IV
# RESULTS

A total of 8 participants were included in the analysis for this study (females n = 2 males n = 6). One participant out of the 8 was excluded from the analysis of mitochondrial function due to their data being deemed an outlier (>2.5 SD's above the mean response). Participants in the study were 22.6 ± 4.2 yrs old with a height of 178.5 ± 6.7cm and weight of 79.3 ± 19.9kg

## Assessments of EIMD

MVC was decreased -22% (p=0.006; Cohen's d = -0.84 SD; Figure 1A) 48-hours post the eccentric exercise protocol. Rating of muscle soreness increased from pre-eccentric exercise to immediately following the eccentric exercise protocol (p = 0.002; Figure 1B). Rating performed 48-hours following the eccentric exercise protocol were increased compared to rating performed directly post damage (p = 0.004) and compared to rating performed pre-damage to 48-hours post damage (p = 0.002).

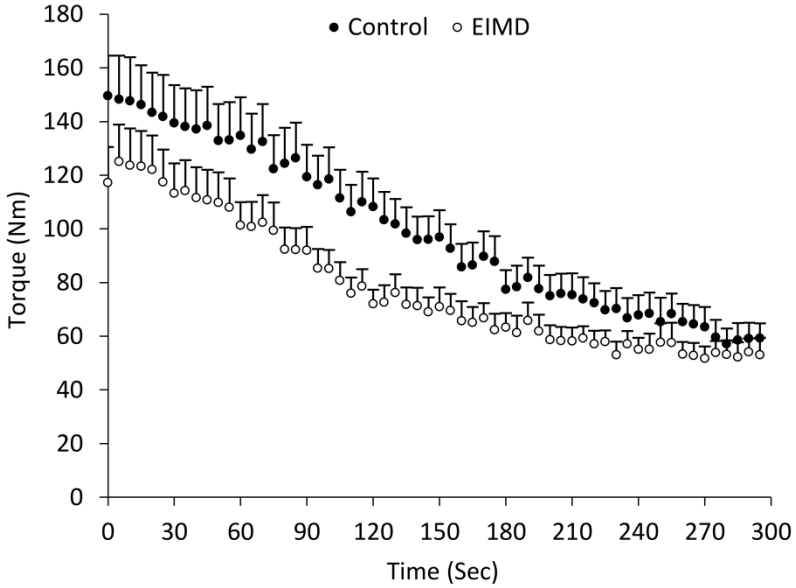
**Figure 1**



**Critical Torque and Impulse Above Critical Torque**

A plot of the mean critical torque values over each of the 60 contractions performed in the control and EIMD condition can be seen in Figure 2.

**Figure 2**




Critical torque was reduced -9.5% in the EIMD condition compared to control condition ($p = 0.04$; $d = -0.42$ SD; Figure 3). IAT was also reduced ($p = 0.008$; Figure 4) in the EIMD condition compared to the control condition, but this reduction was larger in magnitude (-36% with an effect size of $d = -0.84$ SD) than the reduction in CT.

**Figure 3**

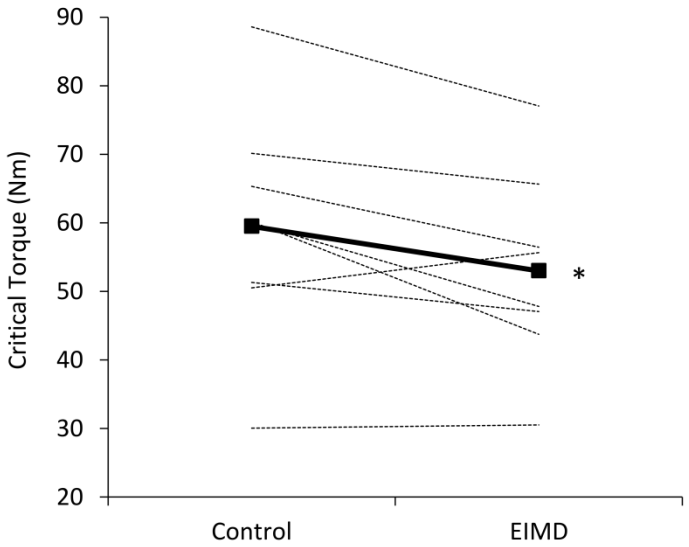
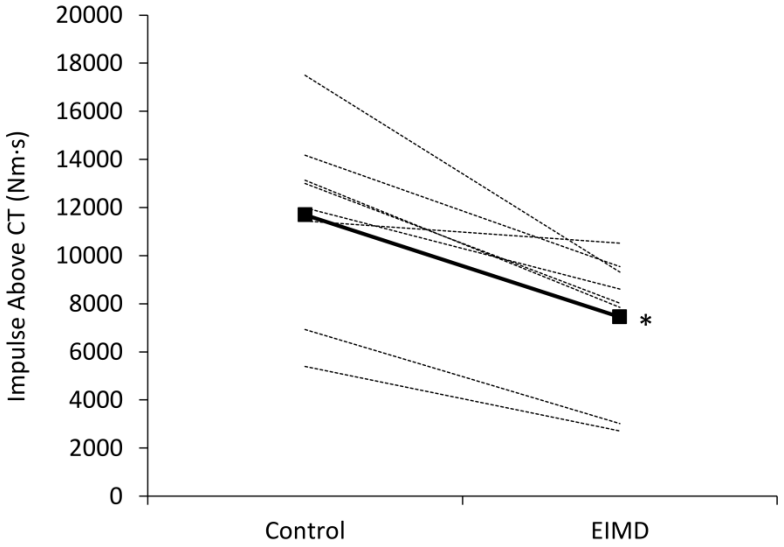



**Figure 4**

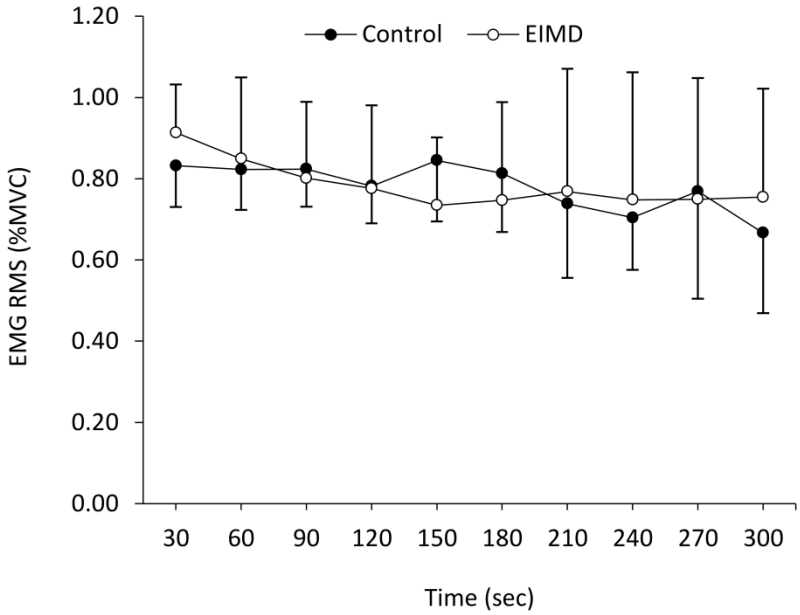



**Muscle Activation**

Average RMS values over each 30 second period (covering 6 consecutive contractions) during the CT test can be seen in Figure 5. There was not a significant

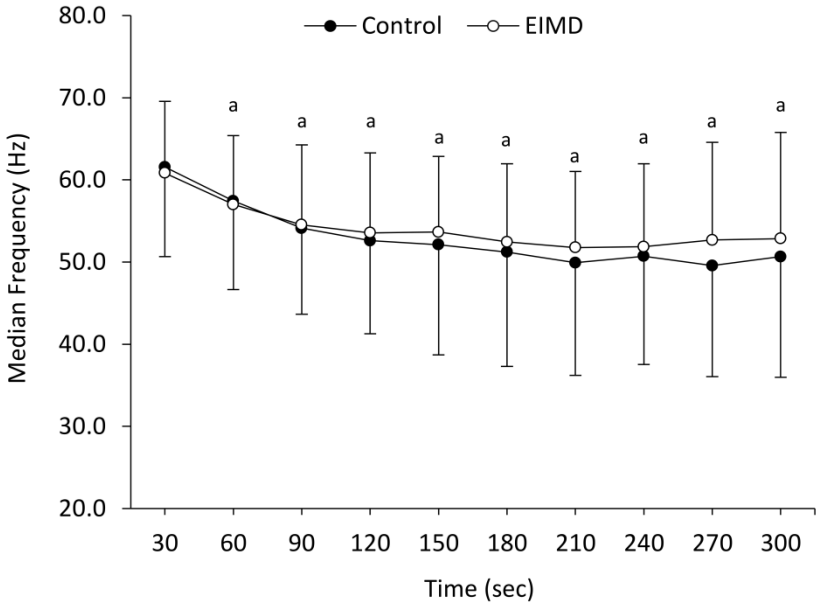
condition x time interaction ($p = 0.28$), nor were there significant main effects for condition ($p = 0.95$) or time ($p = 0.31$).

**Figure 5**




Data for median frequency was also averaged over each 30 second period (covering 5 contractions) during the CT test and can be seen in Figure 6. There was not a significant condition x time interaction ($p = 0.15$). There was also not a significant main effect for condition ($p = 0.57$). There was a significant main effect for time ($p = 0.001$). A Bonforroni post-hoc analysis was run, and all time points were significantly reduced compared to the value from the initial 30-sec period of the test ($p \leq 0.05$).

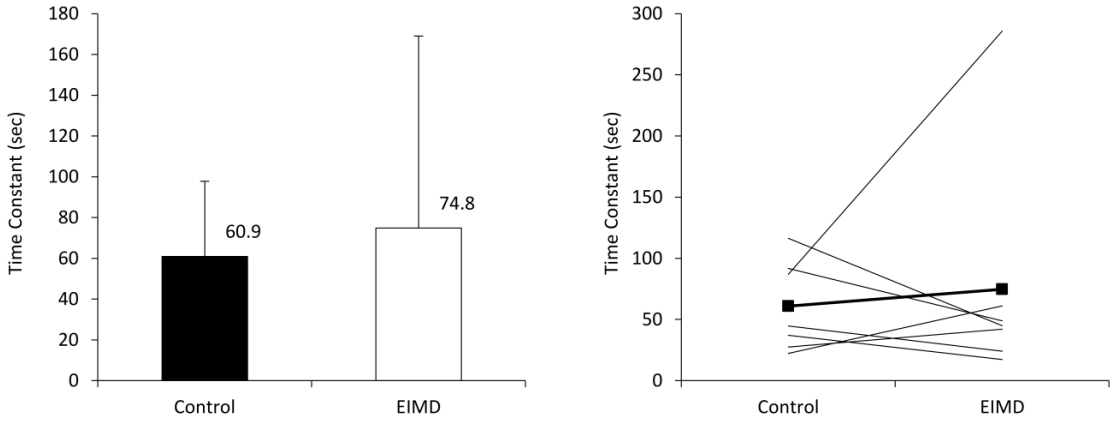
**Figure 6**




**Mitochondrial Function**

Mean time constants from the mitochondrial function test are shown in Figure 7. EIMD had no effect on the recovery time constants when compared to the control condition ($p = 0.69$).

**Figure 7**



# CHAPTER V
# DISCUSSION

There is a growing body of evidence that critical power is one of the strongest physiological predictors of endurance exercise performance/tolerance [56-58]. It is also well established that eccentric exercise induced damage to skeletal muscle alters disrupts sarcomere integrity [16] and leads to a sequelae of secondary issues such as loss of force production [15, 18, 19, 54], decreases in range-of-motion [54], and delayed-onset muscle soreness [18, 19, 54]—all of which may work in concert to decrease physical function. EIMD has been shown to compromise in movement economy [17], decrease peak $VO_2$ [18, 19], increase inflammatory cytokines in brain areas related to volitional fatigue [59], and decreased power outputs [18, 60]. Whether or not EIMD directly impairs oxidative metabolic function is still unclear with some studies showing no impairments during exercise [22] and others finding subtle, but measurable changes in the $P_i$ to PCr ratio [20, 21]. With critical power likely being dependent on aerobic metabolic function, a compromise in mitochondrial function and $VO_2$ peak as a result of EIMD could result in a lowering of critical power and explain some of the reduced exercise tolerance observed in previous studies. Therefore this study had two primary aims: 1) to determine whether EIMD in the knee extensors altered the work-time relationship as assessed by critical torque and 2) to determine whether EIMD altered mitochondrial function of the quadriceps muscles as assessed by NIRS. The primary novel findings of this study were that EIMD reduced critical torque 9.5% and impulse above end test torque (i.e W') was decreased by 36%. Interestingly, an accompanying reduction in mitochondrial function was not observed.

**Confirmation of EIMD**

To determine whether participants were successfully damaged following the eccentric exercise protocol, MVC was measured immediately following eccentric exercise and 48-hours later—prior to the final critical torque test. Ratings of perceived muscle soreness were provided using a VAS scale prior to and immediately following eccentric exercise as well as 48-hour post damage. A significant decline in MVC was been shown to be the most valid "indirect" marker of significant EIMD and myofibullar disruption [61]. All participants included in the analysis displayed a significant decrease (-22%) in MVC. The 4 excluded participants showed either a very small (>5%) reduction, no reduction, or an increase in MVC 48-hours following eccentric exercise. We were therefore confident that we had successfully induced muscle damage in the participants included in the analysis.

**EIMD and Critical Torque**

To our knowledge this is the first study to examine the effects of EIMD on the work-time relationship. Our findings of a significant reduction in critical torque following EIMD are consistent with previous studies demonstrating impairments in physical function and exercise tolerance following EIMD [17-19, 45, 60]. It has been shown that critical torque can be manipulated without changes in training status. Moritani et al. [9] found that critical power was decreased when tests were performed in hypoxic conditions and a recent study by Broxterman et al. [24] found that critical power decreased during blood flow occlusion to the exercising muscles. Additionally, critical power has been shown to increase under hyperoxic conditions [5]. Collectively

these findings strongly suggest a relationship between CP and aerobic metabolic function. The extent to which EIMD alters aerobic function is a matter of some debate. Mitochondrial function was shown to be impaired following EIMD in a recent study by Foure et al. [62], but this finding is in contrast to several previous investigations who found EIMD altered resting mitochondrial metabolism, but not metabolism during exercise [20, 22]. In the present study we did not observe significant changes in NIRS assessed mitochondrial function. The equivocal findings among studies may be related to the different measures used to assess mitochondrial function (P-31 MRS vs. NIRS) and to the different magnitudes of EIMD induced in each study as it is plausible that greater damage might be required to elicit measurable decrements in mitochondrial function.

While the effects of EIMD on cellular aerobic metabolism remain somewhat unresolved, consist with our findings of reduced CT, EIMD has been shown to decrease peak $VO_2$ [18, 19], reduce ventilatory and lactate threshold [18, 19], and to reduce an integrative assessment of exercise performance in the form of a cycling time-trial (TT) [45]. Interestingly, the magnitude of reduction in CT (-9.5%) observed in the present study is quite similar to the magnitude of reduction in $VO_2$ (~10%) [18, 19] and TT performance (~6%). Eccentric exercise has been shown to selectively damage type 2 muscle fibers (Liber & Friden, 1988) which would place a greater metabolic stress upon the undamaged type I fibers—even if their oxidative capacity remains uncompromised. Attainment of CT is related to the depletion of intramuscular creatine phosphate stores, a drop in intramuscular pH from hydrogen ion accumulation, and the accumulation of other metabolic by-products. It is therefore plausible that following EIMD greater

metabolic stress is placed upon the undamaged muscle fibers leading to an earlier onset of lactate accumulation, as observed previously [18, 19], and an earlier onset of metabolic acidosis. All of which would lead to a lower of CT.

**EIMD and Impulse Above End Test Torque**

Perhaps the most interesting, and unexpected finding of our experiment was the 36% reduction in IAT, an isometric analog to W', following EIMD. EIMD appears to disproportionately affect IAT compared to CT (36% reduction vs. a 9.5% reduction). The physiological determinants of IAT remain unresolved, but it is thought to be related to stored anaerobic energy in the muscle (e.g. creatine phosphate and oxygen), glycogen stores, and the accumulation of fatigue inducting metabolites (e.g. inorganic phosphate and hydrogen ions) [63]. EIMD has been shown to increase the ratio of $P_i$ to PCr in resting skeletal muscle [20, 62] due to an increase in resting $P_i$ and to impair glycogen re-synthesis [64, 65] in the days following eccentric exercise. Additionally, EIMD leads to the death of a population of muscle fibers and to sub-lethal membrane disruption in another population of fibers. As a consequence, the total available store of PCr within a muscle has likely decreased. Having less PCr available may play a role in the reduced IAT observed in the present study as could an increase in $P_i$. Previous studies [5, 57] have demonstrated exhaustion occurs when certain level of intramuscular $P_i$ are achieved. If these levels are higher at rest, it would take less of an increase to reach the level required to evoke exhaustion. The most likely explanation is that EIMD alters multiple aspects of the intracellular environment leading to earlier depletion of

anaerobic stores and attain of critical pH, $P_i$, and PCr levels thus resulting in a reduced IAT.

**EMG**

No differences were observed between the control and EIMD damage in regards to EMG RMS and median frequency. RMS provides a rough indicator of skeletal muscle activation [38] (i.e. the magnitude of the signal from the central nervous system that reaches the muscle and signals for it to generate force). The finding that RMS did not differ over time during the CT test nor between conditions provides evidence that central motor drive was consistent throughout each CT test. One possible explanation for the decline in MVC and potentially CT in this study was that participants did not provide a "maximal" effort following EIMD due to DOMS. The RMS findings provide evidence this was not the case and that a similar, near maximal effort was provided in both conditions. EMG median frequency decreased over time during the CT test in both conditions. This finding is consistent with many previous studies (see [66, 67] for review). The decrease in median frequency is generally thought to be a consequence of slowed action potential propagation [66, 67] along the motor axons and the sarcolemma. As such it is a consequence of the development of peripheral fatigue rather than a cause, *per se*, of the fatigue. The similar decline in median frequency between the two experimental conditions further confirms a similar motor drive to the muscles and the development of a similar level of fatigue over the course of the 60 contractions performed in the test.

## Conclusion

The primary aim of this study was to determine the effect or exercise induced muscle damage on critical torque and mitochondrial function. We found a 9.5% decrease in critical torque and a 36% decrease in impulse above end test torque. These decreases were not accompanied by any significant changes in mitochondrial function as determined by NIRS. This leads to the thought that critical torque is reliant on more than just aerobic capacity. These findings may have large implications on a variety of athletes. The drop in critical torque may be important to distance athletes who perform at levels near critical torque for extended periods of time. The large drop in impulse above end test torque could have severe implications on intermittent sports such as rugby and soccer, where athletes cross back and forth between the heavy and severe exercise domains

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# APPENDIX A: INFORMED CONSENT

**Consent Form**
**University of Oklahoma, Norman Campus (OU)**
**University of Oklahoma Health Sciences Center (OUHSC)**

## EFFECTS OF EXERCISE INDUCED MUSCLE DAMAGE ON CRITICAL TORQUE AND MITOCHONDRIAL FUNCTION

***Principle Investigator: Christopher D. Black, Ph.D.***
***Sponsor: Department of Health and Exercise Science***

This is a research study. Research studies involve only individuals who choose to participate. Please take your time to make your decision. Discuss this with your family and friends.

**Why Have I Been Asked To Participate In This Study?**
You are being asked to take part in this study because you are recreationally active (e.g., you participate in physical activity less than 5 hours per week) and have participated in little or no lower body resistance training in the past 6 months.

**Why Is This Study Being Done?**
The purpose of this study is to determine the effects of muscle damaging exercise on critical strength and mitochondrial (cell energy) function in the knee extensor muscles.

**How Many People Will Take Part In The Study?**
About twenty people (men or women) between the ages of 18-40 will take part in this study.

**What Is Involved In The Study?**
You will be asked to complete various health history and screening questionnaires prior to beginning the study. You will be asked to complete two days of familiarization, and three days of experimental testing. Familiarization days will take roughly 45-60 minutes. Testing days will take roughly 60- 75 minutes.

**How Long Will I Be In The Study?**
You will be visiting the laboratory five times. A minimum of 48 hours will separate the familiarization trials from the testing trials (visit 2 from visit 3). 48 hours will separate the muscle damage day from the final visit (visit 4 from visit 5). The total time commitment is ~5-6 hours over 6-7 days

The following list is provided to detail your involvement in the study.
**Visit 1:**

- **Forms and Questionnaires:** Written and verbal descriptions of the experiment will be provided, and any questions will be answered. You will be asked to fill

out a physical activity readiness questionnaire (PAR-Q), medical history questionnaire, and a rhabdomyolysis risk assessment questionnaire.

- **Resting blood pressure**: A measurement of your resting blood pressure will be taken after a few minutes of resting in a seated position. The blood pressure cuff will be placed around your upper arm and will inflate and then deflate to determine your blood pressure.
- **Equipment Familiarization- KinCom, Maximal Strength, Critical Strength Test:**

  You will be seated in a KinCom isokinetic dynamometer machine. Your hip and knee angles will be adjusted to specific positions, and your body will be secured to the seat and attachments with straps. You will then be asked to perform three 3-second maximal voluntary contractions (MVCs) separated by 3 minutes rest each. An MVC is an assessment of the maximal strength of your thigh muscles and it will be determined by asking you to extend your leg as forcefully as possible. Following the final MVC, a 2-minute break will be provided followed by a 2-minute exercise protocol involving rhythmical MVCs at a cadence of a 3-second contraction followed by 2 seconds rest.
- **Equipment Familiarization- Near-infrared Spectroscopy:** You will be asked to lie on your back on a table. Your ankle will be put in a raised position, and a blood pressure cuff will be fastened around your upper thigh. This cuff will undergo a series of inflations (to approximately 250-280 mmHg) of different durations to allow for familiarization to the cuff location and sensations of inflation/deflation. During this period of time a near-infrared spectrometer will be placed on your thigh. This device sends light signals into blood, muscle and fat tissue. Some light that is sent comes back to the sensor from the muscle, fat, and blood, while some light is lost due to deflection

**Visit 2: 24-72 hours after Visit 1**

- You will repeat familiarization protocols in the same manner as Visit 1.

**Visit 3: 24-72 hours after Visit 2**

- **Recall Questionnaire:** You will be asked to fill out a recall questionnaire regarding your diet and exercise over the last 24 hours
- **Near-infrared Spectroscopy:** You will assume the same supine position as during familiarization. The pressure cuff will be secured around the upper thigh, and the near-infrared probe will be secured to your thigh. The cuff will then be inflated for 60 seconds, followed by 3-5 minutes of rest and then the cuff will be inflated again for 60 seconds followed by 3-5 minutes of rest. You will then be asked to perform a brief series of knee extensions using a light weight attached to your ankle. This will be followed by 5-6 minutes of rhythmical cuff inflation at a cadence of 10 seconds of inflation followed by 10 seconds deflation. The near-infrared spectroscopy protocol will take place two times.

  **KinCom Maximal Strength and Critical Strength:** You will be seated in the KinCom machine in the same manner as during familiarization trials. A set of electrodes will be placed on your thigh (to measure the electrical

activity of the muscle during exercise) and the near-infrared spectroscopy probe will be placed on your thigh as well (shaving of body hair may be necessary). You will then be asked to perform three 3-second maximal voluntary contractions (MVCs) separated by 3 minutes rest each. An MVC is an assessment of the maximal strength of your thigh muscles and it will be determined by asking you to extend your leg as forcefully as possible. You will be then asked to perform rhythmical MVCs following a cadence of 3-seconds of contraction to 2-seconds of rest for 5 minutes.

**Visit 4: 24-72 hours after Visit 3**

- **Rating of perceived muscle soreness:** You will be asked to perform a single leg squat with your dominant leg, and indicate on a scale your current soreness level of the quadriceps. This will occur three times in a row.
- **KinCom Eccentric Exercise:** You will be seated in the KinCom in a similar matter as in the previous visit. Two electrical stimulation pads will be placed on your thigh muscles. Electrical current will then be applied to the pads in order to make your thigh muscles contract. The current will be increased until you decide it has become uncomfortable. It will then be reduced to the highest level you find comfortable. Three, 3-second MVCs will then be taken. You will be then perform 4 sets of 10 of isokinetic eccentric knee flexions where electrical stimulation will be applied to your thigh muscles so they contract against the KinCom machine as it pushes your leg downward. MVC will be assessed after the 4 sets. If your MVC has not declined by ~30% then you will perform additional sets of 10 eccentric knee flexions until your MVC declines by ~30%.
- **Rating of perceived muscle soreness:** You will once again be asked to perform 3 single leg squats and indicate current soreness level.

**Visit 5: 48 hours after Visit 4**

- You will be asked to rate your feelings of muscle soreness as described previously, and then visit 5 will proceed in an identical manner to visit 3.

There may be certain circumstances in which your participation may be terminated by the investigator without regard to your consent.
For example:

- If you have taken any vitamins, consumed alcohol, or taken any drugs prior to testing
- If it is in your best medical interest
- You fail to follow study requirements
- The study is stopped by the sponsor

**What Are The Risks of The Study?**

- You may experience heavier than normal breathing from the exercise protocols used in this study.
- You may find the KinCom seat or attachments uncomfortable.
- You may experience muscle soreness for several days after the eccentric exercise protocol.

- You may experience rhabdomyolysis from the eccentric exercise protocol. Rhabdomyolysis is a potentially serious condition, although uncommon in recreationally active individuals, caused by a breakdown of muscle tissue that releases a damaging protein into the blood. This is extremely unlikely, <1%.
- Inflation of the blood pressure cuff may cause temporary discomfort and will stop when pressure in the cuff is decreased.

There are no other known risks associated with the protocols outlined in the proposal. Exercise testing of apparently healthy subjects under laboratory supervision is safe.

According to recent American College of Sports Medicine's Guidelines for Exercise Testing, the exercise tests described above can be safely performed in individuals who meet this studies inclusion criterion.

For more information about risks and side effects, ask the researcher if you have questions at any time.

**Are There Benefits to Taking Part in The Study?**

If you agree to take part in this study, there is no medical benefit to you. We hope the information learned from this study will benefit clinical and athletic populations with possible interventions and guidelines for anyone that may experience muscle soreness from unaccustomed physical activity.

**What Other Options Are There?**

You may choose not to participate.

**What About Confidentiality?**

Efforts will be made to keep your personal information confidential. You will not be identifiable by name or description in any reports or publications about this study. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. You will be asked to sign a separate authorization form for use or sharing of your protected health information.

There are organizations that may inspect and/or copy your research records for quality assurance and data analysis. These organizations include the Department of Health and Exercise Science and the OUHSC Institutional Review Board.

**What Are the Costs?**

As a participant, you will not incur any additional costs.

**Will I Be Paid For Participating in This Study?**

Yes, you will receive a $20 gift card for your participation.

**What if I am Injured or Become Ill While Participating in this Study?**

In the case of injury or illness resulting from this study, emergency medical treatment is available. No funds have been set aside by The University of Oklahoma

Health Sciences Center, The University of Oklahoma-Norman, or the principle investigator to compensate you in the event of injury.

The current study involves low risk; however, there is always the possibility of a problem during exercise. Therefore, in case of a medical emergency the phone numbers for campus police (405-325-2864), Goddard Health Center (405-325-4611), Norman police (911), ambulance (911), and fire department (911) are posted in the testing room and research laboratory suite. Medical professionals are within minutes of the testing labs. All investigators are CPR, and Automated External Defibrillator certified. The P.I. will be present at each experimental visit or immediately available if needed.

**What Are My Rights As a Participant?**

Taking part in this study is voluntary. You may choose not to participate. Refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled. If you agree to participate and then decide against it, you can withdraw for any reason and leave the study at any time. Please discuss leaving the study with the principal investigator. You may discontinue your participation at any time without penalty or loss of benefits, to which you are otherwise entitled.

We will provide you with any significant new findings developed during the course of the research that may affect your health, welfare or willingness to continue your participation in this study.

You have the right to access the medical information that has been collected about you as a part of this research study. However, you may not have access to this medical information until the entire research study has completely finished and you consent to this temporary restriction.

**Whom Do I Call If I have Questions or Problems?**

If you have questions, concerns, or complaints about the study or have a research-related injury, contact Dr. Christopher Black at 706-255-3750 (cell) or 405-325-7668 (office).

If you cannot reach the Investigator or wish to speak to someone other than the investigator, contact the OUHSC Director, Office of Human Research Participant Protection at 405-271-2045.

For questions about your rights as a research participant, contact the OUHSC Director, Office of Human Research Participant Protection at 405-271-2045.

**Signature:**

By signing this form, you are agreeing to participate in this research study under the conditions described. You have not given up any of your legal rights or released any individual or entity from liability for negligence. You have been given an opportunity to ask questions. You will be given a copy of this consent

document.

I agree to participate in this study:

| | | |
|---|---|---|
| PARTICIPANT SIGNATURE (age ≥18) (*Or Legally Authorized Representative)* | Printed Name | Date |
| SIGNATURE OF PERSON OBTAINING CONSENT | Printed Name | Date |

# APPENDIX B: HIPPA FORM

**AUTHORIZATION TO USE or DISCLOSE PROTECTED HEALTH INFORMATION FOR RESEARCH**

*An Informed Consent Document for Research Participation may also be required. Form 2 must be used for research involving psychotherapy notes.*

Title of Research Project: **Effect of Exercise Induced Muscle Damage on Critical Torque and**

**Mitochondrial Function**

Leader of Research Team: **Christopher D. Black., Ph.D.**

Address: **1401 Asp Ave., #110 HHC, Norman, OK 73019**

Phone Number**: 405-325-7668 (office); 706-255-3750 (cell)**

If you decide to join this research project, University of Oklahoma Health Sciences Center (OUHSC) researchers may use or share (disclose) information about you that is considered to be protected health information for their research. Protected health information is information about past, present, and future medical treatment or condition that is identifiable to you. It will be called PHI in this Authorization.

**PHI To Be Used or Shared**. Federal law requires that researchers get your permission (authorization) to use or share your PHI. If you give permission, the researchers may use or share with the people identified in this Authorization any PHI related to this research from your medical records and from any test results. Information used or shared may include all information relating to any tests, procedures, surveys, or interviews as outlined in the consent form; medical records and charts; name, address, telephone number, date of birth, race, and government-issued identification numbers.

**Purposes for Using or Sharing PHI.** If you give permission, the researchers may use your PHI to determine if it is safe for you to participant in the exercise used in this study.

**Other Use and Sharing of PHI**. If you give permission, the researchers may also use your PHI to develop new procedures or commercial products. They may share your PHI with other researchers, the research sponsor, and its agents, the OUHSC Institutional Review Board, auditors and inspectors who check the research, and government agencies such as the Food and Drug Administration (FDA) and the Department of Health and Human Services (HHS). The researchers may also share your PHI with your physician and/or a Univeristy of Oklahoma physician in the event of a serious health risk or adverse event that occurs during the study.

**Confidentiality**. Although the researchers may report their findings in scientific

journals or meetings, they will not identify you in their reports. The researchers will try to keep your information confidential, but confidentiality is not guaranteed. The law does not require everyone receiving the information based on this authorization to keep it confidential, so they could release it to others, and federal law may no longer protect it.

**YOU UNDERSTAND THAT YOUR PROTECTED HEALTH INFORMATION MAY INCLUDE INFORMATION REGARDING A COMMUNICABLE OR NONCOMMUNICABLE DISEASE.**

**Voluntary Choice**. The choice to give OUHSC researchers permission to use or share your PHI for their research is voluntary. It is completely up to you. No one can force you to give permission. However, you must give permission for OUHSC researchers to use or share your PHI if you want to participate in the research and, if you cancel your authorization, you can no longer participate in this study.

Refusing to give permission will not affect your ability to get routine treatment or health care from OUHSC.

**Cancelling Permission**. If you give the OUHSC researchers permission to use or share your PHI, you have a right to cancel your permission whenever you want. However, cancelling your permission will not apply to information that the researchers have already used, relied on, or shared.

**End of Permission.** Unless you cancel it, permission for OUHSC researchers to use or share your PHI for their research will never end. You may cancel your permission at any time by writing to:

| | | |
|---|---|---|
| Privacy Official<br><br>University of Oklahoma Health Sciences Center<br>PO Box 26901<br>Oklahoma City, OK 73190 | or | Privacy Board<br>University of Oklahoma Health Sciences Center<br>PO Box 26901<br>Oklahoma City, OK 73190 |

If you have questions, call: (405) 271-2511 or (405) 271-2045.

**Access to Information.** You have the right to access the medical information that has been collected about you as a part of this research study. However, you may not have access to this medical information until the entire research study is completely finished. You consent to this temporary restriction.

**Giving Permission**. By signing this form, you give OUHSC and OUHSC's researchers led by
Christopher D. Black, permission to share your PHI for the research project called Effect of Exercise Induced Muscle Damage on Critical Torque and Mitochondrial Function

**Patient/Participant Name: _____**

_____ _____

Signature of Patient-Participant or Parent if Participant is a minor — Date

*Or*

_____ _____

Signature of Legal Representative** — Date

**If signed by a Legal Representative of the Patient-Participant, provide a description of the relationship to the Patient-Participant and the Authority to Act as Legal Representative:

_____

OUHSC may ask you to produce evidence of your relationship.

***A signed copy of this form must be given to the Patient-Participant or the Legal Representative at the time this signed form is provided to the researcher or his representative.***

**IRB No.: 5887**

# APPENDIX C: HEALTH STATUS QUESTIONNAIRE

## Health Status Questionnaire

**Part 1. Information about the individual**

1. _____
   Date

2. _____ _____
   Legal Name Nickname

3. _____ _____
   Mailing Address Home Phone
   _____ _____
   Cell or Business Phone

4. _____ _____
   Personal Physician Phone
   _____
   Address

5. _____ _____
   Person to contact in emergency Phone

6. Gender (circle one) Female Male

7. Age _____

8. Height _____ Weight_____

9. Do you smoke? Yes No

10. If you are a smoker, indicate number smoked per day:
    Cigarettes: 40 or more 20-39 10-19 1-9
    Cigars or pipes only: 5 or more or any inhaled Less than 5, none inhaled

11. Are you currently taking prescription or over-the-counter medication(s)? If so, please list the medication, daily dose, and why you are taking it.

12. Are you currently taking any vitamins or nutritional supplements? If so, please list the vitamin/supplement, the daily dose, and why you are taking it.

**Part 2. Medical History**

Assess your health needs by marking all **true** statements

**History**
You have had:
___ A heart attack
___ Heart surgery
___ Cardiac catheterization
___ Coronary angioplasty (PTCA)
___ Pacemaker-implantable cardiac defibrillatory/ rhythm disturbance
___ Heart valve disease
___ Heart failure
___ Heart transplantation
___ Congenital heart disease
___ Peripheral arterial disease
___ Stoke

**Signs/Symptoms**
___ You experience discomfort and/or pain with exertion in the chest, neck, jaw, arms
___ You experience unreasonable breathlessness at rest or with mild exertion
___ You experience dizziness, fainting, or blackouts
___ You experience ankle edema
___ You experience heart palpitations or tachycardia (unpleasant awareness of force or rapid heart beats)
___ You have or experience intermittent claudication (muscle pain due to ischemia)
___ You have a heart murmur
___ You take medication(s) for ANY type of heart condition or high blood pressure

**Other health issues**
___ You have diabetes
___ You have a thyroid disorder
___ You have a renal (kidney) disorder
___ You have liver disease (e.g. cirrhosis)
___ You have COPD, asthma, cystic fibrosis or other lung disease
___ You have burning or cramping sensation in your lower legs when walking short distances
___ You have musculoskeletal problems that limit your physical activity (arthritis, etc.)
___ You are pregnant

## If you answered yes to any of these statements please consult your physician or appropriate health care professional before engaging in exercise.

**Part III: Cardiovascular Risk Factors**

**Age**

___ You are a man older than 45 years
___ You are a woman older than 55 years, have had a hysterectomy, or are postmenopausal

**Medical/Lifestyle**

___ You smoke, or quit smoking within the previous 6 months

___ Your blood pressure is >140/90 mm Hg and has been confirmed by a doctor on two separate occasions **BP _____**

___ Your blood cholesterol level is >200 mg/dl or LDL cholesterol is >130 mg/dl

___ You have a close blood relative who had a heart attack or heart surgery before age 55 (father or brother) or age 65 (mother or sister)

___ You are physically inactive (i.e., you get <30 minutes of physical activity 3 days per week)

___ You have impaired fasting glucose (> 100mg/dl) that has been confirmed by a doctor on two separate occasions

___ Your BMI is >30 **BMI_____**

**ACSM Risk Stratification Category**

| | |
|---|---|
| **Low Risk** | Men < 45and women < 55 years of age who did not mark more than 1 medical/lifestyle factor |
| **Moderate Risk** | Men ≥ 45 and women ≥ 55 years of age, or those who marked 2 or more medical/lifestyle factors |
| **High Risk** | Individuals who marked one or more statements under Medical History |

I understand my signature signifies that I have read and understand all the information on the questionnaire, that I have truthfully answered all the questions, and that any questions/concerns I may have had have been addressed to my complete satisfaction.

Name (please print) _____

Signature _____ Date _____

# APPENDIX D: PHYSICAL ACTIVITY READINESS QUESTIONNAIRE

# PAR-Q & YOU

(A questionnaire for People Aged 15-69)

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. However, some people should check with your doctor before you start.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below. If you are between the ages of 15 and 69, the PAR-Q will tell you if you should check with your doctor before you start. If you are over 69 years of age, and you are not used to being very active, check with your doctor.

Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly: check **YES** or **NO**

| | | |
|---|---|---|
| YES ☐ | NO☐ | **1. Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?** |
| YES ☐ | NO☐ | **2. Do you feel pain in your chest when you do physical activity?** |
| YES ☐ | NO☐ | **3. In the past month, have you had chest pain when you were not doing physical activity?** |
| YES ☐ | NO☐ | **4. Do you lose your balance because of dizziness or do you ever lose consciousness?** |
| YES ☐ | NO☐ | **5. Do you have a bone or joint problem (for example, back, knee or hip) that could be made worse by a change in your physical activity?** |
| YES ☐ | NO☐ | **6. Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?** |
| YES ☐ | NO☐ | **7. Do you have a diabetes or thyroid condition?** |
| YES ☐ | NO☐ | **8. Do you know of any other reason why you should not do physical activity?** |

**If you answered "Yes":**

**YES to one or more questions**

A medical clearance form is required of all participants who answer 'yes' to any of the eight PAR-Q questions.
Note: Personal training staff reserve the right to require medical clearance from any client they feel may be at risk.

- Discuss with your personal doctor any conditions that may affect your exercise program.
- All precautions must be documented on the medical clearance form by your personal doctor.

**NO to all questions**

If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can:

- start becoming much more physically active - begin slowly and build up gradually. This is the safest and easiest way to go.
- take part in a fitness appraisal - this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively. It is also highly recommended that you have your blood pressure evaluated. If your reading is over 144/94, talk with your doctor before you start becoming much more physically

**DELAY BECOMING MUCH MORE ACTIVE:**

- If you are not feeling well because of a temporary illness such a cold or a fever - wait until you feel better; or
- If you are or may be pregnant - talk to your doctor before you start becoming more active.

**PLEASE NOTE:** If your health changes so that you then answer YES to any of the above questions, tell your fitness or health professionals.
Ask whether you should change your physical activity plan.

active.

Informed Use of the PAR-Q: The Canadian Society for Exercise Physiology, Health Canada, and their agents assume no liability to persons who undertake physical activity, and if in doubt after completing this questionnaire, consult your doctor prior to physical activity.

NOTE: If the PAR-Q is being given to a person before he or she participates in a physical activity program or a fitness appraisal, this section may be used for legal or administrative purposes.

**"I have read, understood and completed this questionnaire. Any questions I had were answered to my full satisfaction."**

**NAME**_____

**SIGNATURE**_____
**DATE**_____

**SIGNATURE OF PARENT**_____
**WITNESS**_____
**or GUARDIAN (for participants under the age of majority)**

**Note: This physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if your condition changes so that you would answer YES to any of the seven questions.**

Supported by: Health Canada Santé Canada

Physical Activity Readiness Questionnaire – PAR-Q (revised 2006 by CW)

# APPENDIX E: RHABDOMYOLYSIS SCREENING QUESTIONNAIRE

**Screening questionnaire**

Participant ID:_____
Date: _____

1. Do you participate in some form of physical activity at least 3 days per week?
   Yes or No

2. If you answered "Yes" to #1, please list and describe the type and frequency of activity in which you typically engage
   _____
   _____
   _____
   _____

3. Have you had any shoulder, elbow, and/or wrist injuries in the previous 6 months?
   Yes or No

4. Have you taken any type of pain relievers within the previous 7 days?
   Yes or No

5. Are you taking any medications, prescription or over-the-counter including birth control?
   Yes or No

6. If you answered "Yes" to #4 or 5, please list the medications, the reasons for taking them, the prescribed dosage, and how long you have been taking them on a consistent basis.
   _____
   _____
   _____
   _____

7. Have you consumed any alcohol, tranquilizers, sleeping pills, antidepressants, opiates, cocaine, amphetamines, PCP, or barbiturates within the previous 7 days days?
   Yes or No

8. Have you consumed any antibiotics, laxatives, diuretics, neuroleptics, or theophyline within the previous 7 days?
   Yes or No

9. Are you consuming any performance enhancing drugs?
   Yes or No

10. Are you consuming any vitamins or dietary supplements?
    Yes or No

11. If you answered "Yes" to #7 to 10, please list what you have been taking?
    _____
    _____
    _____
    _____

12. Have you been ill within the previous week or are you currently ill (cold, flu, etc.)?
    Yes or No

13. Have you made in changes in your diet in the last month?
    Yes or No

14. Do you have to maintain a specific type of diet for any reason?
    Yes or No

15. If so, why are you having to maintain the diet?
    _____
    _____
    _____

16. Have you been diagnosed with diabetes or high blood pressure?
    Yes or No

17. Do you have any history of kidney or liver dysfunction?
    Yes or No

18. Do you have any history of heat illness?
    Yes or No

19. Do you have any history of swelling after exercise?
    Yes or No

20. Do you have any history of bruising easily?
    Yes or No

21. Do you have a family history of muscle disease?
    Yes or No

22. Are you currently undergoing statin or thyroid replacement therapy?
    Yes or No

## APPENDIX F: VISUAL ANALOG SCALE

# Visual analog pain intensity scale

No pain at all

_____

Most intense pain imaginable

# APPENDIX G: IRB APPROVAL LETTER

The UNIVERSITY of OKLAHOMA

## Institutional Review Board for the Protection of Human Subjects Initial Submission – Board Approval

**Date:** October 23, 2015

**To:** Christopher D Black, PhD

**IRB#:** 5887
**Meeting Date:** 10/19/2015
**Approval Date:** 10/23/2015
**Expiration Date: 09/30/2016**

**Study Title:** Effect of Exercise Induced Muscle Damage on Critical Torque and Mitochondrial Function

**Reference Number:** 643253
**Study Status:** Active - Open
**Collection/Use of PHI:** Yes

At its regularly scheduled meeting the IRB reviewed the above-referenced research study. Study documents (e.g. protocol, consent, survey, etc.) associated with this submission are listed on page 2 of this letter. To review and/or access the submission forms (e.g. application) as well as the study documents approved for this submission, open this study from the *My Studies* option, click to open this study, look under Protocol Items to click on the current *Application*, *Informed Consent* and *Other Study Documents*.

**If this study required routing through the Office of Research Administration (ORA), you may *not begin your study yet*, as per OUHSC Institutional policy, until the contract through ORA is finalized and signed.**

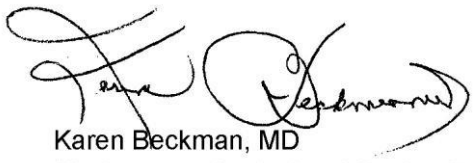
As principal investigator of this research study, it is your responsibility to:

- Conduct the research study in a manner consistent with the requirements of the IRB and federal regulations at 45 CFR 46 and/or 21 CFR 50 and 56.
- Request approval from the IRB prior to implementing any/all modifications.
- Promptly report to the IRB any harm experienced by a participant that is both unanticipated and related per IRB Policy.
- Maintain accurate and complete study records for evaluation by the HRPP quality improvement program and if applicable, inspection by regulatory agencies and/or the study sponsor.
- Promptly submit continuing review documents to the IRB upon notification approximately 60 days prior to the expiration date indicated above.

In addition, it is your responsibility to obtain informed consent and research privacy authorization using the currently approved, stamped forms and retain all original, signed forms, if applicable.

If you have questions about this notification or using iRIS, contact the IRB @ 405-271-2045 or irb@ouhsc.edu.

Sincerely,



Karen Beckman, MD
Chairperson, Institutional Review Board

Study documents associated with this submission:

| Study Document | | | |
|---|---|---|---|
| **Title** | **Version Number** | **Version Date** | **Outcome** |
| VAS Scale | Version 1.0 | 09/01/2015 | Approved |
| Rhabo Risk Assessment | Version 1.0 | 09/01/2015 | Approved |
| Par-Q | Version 1.0 | 09/01/2015 | Approved |
| HIPAA Form | Version 1.1 | 09/01/2015 | Approved |
| Email Recruitment Script | Version 1.1 | 09/01/2015 | Approved |
| Recruitment Flyer | Version 1.1 | 09/01/2015 | Approved |
| Protocol | Version 1.2 | 09/01/2015 | Approved |
| Medical History | Version 1.1 | 09/01/2015 | Approved |

| Study Consent Form | | | |
|---|---|---|---|
| **Title** | **Version Number** | **Version Date** | **Outcome** |
| EIMD and Critical Torque Consent | Version 1.7 | 10/21/2015 | Approved |

**Information for Industry Sponsors: the columns titled Version Number and Version Date are specific to the electronic submission system (iRIS) and should not to be confused with information included in the Document and/or Consent title(s).**

# APPENDIX H: IRB REVISION

The UNIVERSITY of OKLAHOMA

**Institutional Review Board for the Protection of Human Subjects**

**Modification/Notification – Expedited Approval**

**Date:** February 11, 2016

**IRB#:** 5887
**Approval Date:** 02/11/2016

**To:** Christopher D Black, PhD

**Study Title:** Effect of Exercise Induced Muscle Damage on Critical Torque and Mitochondrial Function

**Reference Number:** 648336

**Modification/Notification Summary:** Changing the eccentric exercise protocol from maximal voluntary contractions to electrically stimulated contractions in order to normalize the location of the muscle damage among participants and to the location where the EMG and NIRS measures will be made. Additionally, participant compensation has been added in the form of a $20 gift card.

On behalf of the Institutional Review Board (IRB), I have reviewed and granted expedited approval of the above-referenced modification/notification. To review and/or access the submission form (e.g. modification form) as well as the study documents approved for this submission, open this study from the *My Studies* option, look under *Protocol Items*, click to open/view the current approved *Application*,
*Informed Consent*, or *Other Study Documents*.

If this modification includes revisions to the consent or privacy authorization forms, you are reminded to obtain informed consent and research privacy authorization using the currently approved, stamped forms and retain all original, signed forms, if applicable.

If you have questions about this notification or using iRIS, contact the HRPP office at (405) 271-2045 or irb@ouhsc.edu. The HRPP Administrator assigned for this submission: Rebecca R Hicks.

Sincerely,

Eliot Schechter, MD
Vice Chairperson, Institutional Review Board

Study documents associated with this submission:

| Study Document | | | |
|---|---|---|---|
| **Title** | **Version Number** | **Version Date** | **Outcome** |
| Email Recruitment Script | Version 1.2 | 02/02/2016 | Approved |
| Recruitment Flyer | Version 1.2 | 02/02/2016 | Approved |
| Protocol | Version 1.5 | 02/02/2016 | Approved |

| Study Consent Form | | | |
|---|---|---|---|
| **Title** | **Version Number** | **Version Date** | **Outcome** |
| EIMD and Critical Torque Consent | Version 1.10 | 02/02/2016 | Approved |

**Information for Industry Sponsors: the columns titled Version Number and Version Date are specific to the electronic submission system (iRIS) and should not to be confused with information included in the Document and/or Consent title(s).**