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EXAMINATION OF PHYSIOLOGICAL AND PERCEPTUAL RESPONSES DURING SUSTAINED, ISOMETRIC, FATIGUING, HANDGRIP EXERCISE ANCHORED TO RATINGS OF PERCEIVED EXERTION

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EXAMINATION OF PHYSIOLOGICAL AND PERCEPTUAL RESPONSES DURING SUSTAINED, ISOMETRIC, FATIGUING, HANDGRIP EXERCISE ANCHORED TO RATINGS OF PERCEIVED EXERTION

THESIS

A thesis submitted in partial fulfillment of the
requirements for the degree of Master of Science in the
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at the University of Kentucky

By

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ABSTRACT OF THESIS

EXAMINATION OF PHYSIOLOGICAL AND PERCEPTUAL RESPONSES DURING SUSTAINED, ISOMETRIC, FATIGUING, HANDGRIP EXERCISE ANCHORED BY RATINGS OF PERCEIVED EXERTION

The purposes of this study were to: 1) Examine the patterns of force responses relative to critical force (CF) during submaximal, fatiguing, isometric handgrip exercise anchored to different rating of perceived exertion (RPE) levels (RPE=3, 5, and 7); 2) assess the loss of force during the task and the level of performance fatigability after each RPE hold; 3) examine the time course of changes and patterns of neuromuscular [electromyography (EMG) amplitude (AMP), mean power frequency (MPF), mechanomyography (MMG) AMP and MPF, and neuromuscular efficiency (NME) (i.e. force/EMG AMP)] and muscle oxygen saturation (% SmO_2) responses during each RPE hold; 4) examine which theory (i.e. corollary discharge, afferent feedback, sensory tolerance limit) best explains the regulation of exercise during each RPE hold. Twelve, healthy men between 18 and 35 years performed submaximal, continuous, isometric contractions to task failure at one of four randomly determined percentages of maximal voluntary isometric contraction (MVIC) (30, 40, 50, and 60%) on separate days. The amount of work performed (W_{lim}) was obtained by multiplying the force by the corresponding time to task failure (T_{lim}). The four W_{lim} values were plotted as a linear function of the T_{lim} values, and the CF was defined as the slope coefficient of W_{lim} versus T_{lim} relationship. Subjects performed constant RPE handgrip holds at one of the three randomly ordered RPE levels (RPE= 3, 5, and 7). EMG and MMG, AMP and MPF were calculated in standardized segments of 5% T_{lim} (0-100% T_{lim}) during each hold and normalized to the respective values at the pre-MVIC. SmO_2 response was recorded in standardized segments of 5% T_{lim} (5-100% T_{lim}). For the T_{lim} and performance fatigability, 2(Time: pre- vs post-hold) x 3(RPE: 3, 5, and 7) repeated measure ANOVAs and post-hoc t-tests with a Bonferroni corrected alpha level ($p<0.017$) were used. The time course of changes in force, EMG AMP, EMG MPF, MMG AMP, MMG MPF, and NME were examined using separate, 3(RPE:3, 5, and 7) x 21(time:0-100% T_{lim}) repeated measures ANOVAs, with follow up one-way repeated measures ANOVAs and post-hoc t-tests with Bonferroni for comparisons across time ($p<0.0025$) and between RPE levels ($p<0.017$). For SmO_2 responses, a 3(RPE: 3, 5, and 7) x 20(time: 5-100% MVIC) repeated measures ANOVA, with a follow up one-way ANOVA and post-hoc t-tests with Bonferroni for comparisons across time ($p<0.0026$) and between RPE levels ($p<0.017$) were used. The absolute (kg) and relative (% MVIC) CF were 9.0±2.3kg, and 19.4±3.8% MVIC, respectively. There were no differences in T_{lim} between RPE 3, 5, and 7 ($p=0.569$-0.744). There were decreases in force, relative to the initial value (0% T_{lim}), from 20% to 100% T_{lim} for RPE 3, from 45% to 100% T_{lim} for RPE 5, and from 15% to 100% T_{lim} for RPE 7.

Based on the force profiles for each RPE, the patterns of responses were examined according to three phases, phase 1 (initial force to 15% T_{lim}), phase 2, (20-85% T_{lim}), and phase 3 (90-100% T_{lim}). For the performance fatigability, there were no difference in pre-MVIC (p=0.494-0.894) among RPE 3, 5, and 7, but the post-MVIC value of RPE 3 was greater than RPE 5 (p=0.008), but not RPE 7 (p=0.024), and there was no difference in RPE 5 and 7 (p=0.924). For EMG AMP, there were decreases, relative to 0% T_{lim}, at 20% and 25%, and from 35% to 100% T_{lim} at RPE 3, at 30%, 55%, 60%, and 100% T_{lim} at RPE 5, and at 30% and from 40% to 100% T_{lim} at RPE 7. For EMG MPF, there were decreases, relative to 0% T_{lim}, at 15%, 25%, 30%, and from 45% to 95% T_{lim}, collapsed across RPE. For MMG AMP, there were no significant changes, relative to 0% T_{lim}, at any time points (p=0.005-0.036), collapsed across RPE, and RPE 7 was greater than RPE 3 (p=0.013) and RPE 5 (p=0.001), collapsed across time. For MMG MPF, there were no significant changes, relative to 0% T_{lim}, at any time points (p=0.027-0.920). For NME, there were no differences, relative to 0% T_{lim}, at any time points (p=0.004-0.780) for RPE 3 but decreases from 50% to 65% and from 80% to 100% for RPE 5, and a decrease at the last time point (100% T_{lim}) for RPE 7. For SmO_2, there was no significant differences, relative to the initial value (5% T_{lim}), at any time point for RPE 3,5, and 7 (p=0.017-0.774). Overall, during phase 1 (0-15% T_{lim}), the integrated process of anticipatory (i.e., feedforward) regulation and group III afferent neurons (i.e., inhibitory feedback) was likely primarily responsible for the decrease in force. However, afferent feedback primarily from group IV neurons may also have led to force reductions in the later stages of phase 1 and carried over into phase 2 (20-85% T_{lim}). During phase 2 and 3 (90-100% T_{lim}), a combination of afferent feedback and the feedforward pathway via corollary discharges likely contributed to the continuous, voluntary reduction in force to maintain the predetermined RPEs. In phase 3, the sensory tolerance limit (i.e., sum of afferent feedback and feedforward signals) may explain the force reduction to task failure at a similar time across each RPE. This study suggested that force alterations, the accompanying metabolic and/or neuromuscular responses, and performance fatigability were affected by different mechanisms depending on phases (1 vs. 2 and 3) and/or RPE (3 vs. 5 vs. 7), which may provide insights when prescribing continuous or repetitive handgrip tasks in occupational or industrial settings.

KEYWORDS: Handgrip, Muscle Fatigue, Rating of Perceived Exertion, Critical Force

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CHAPTER 1. INTRODUCTION

Muscle fatigue has been defined as any exercise-induced reduction in the ability of muscle to generate force or power output (Vollestad 1997, Al-Mulla et al. 2011, Kent-Braun et al. 2002). The detection and prediction of muscle fatigue provides important information to a variety of fields (e.g., sport injury rehabilitation and performance, ergonomics, clinical settings, occupational health, industrial work settings) (Al-Mulla et al. 2011). For example, localized muscle fatigue in the workplace may cause work-related musculoskeletal disorders and injuries if a given task requires elevated static muscle activity (Al-Mulla et al. 2011). It has been suggested that an automated system that could predict and detect when fatigue occurs may be useful in work-related scenarios where muscle fatigue can lead to injury (Al-Mulla et al. 2011). This automated system would guide users in their training and act as a warning device before fatigue sets in to avoid unnecessary strain on the working muscle so as to prevent work-related musculoskeletal disorders and injury (Al-Mulla et al. 2011). However, the specific force level that constitutes “unnecessary strain” and the factors mediating fatigue were not well defined on an individual basis.

Previous researchers have described the etiology of muscle fatigue during various types of exercise to elucidate the processes and mechanisms involved (Monod and Scherrer 1965, Vollestad 1997, Al-Mulla et al. 2011). It has been suggested that the magnitude and mechanisms of muscle fatigue vary widely depending, to a large extent, on the individual, the specific muscle or muscle group and the exercise task (Kent-Braun et al. 2002). For instance, differences in fatigability across sex may occur as a result of differences in neural drive, fiber-type composition, contractile function, muscle membrane excitability, metabolic capacity, or muscle mass and blood flow (Kent-Braun et al. 2002). For example, during sustained submaximal handgrip exercise in men and women at different intensities (i.e., 30, 50, and 75% of maximal voluntary contraction), women exhibited more fatigue resistance (i.e., longer time to exhaustion) than men at each of the three intensities (West et al. 1995). The authors indicated that the sex difference in fatigability may be attributed to variations in metabolic byproduct accumulation, fiber type distribution, and varying blood flow between contractions of different absolute forces (West et al. 1995). Thus, due to the variability in fatigability driven by these characteristics, it is important to examine fatiguing exercise responses on an individual basis. Although studies associated with individual variabilities in fatigability have been conducted (Al-Mulla et al. 2011, Kent-Braun et al. 2002), investigations to identify the onset of muscle fatigue and the parameter that estimates non-fatiguing from fatiguing work during a sustained muscle contraction have not sufficiently addressed these different individual characteristics.

Monod and Scherrer introduced a fatigue threshold for local muscular work (<1/3 total muscular mass), termed critical force (CF), to estimate the asymptote of the force-duration curve (Monod and Scherrer 1965). The CF was defined as the …" highest force that can be maintained for a very long time without fatigue" (Monod and Scherrer 1965, p. #) and was estimated from three or four continuous, static (i.e., isometric) muscle contractions to failure at different force levels (Monod and Scherrer 1965, Hendrix et al., 2009 a&b, Keller et al. 2021). A linear relationship between the total work performed (W_{lim}) versus time to exhaustion (T_{lim}) was obtained ($W_{lim}=a+b\cdot T_{lim}$) from this series of muscle contractions to failure (Monod and Scherrer 1965, Hendrix et al., 2009 a&b, Keller et al. 2021). The CF was determined as the slope of the W_{lim} versus T_{lim} relationship, above which fatigue will occur during a sustained muscle contraction at a predictable T_{lim}, but below which fatigue cannot occur (Monod and Scherrer 1965, Hendrix et al., 2009 a&b, Burnley et al. 2012, Keller et al. 2021). The CF has been reported to occur at approximately 15-22% of maximum voluntary isometric contraction (MVIC) (Monod and Scherrer 1965, Hendrix et al., 2009 a&b) and is associated with circulatory conditions in the muscle including blood flow and oxygen availability for energy metabolism (Monod and Scherrer 1965, Moritani et al. 1981, Hendrix et al., 2009 a&b). That is, during exercise at or below the CF, it has been suggested that exercise is not limited by an alteration in muscle blood flow, but exercise above the CF results in fatigue due to an increase in intramuscular pressure and occlusion of the vascular beds (Monod and Scherrer 1965, Hendrix et al., 2009 a&b, Burnley et al. 2012). Thus, theoretically, the CF provides an estimate of the highest isometric force level that can be maintained without fatigue (Monod and Scherrer 1965, Hendrix et al., 2009 a&b, Burnley et al. 2012).

Although CF has been suggested as a threshold that demarcates fatiguing and non-fatiguing forces during a continuous isometric exercise (Monod and Scherrer 1965, Hendrix et al., 2009a, Burnley et al. 2012), there are several limitations in the application of CF to examine fatigue responses (Monod and Scherrer 1965, Hendrix et al., 2009 a&b, Keller et al. 2021). It has been reported that CF values from five different mathematical models overestimated the force levels that could be maintained for an extended period without fatigue (Hendrix et al., 2009a). The determination of CF is further limited by the requirement for multiple tests to failure (i.e., at least three or four work bouts) on separate days, which limits the applicability of the test (Monod and Scherrer 1965, Hendrix et al., 2009 a&b, Keller et al. 2021). In addition to these methodological limitations, the CF model is a performance-based test that provides a mechanical output (force), but does not consider additional factors, such as perceptual responses regulating (Monod and Scherrer 1965, Hendrix et al., 2009 a&b, Burnley et al. 2012, Keller et al. 2021) force during a prolonged, submaximal, fatiguing, isometric exercise. Importantly, authors have indicated a distinction between perceptions of fatigue and performance fatigability, where perceptions of fatigue are defined as subjective sensations of weariness, increasing sense of effort, and mismatch between effort expended and actual performance or exhaustion (Kluger et al. 2013, Pageaux 2016). In contrast, performance fatigability refers to the objective magnitude or rate of change in a performance criterion (i.e., force output) resulting from a given fatiguing task (Kluger et al. 2013). It has been suggested that humans are able to differentiate between perception of effort and perception of force due to their different mechanisms of perceptual pathways (Pageaux 2016). Specifically, it was argued that perception of effort is associated with the conscious perception of the central motor command sent to the working muscles, whereas perception of force is related to the perceptions coming from the efferent copy (i.e., corollary discharge) of the central motor command and afferent feedback from the contracting muscles (Pageaux 2016). The author (Pageaux 2016) also indicated that the perception of effort is sensitive to psychological and physiological manipulations of perceived exertion and recommended that confounding factors be avoided in the definition of effort (e.g., inclusion of discomfort). Thus, future studies that seek to examine the underlying mechanisms of perceived exertion and the role of perception of effort in the regulation of performance should refer to this definition (Pageaux 2016). Based on the previous studies (Kluger et al. 2013, Pageaux 2016), an examination of fatiguing responses during exercise anchored by a perceived exertion level, rather than a constant force, may reflect more complex physio-psychological mechanisms that modulate exercise performance.

The rating of perceived exertion (RPE) scale was introduced by Borg (1982) and has been used for the estimation of fatigue while performing submaximal muscle contractions (Morrin et al. 2018, Keller et al. 2019). It was reported that there is a strong correlation between subjective (i.e., RPE) and objective (i.e., electromyographic spectral changes) measurements of muscle fatigue (Al-Mulla et al., 2011). A study introduced self-reported calibration using RPE scale, which was valid to measure a force of handgrip muscle contraction (Spielholz 2006). Specifically, a “grip-to-scale” calibration procedure required each subject to exert handgrip forces corresponding to different Borg scale levels (RPE=2 or 5) (Spielholz 2006). For example, when each subject was asked to “grip to a 2, or light” and “grip to a 5” on a category scale ranging from 0 to 10 (CR-10 scale), the corresponding handgrip force values were recorded. The results showed the significant reduced mean estimation error for handgrip task (Spielholz 2006). Moreover, a study reported that an isometric handgrip exercise anchored at a RPE=6 on the CR-10 scale may be an effective tool of self-regulating isometric exercise prescription aimed in decreasing blood pressure both in pre-hypertensive and hypertensive patients (Morrin et al. 2018). Thus, RPE scale has been indicated as a method that may be used to measure fatigue responses more objectively by identifying the diverse stages of mechanical fatigue (Borg 1982, Spielholz 2006, Morrin et al. 2018, Al-Mulla et al., 2011). However, it is still difficult to identify time courses of altered physiological mechanisms during a continuous, fatiguing task due to its complexities and variabilities.

Three primary theories (i.e., Corollary Discharge, Afferent Feedback, Sensory Tolerance Limit) have been suggested as the physio-psychological mechanism of regulation of exercise intensity (e.g., force regulation) during a prolonged, submaximal, fatiguing muscle contraction anchored by RPE (Keller et al. 2019, Tucker et al. 2006, Kaufman et al. 2002, Marcora 2009, Hureau et al. 2018). These theories have been further explored during submaximal, exercise anchored by RPE, which was presented as an alternative to the more traditional method of anchoring by force (Keller et al. 2019). For exercise anchored to RPE, it was necessary to reduce force to maintain the constant RPE value throughout the exercise (Keller et al. 2019). Specifically, during submaximal, isometric muscle action anchored by a RPE, the regulated force production throughout the exercise was explained by the initially derived feedforward mechanism and then continuously altered afferent feedback mechanism (Keller et al. 2019). During the initial stage of exercise, there is a precipitous decrease in force production which may result from an anticipatory regulation of exercise intensity via corollary discharges, which are sent to the motor control center and somatosensory areas of the brain, where the identical messages create corresponding RPE to the efferent motor commands (Keller et al. 2019, Tucker et al. 2006). It has been argued that the sense of effort during exercise is centrally generated within the cortex, which forwards inhibitory neural signals via corollary discharge pathway from motor to sensory areas (Marcora 2009). As exercise continues, however, afferent feedback from group III and IV fibers afferents in the active muscles contributed to a period of slower reductions in force production (Keller et al. 2019, Tucker et al. 2006, Kaufman et al. 2002). It was reported that group III and IV muscle afferent feedback directly impact on the perception of effort during exercise (Keller et al. 2019).

The “sensory tolerance limit theory” integrated these two mechanisms (i.e., corollary discharges, afferent feedback), explaining that the sum of afferent feedback (e.g., engaged muscles, cardiovascular and/or respiratory muscles, organs, and muscles indirectly involved in the task) and corollary discharges associated with central command are integrated within the brain, by which the magnitude of central motor drive is regulated to ensure that voluntary muscle activities remain tolerable and steady (Hureau et al. 2018). Thus, the mechanisms underlying fatiguing, submaximal exercise at a constant RPE are likely best explained by an integration of these theories.

It has been suggested that the degree of performance fatigability (i.e., a reduction in force production by engaged muscle) may be related to the amount of muscle mass involved, exercise intensity, and associated disruption to homeostasis in multiple physiological systems, which inform the amount of afferent feedback and/or feedforward mechanisms (Thomas et al. 2018). For example, for the same mode of exercise, it has been suggested that greater magnitudes of performance fatigability occur with higher exercise intensities because a greater proportion of the muscle mass will be activated and exhausted as the force requirements of the task increase (Thomas et al. 2018). The magnitude of performance fatigability was also reported to be higher in a condition where a smaller amount of muscle mass was recruited (e.g., single limb) than that of larger active muscle mass (e.g., double limb, or whole-body locomotor) (Thomas et al. 2018). Specifically, as the active muscle mass increases (e.g., running, cycling), the sensory input from a larger muscle mass and greater disruption to homeostasis in other physiological system (e.g., cardiovascular, respiratory) increases, and then these adjustments collectively contribute to modulating the symptom of fatigue, thus the magnitude of performance fatigability is lower compared to local muscle actions (i.e., single limb) (Thomas et al. 2018). Currently, there is a discrepancy in the literature regarding the magnitude of performance fatigability across exercise mode (e.g., unilateral vs bilateral vs whole-body exercises, upper body vs lower body) and intensity (Keller et al. 2020). For example, it was reported that the lower magnitude of performance fatigability following bilateral tasks compared to unilateral may be due to the bilateral coupling and interhemispheric inhibition, whereas whole-body exercises (e.g., running and cycling) and unilateral muscle actions likely are not affected by mechanisms inherent to bilateral tasks (Keller et al. 2020). Moreover, Keller et al. (2020), investigated performance fatigability following sustained, bilateral, isometric, leg extensions anchored at different RPEs (RPE=1,5, and 8) and anchored by the force (Force at RPE=1,5, and 8) corresponding to the RPEs. It was demonstrated that performance fatigability was not different across these anchoring schemes or intensities, and, thus, may be influenced by the sensory tolerance limit, not by muscle mass, exercise intensity, time to exhaustion, or an anchor scheme (i.e., RPE or force) (Keller et al. 2020). A recent study supported the findings of Keller et al. 2021, suggesting that performance fatigability was modulated by sensory tolerance limit and was unvarying among dominant, non-dominant, and the bilateral condition following sustained, bilateral, leg extensions at constant forces (Force=1,5, and 8) above and below CF (Keller et al. 2021). However, it is still unclear what factors impact the degree of performance fatigability associated with upper-body, unilateral tasks (e.g., handgrip exercise) following sustained, isometric exercise anchored at different RPE levels. Therefore, additional research is needed to further examine underlying mechanisms determining the magnitude of performance fatigability following fatiguing, upper-body, unilateral, isometric exercise.

Non-invasive techniques (e.g., electromyography, mechanomyography, near infrared spectroscopy) have been used to examine the processes and mechanisms of muscle fatigue during sustained isometric exercise (Al-Mulla et al., 2011). The time and frequency domains of the electromyographic (EMG) and mechanomyographic (MMG) signals have been used to examine the motor unit activation strategies during fatiguing tasks (Beck et al. 2004, Coburn et al. 2005, Smith et al. 2016). It has been demonstrated that the amplitude of the EMG signal (EMG AMP) is related to muscle excitation (i.e., motor unit recruitment, firing rate, synchronization) and the mean power frequency (EMG MPF) is associated with action potential conduction velocity of activated motor units (Beck et al. 2004, Coburn et al. 2005, Smith et al. 2016). It has been also reported that the amplitude of MMG (MMG AMP) reflects motor unit recruitment and the mean power frequency of MMG (MMG MPF) is associated with global firing rates of the unfused, active motor units (Beck et al. 2004, Coburn et al. 2005, Smith et al. 2016). During a submaximal, continuous isometric muscle contraction at constant force, previous investigators report consistent patterns of neuromuscular responses such that the muscle excitation (EMG AMP) and motor unit recruitment (MMG AMP) continuously increased to produce the required force and are associate with the fatigue-induced decreases in motor unit action potential conduction velocity (EMG MPF) and global motor unit firing rate (MMG MPF) (Coburn et al. 2005, Smith et al. 2016). However, the time courses of changes and patterns of force and neuromuscular responses are accompanied by diverse physiological mechanisms during constant RPE exercise (Keller et al. 2018, Keller et al. 2019). For example, anchoring a fatiguing, sustained isometric leg extension muscle contraction to RPE=5 in women lead to an increase in MMG AMP, but there were no changes in other neuromuscular parameters (i.e., EMG AMP, EMG MPF, MMG MPF) (Keller et al. 2018). This study indicated that EMG AMP, EMG MPF, and MMG MPF tracked the RPE, but were dissociated from the reduction in force (Keller et al. 2018, Keller et al. 2019). Another study reported that during a sustained, isometric leg extension anchored to RPE=5 in men and women, EMG MPF, MMG AMP, MMG MPF were not altered, whereas there was a mean decrease in EMG AMP and force, which likely reflected a reduction in neural drive due to an accumulation of metabolic byproducts (Keller et al. 2019). Therefore, further investigations of time courses of patterns of neuromuscular responses to other muscle actions (e.g., isometric handgrip exercise) at different level of RPE would provide insight into diverse neuromuscular mechanisms occurring during an exercise anchored by RPE in men and women.

Near infrared spectroscopy (NIRS) has been introduced as another non-invasive method to assess the skeletal muscle fatigue (Barstow 2019, Mantooth et al. 2018, Keller and Kennedy 2021, Al-Mulla et al., 2011). It has been suggested that the NIRS examines the muscle tissue oxygen saturation (SmO_2), which is calculated via spatially resolved spectroscopy using the equation, $\mathrm{SmO2} = \frac{\text{oxygenated hemoglobin}}{\text{oxyenated hemogloblin } + \text{deoxygenated hemoglobin}}$*100, and the primary sources of the NIRS signals are hemoglobin (Hb) and myoglobin (Mb) heme (Barstow 2019, Mantooth et al. 2018, Keller and Kennedy 2021). Theoretically, a reduction in SmO_2 indicates an imbalance between tissue O_2 consumption and arterial flow, such that the supply cannot match the demand (Keller and Kennedy 2021). It was shown that during sustained submaximal handgrip exercises at different force levels (i.e., 20, 40, 60 and 80% of maximum handgrip strength) in men and women, men showed greater desaturation than women as fatigue progressed at higher relative task intensities (Mantooth et al. 2018). A recent study investigated effects of sex and fatigue on the time courses of responses of SmO_2 during a fatiguing handgrip task, suggesting that sex differences in fiber type and mitochondria may be the primary mechanisms to explain the differences in muscle oxygenation (Keller and Kennedy 2021). Despite these findings, the SmO_2 responses have only been examined for constant force exercise during a single, submaximal, isometric hold (Barstow 2019, Mantooth et al. 2018, Keller and Kennedy 2021). Muscle oxygenation influences fatigue development that can in turn affect worker health and productivity (Mantooth et al. 2018, Al-Mulla et al., 2011), and perception of effort is exacerbated in the presence of physical fatigue (Pageaux 2016). However, no studies investigated the time courses of response of SmO_2 during a fatiguing task anchored by RPE. Therefore, further studies are necessary to examine the time courses of response of SmO_2 and the effect of sex difference on its response during a fatiguing exercise at a constant RPE to provide better understanding or physiological mechanisms underlying the perception of effort.

In summary, the processes and mechanisms of muscle fatigue vary depending on a number of factors including muscle type, sex, exercise mode, and intensity (Kent-Braun et al., 2002). The time courses of changes and patterns of physiological responses during fatiguing task can be examined by various non-invasive methods (i.e., EMG, MMG, NIRS) to provide insights into neuromuscular and metabolic mechanisms of fatigue (Al-Mulla et al., 2011). Many researchers have investigated the physiological responses during various isometric muscle contractions related to an associated level of CF and an anchored RPE (Monod and Scherrer 1965, Hendrix et al. 2009 a&b, Burnley et al. 2012, Keller et al. 2021, Morrin et al. 2018, Keller et al. 2019, Smith et al. 2016, Mantooth et al. 2018, Keller and

Kennedy 2021). However, previous studies have not compared CF and the changes in force output during isometric, sustained handgrip exercise anchored to an RPE. Moreover, it is necessary to examine simultaneous, combined assessments of the time course of changes in neuromuscular (i.e., EMG and MMG) and muscle oxygen saturation responses to provide better understandings of time course of local muscle fatigue during a sustained isometric handgrip exercise performed at a constant RPE. Lastly, it is currently unclear the magnitude of force production loss during isometric handgrip exercise anchored to differing levels of RPE or for maximum handgrip strength performed immediately before and after (i.e., performance fatigability) task failure at a constant RPE.

Therefore, the purposes of this study were to: 1) Examine the patterns of response in force relative to CF during constant RPE holds to failure at an RPE 3, 5, and 7; 2) assess the loss of force during the task and the level of performance fatigability of the exercised hand after each fatiguing handgrip task; 3) examine the time course of changes and patterns of neuromuscular and muscle oxygen saturation responses (EMG and MMG AMP and MPF, NME, %SmO_2) during each RPE hold (RPE =3, 5, and 7); and 4) examine which theory (i.e., corollary discharge, afferent feedback, sensory tolerance limit) best explains the regulation of exercise anchored to RPE. Based on the results of literature, it was hypothesized that 1) the CF (15-22% of MVIC) will be higher than the end force output anchored at each constant, submaximal RPE level (RPE= 3,5,7); 2) similar degrees of performance fatigability will occur at different RPE levels of exercise tasks (RPE 3=5=7); 3) various physiological responses will occur including an decrease in EMG AMP without changes in EMG MPF, MMG AMP, MMG MPF; 4) a neurophysiological mechanism (i.e., sensory tolerance limit) will allow subjects to maintain a constant RPE during a hold to failure handgrip task.

CHAPTER 2. REVIEW OF LETERATURE

2.1 Development of Critical Force Model

Monod & Scherrer, 1965

The purpose of this study was to investigate the relationship between the amount of static work a muscle can do and the amount of time a muscle can maintain a certain amount of force without fatigue. Monad and Scherrer suggested that "… static work has a physiological reality" (p. 333) and "The simplest appreciation of static work capacity is obtained for a given force by the measure of the maximum sustaining time of this force" (p. 333). Thus, the time to exhaustion (T_{lim}) was determined by having subjects sustain an isometric contraction for as long as possible, and the isometric analog of mechanical work called the limit work (W_{lim}) was obtained as the product of a given force of the isometric muscle action and the sustaining time ($W_{lim}=F \cdot T_{lim}$). A linear relationship between W_{lim} versus T_{lim} was obtained ($W_{lim}=a+b \cdot T_{lim}$) to estimate the critical force (CF) and anaerobic work capacity (AWC). Critical force was determined as the slope of the W_{lim} versus T_{lim} relationship and the y-intercept was defined as AWC. The finding was that this CF is the highest force that can be maintained for a very long time without fatigue and CF is the isometric force threshold above which fatigue will occur during a sustained muscle action at a predictable T_{lim}, but below which fatigue cannot occur. The AWC represents the total work done using only stored energy sources within a muscle (e.g., glycogen, phosphocreatine, adenosine triphosphate, and oxygen bound to myoglobin). The authors suggested that CF is linked to circulatory conditions in the muscle including blood flow and oxygen availability for energy metabolism.

Moritani et al., 1981

The purpose of this study was to extend the application of the mathematical model (i.e., critical power (CP) model) from Monod & Scherrer (1965) to a total body exercise, cycle ergometry. Eight men and eight women performed cycling trials at different constant power outputs (P) (i.e., 275, 300, 350, 400 W for men; 175, 200, 250, 300 W for women), and the time to exhaustion (T_{lim}) was determined as an inability to maintain a set cadence (i.e., 60 rpm). During the trials, gas exchange parameters were measured to determine $\dot{V}O_2$max and the anaerobic threshold. The results showed a highly linear relationship between total amount of work ($W_{lim} = P \cdot T_{lim}$) and T_{lim} ($r^2 = 0.982$-0.998). The authors also suggested an equation ($T_{lim}= a/(P-b)$) indicating that when the given P exceeds the CP or (b) of a subject, the muscle utilizes its energy reserves (i.e., anaerobic work capacity) or (a), and fatigue will occur when these energy reserves are depleted. On the other hand, when the imposed P approaches to CP or b, and (P-b) approaches zero, theoretically the work may be indefinitely maintained by using circulatory conditions in the muscle. It is concluded that the mathematical CP model from Monod & Scherrer 1965 was applicable to a total body fatiguing exercise (i.e., cycle ergometer).

Hendrix et al., 2009

The purpose of this study was to investigate the differences in estimates of critical torque (CT) and anaerobic work capacity (AWC) among five linear and nonlinear mathematical models, as well as compare the estimated time to exhaustion (ETTE) values related to the CT values from these five different models. Nine subjects performed a maximum voluntary isometric contraction (MVIC), and four (separated by a minimum of 24 hours) fatiguing leg extension contractions at a randomly ordered percentage of MVIC (30%, 45%, 60%, or 75%) to determine the time to exhaustion (T_{lim}) and CT. The CT and AWC were estimated from the following five different models:

1) The linear total isometric work (Lin-TIW) calculated the total amount of work (W_{lim}) by multiplying the torque of the muscle action by the T_{lim} (W_{lim} = torque $\cdot$ T_{lim}). The W_{lim} were then plotted as a function of the T_{lim}:

   W_{lim} = AWC + CT (T_{lim}).

2) The linear torque (Lin-1/ T_{lim}) model calculated the torque using two equations for W_{lim}, which are W_{lim} = torque $\cdot$ T_{lim} and W_{lim} = AWC + CT (T_{lim}):

   torque = AWC (1/ T_{lim}) + CT.

3) The nonlinear 2-parameter (Non-2) model is based on the hyperbolic relationship between torque and T_{lim} and is derived from the Lin-1/ T_{lim} model by solving for T_{lim}:

   T_{lim} = AWC / (torque – CT).

4) The Non-3 model is nonlinear including the addition of the maximal instantaneous torque ($Torque_{max}$) parameter, which intended to overcome the assumption of the Non-2 model indicating that the torque is infinite as time approaches zero:

   T_{lim} = (AWC/ (torque- CT)) – (AWC/ $Torque_{max}$ - CT)).

5) The EXP model include $Torque_{max}$ parameter and undefined time constant (τ), but not include AWC:

$$\text{torque} = CT + (\text{Torque}_{max} - CT)\ \exp(-T_{lim}/\tau).$$

The results showed that the EXP model indicated greater mean CT and lower ETTE values than the other four models, but there were no significant differences between the four models for AWC. It was also reported that the participants could maintain the CT levels from all five models for less than 17 minutes. It was concluded that the CT values from these five models overestimated the torque levels that the leg extensor muscle can maintain for an extended period of time without fatigue due to the use of shorter time duration (i.e., less than 5 min) to estimate CT. This study demonstrated that both linear and nonlinear mathematical models were appliable to a fatiguing isometric muscle contraction of leg extensors (r^2 range = 0.707-1.00).

Hendrix et al., 2009

The purpose of this study was to determine if the mathematical model used for establishing the electromyographic fatigue threshold (EMG_{FT}) during cycle ergometry was applicable to isometric muscle actions of forearm flexors, and to compare the mean torque level from the critical force (CF) test to that of the EMG_{FT} test. Ten subjected completed maximum voluntary isometric contraction (MVIC) during a second visit and they performed a continuous, fatiguing muscle contraction at one of the randomly ordered percentages of MVIC (30, 45, 60, or 75%) to determine CF and EMG_{FT} during visit 2 to 5. The slope coefficient of the linear relationship between total isometric work (W_{lim} in N m s) and time to exhaustion (T_{lim}) was defined as the CF. The rate of increase in EMG amplitude was plotted as a function of time for three or four percentages of MVIC workbouts. EMG_{FT} was then defined as the y-intercept of the isometric torque versus EMG fatigue curve slope coefficient (EMG amplitude versus time) relationship. Results showed that there was a significant ($p<0.05$) mean difference between CF (6.6 ± 3.2 N m) and EMG_{FT} (10.9 ± 4.7 N m) indicating that for each subject, CF was less than EMG_{FT}. It was also reported that the values for CF and EMG_{FT} represented 17.6 ± 5.7% and 29.1 ± 5.3% of MVIC, respectively. It is concluded that the CF and EMG_{FT} represent different fatigue thresholds during isometric muscle actions of the forearm flexors, which means that CF can be maintained for a longer period of time than EMG_{FT}. Moreover, it was suggested that CF is not limited by a force-related reduction of muscle blood flow due to an increase in intramuscular pressure and occlusion of the vascular beds.

Burnley et al., 2012

The purpose of this study is to establish whether critical torque (CT) represents a threshold dictating the nature of neuromuscular fatigue development during intermittent isometric quadriceps contractions. Nine healthy men participated in this study consisting of eight visits. The CT was determined from the first 5 visits and defined as the slope of relationship between torque and total contraction time. The target forces were defined as severe 1 (S1) to severe 5 (S5) obtained from ~35 to 55% of the maximal voluntary contraction (MVC) trials. During visits 7-8, the subjects performed intermittent, isometric fatiguing exercises (3-s contraction, 2-s rest) to failure 10 and 20% below the CT (denoted CT -10% and CT-20%). During the session, dynamometer torque and electromyogram of right vastus lateralis were recorded. Peripheral fatigue was determined from the fall in potentiated doublet torque, and central fatigue was determined from voluntary activation.

As a result, above CT, total contraction time was ~3-18 min and there was no MVC difference between the target torque S1 (88.7 ± 4.3 N·m) vs MVC (89.3 ± 8.8 N·m). The electromyographic (EMG) activity gradually increased throughout the trials, and there was no difference of EMG activity at the end of task and at the final MVC. On the other hand, the total contraction time below CT was approximately 60 min on most occasions. During fatiguing exercise below CT, the EMG at the beginning of the task and at the end of the task were not different, and the EMG at the final MVC was significantly greater than at the end of task, indicating that there was a substantial reserve in MVC torque at the end of the task. The peripheral (i.e., reductions in the doublet torque) and central (i.e., voluntary activation) fatigue above CT developed greater than below CT. It was concluded that the CT may represent a neuromuscular fatigue threshold.

Keller et al., 2021

The purpose of this study was to investigate the magnitude of performance fatigability and intensity-specific neuromuscular patterns of responses during fatiguing, bilateral, isometric leg extensions above and below critical force (CF). On separate days, twelve subjects performed one of three randomly ordered fatiguing isometric leg extensions at a force value that corresponded to RPE=1, RPE=5, or RPE 8. Electromyographic (EMG) amplitude (AMP) and mean power frequency (MPF) and mechanomyographic (MMG) AMP and MPF and force values are normalized to corresponding maximum voluntary isometric contractions (MVIC) and were examined in 5% segments of time to exhaustion during each fatiguing leg extension.

Subjects completed pre-MVIC and post-MVIC before and after each sustained leg extension to assess the performance fatigability, which was defined as the percent reduction of force. The results showed that 1) the mean performance fatigability was unvarying above (RPE=5, RPE=8) and below CF (RPE=1); 2) neuromuscular patterns of responses (EMG AMP, MMG AMP, MMG MPF) were similar above and below CF, but there was reduction in EMG MPF only above CF; and 3) individuals had significant variations for the neuromuscular patterns of responses above and below CF. Based on the results, it was concluded that 1) the sensory tolerance limit may modulate the magnitude of performance fatigability; 2) there was likely a greater degree of peripheral fatigue above CF; 3) the neuromuscular patterns of responses should be investigated on a subject-by-subject basis.

Summary

A mathematical model for determining the critical threshold has been presented and applied to various muscular contractions (i.e., dynamic contraction, continuous static contraction, intermittent static contraction) (Monod and Scherrer 1965, Moritani et al. 1981, Hendrix et al. 2009 a&b, Burnley et al. 2012, Keller et al. 2021). This model is based on a linear relationship between total amount of work performed and time to exhaustion ($W_{lim} = a + b\ T_{lim}$) (Monod and Scherrer 1965, Moritani et al. 1981, Hendrix et al. 2009 a&b). In this equation, it has been demonstrated that the slope coefficient (b) represents the critical threshold that can be applied to various intensity dimensions (e.g., force, torque, power output, or load) to define the intensity at which a muscle or muscle group can work for an extended period of time without fatigue, and is linked to circulatory conditions of the working muscle including blood flow and oxygen availability (Monod and Scherrer

1965, Moritani et al. 1981, Hendrix et al. 2009 a&b). The intercept (a) represents an anaerobic work capacity (AWC) which is related to only stored energy reserves within the muscle (e.g., glycogen, phosphocreatine, ATP, and oxygen bound to myoglobin) (Monod and Scherrer 1965, Moritani et al. 1981, Hendrix et al. 2009 a&b). A meaningful finding has been suggested that a prolonged static work of a local muscle or muscle group has a physiological reality, thus it can be obtained for a given force by measuring time to exhaustion (T_{lim}) for this force (Monod and Scherrer 1965, Hendrix et al. 2009 a&b). Therefore, for fatiguing isometric exercise, work limit (W_{lim}) can be calculated by a product of a given force and T_{lim}, and critical force (CF) is defined as the parameter (b) in the equation ($W_{lim} = a + b\ T_{lim}$). The CF is, theoretically, the isometric force threshold that demarcates fatigue from non-fatigue isometric force levels (Monod and Scherrer 1965, Moritani et al. 1981, Hendrix et al. 2009 a&b, Burnley et al. 2012, Keller et al. 2021). Previous studies have examined linear and nonlinear models in an attempt to determine the most valid estimates of the CF and mechanisms occurring at the CF during isometric muscle actions (Hendrix et al. 2009 a&b, Keller et al. 2021). It has been reported that continuous, fatiguing isometric muscle actions for three or four work bouts at randomly ordered percentages of maximum voluntary isometric contraction (MVIC) that can be sustained for greater than 5 min are necessary to obtain a valid CF value from the W_{lim} versus T_{lim} relationship (Monod and Scherrer 1965, Hendrix et al. 2009 a&b). Also, the CF for isometric muscle actions was approximately 15 – 20% of MVIC, above which fatigue will occur with the onset of a decrease in muscle blood flow due to an increase in intramuscular pressure and occlusion of the vascular beds (Monod and Scherrer 1965, Hendrix et al. 2009 a&b). The CF has been applied from a variety of perspectives to researchers. For example, the CF can be compared with other exercise intensities (e.g., electromyographic fatigue threshold, exercise anchored at a rating of perceived exertion) (Hendrix et al. 2009b, Keller et al. 2021). Moreover, the CF can be used to examine physiological responses (i.e., performance fatigability, electromyographic, and mechanomyographic activities) above and below a theoretical intensity that can be maintained indefinitely (Burnley et al. 2012, Keller et al. 2021).

2.2 Development and applications of perception of effort scales

Borg 1982

Most scientists in health science fields have agreed that it is important to understand how subjective feelings are related with objective findings, thus it is necessary to develop methods to quantify these subjective symptoms. A new ratio-scaling method to determine the perceived exertion during an exercise was developed by Borg. At first, this new category scale, which ranges from 6 to 20, was constructed to measure the perceived exertion from endurance exercise. Because oxygen consumption and heart rate increase linearly with workload, the range from 6 to 20 could be used to denote heart rates ranging from 60 to 200 beats/min. Later, a new category scale with ratio properties, that is, a simple category scale ranging from 0 to 10 (i.e., CR10 scale) was developed. The primary idea was that numbers should be anchored by verbal expressions that are simple and understandable by most people, even for the lay population. The CR10 scale may be efficiently used for determining other subjective symptoms, such as breathing difficulties, aches, and pain.

Spielholz, 2005

The purpose of this study was to assess the efficacy of using self-reported calibration (i.e., subjective rating) to obtain higher levels of accuracy using the Borg CR10 scale to measure handgrip force exertion. Ten male and 10 female state government workers performed handgrip tasks using a handgrip dynamometer. The "grip-to-scale" calibration was performed by subjects to exert hand forces corresponding to different Borg scale levels (i.e., grip to a "2" and "5" on the CR10). The "2" and a "5" on the scale were assumed to indicate 20% and 50% perceived MVC, respectively. Participants completed gripping a clamp until it stopped and then rated the amount of force required on the Borg scale. The data were used to define relationships between scale ratings and actual force application. The calibrated values, uncalibrated measurements, and error were compared using paired t-test ($p < 0.05$). The results showed that the grip-to-scale calibration method significantly reduced the rating error for the handgrip task; mean estimation error for a handgrip task was substantially decreased from 142.8 (± 69.0) to 62.3 (± 58.3) N. It was concluded that calibration of handgrip force ratings using the grip-to-scale method may improve the accuracy of handgrip force measurements using Borg CR10 scale.

Morrin et al., 2018

Isometric exercises (i.e., 30% of MVC) have been demonstrated to lower blood pressure, which is an important consideration for hypertensive patients. The purpose of this study was to investigate the relationship between %MVC, alteration in systolic blood pressure (ΔSBP), and perceived exertion (CR10 scale), and to assess whether the self-regulation of intensity is valid during isometric handgrip exercise. Fourteen pre-hypertensive and hypertensive adults performed an estimation task which was eight, 2-minutes isometric handgrip contractions at a randomly selected intensity ranging from 10% to 40% MVC (5% increase). Subjects were asked to rate the perceived exertion from the CR10 scale every 30 seconds. A linear regression was conducted on the obtained 32 ratings of the CR10 scale and calculated the corresponding %MVC and ΔSBP. It was shown that "level 6" of CR10 scale aligned with a relative force of 33% MVC and ΔSBP of an 38mmHg in average. For production task, subjects performed four, 2-minute isometric handgrip exercise; they were asked to maintain the level 6 during the trials. The results indicated the significant linear relationships between the estimated exertion on the CR10 scale, and %MVC (r=0.845), and ΔSBP (r=0.784). Also, %MVC was not significantly different between estimation and production task. It was concluded that when providing an exercise prescription to prehypertensive and hypertensive adults, the level 6 of CR10 scale may be an effective method of self-regulating isometric handgrip intensity aimed at decreasing blood pressure.

Keller et al., 2019

The purpose of this study was to investigate the patterns of responses for electromyography (EMG), mechanomyography (MMG), and force during a submaximal isometric fatiguing exercise anchored to a rating of perceived exertion equal to 5 (RPE=5) for the leg extensor muscles. Ten recreationally active men performed pre-maximal voluntary isometric contractions (MVICs) followed by the submaximal, isometric leg extension muscle action to RPE=5 without visual feedback for a maximal time-limit of 5 min or until they were not able to sustain RPE=5. Immediately following the fatiguing exercise, post-MVICs were completed. The results showed that the pre-MVIC (62.4 ± 14.3 kg) was significantly greater than post-MVIC (47.9 ± 12.8 kg). During sustained leg extension contractions, there was a negative force versus time relationship (r = -0.980). Moreover, there was a significant, negative EMG amplitude (AMP) (i.e., muscle excitation) versus time relationship (r = -0.789). However, there were no significant relationships for EMG mean power frequency (MPF) (i.e., action potential conduction velocity), MMG AMP (i.e., motor unit recruitment), or MMG MPF (i.e., global firing rate of motor unit) versus time. It was concluded that during the submaximal isometric leg extension exercise, the reduction of force and EMG AMP to sustain RPE=5 may be due to an initial regulation by an anticipatory feedforward mechanism and then continuous integrations of afferent feedback, which results from decrease in neural drive to reduce the accumulation of metabolic byproducts on perceived exertion.

Summary

Based on the importance of understanding how subjective feelings are related to objective findings, many researchers have agreed that it is necessary to develop methods to quantify the subjective responses during exercise (Borg 1982). Borg’s rating of perceive exertion (RPE) scale introduced a new ratio-scaling method to define the perceived exertion (Borg 1982). A simple category scale ranging from 0 to 10 (CR10 scale) was developed and has been applied to further studies (Borg 1982, Spielholz 2006, Morrin et al. 2018, Keller et al. 2019). For instance, it has been suggested that a self-reported calibration using CR10 scale was valid to measure a force of muscle contraction (i.e., handgrip) (Spielholz 2006). Another study has investigated the validity of self-regulation of intensity according to a specific level of CR10 scale during the isometric handgrip exercise (Morrin et al. 2018). It was revealed that exercise anchored at a RPE of the CR10 scale may be an effective method of self-regulating isometric exercise prescription in a clinical setting (e.g., hypertensive patient) (Morrin et al. 2018). A recent study has examined the various physiological patterns of responses (i.e., electromyography, mechanomyography, force) during an exercise anchored at a RPE (Keller et al. 2019). It has been suggested that during a submaximal isometric muscle action anchored by a RPE, the patterns of force and neuromuscular responses are accompanied by diverse physiological mechanisms. Specifically, the decreases in force and electromyographic amplitude (i.e., muscle excitation) may reflect a reduction in neural drive to attenuate the effect of metabolic byproducts, and the regulated force production throughout the exercise can be explained by the roles of a feedforward mechanism at the initial stage of exercise and then afferent feedback mechanism (Keller et al. 2019).

2.3 Mechanisms of fatigue associated with an exercise anchored by RPE.

2.3.1 Physiological factors associated with an exercise anchored by RPE (RPE clamp model)

Tucker et al., 2006

The purpose of this study was to investigate the regulation of exercise intensity in a hot environment during cycling exercise at a predetermined, constant rating of perceived exertion (RPE). The authors introduced a RPE clamp model that posits the conscious perceptual effort may regulate function so that the work rate remains at an intensity that can be safely maintained for expected duration of the exercise. That is, this regulatory control should be evident during exercise anchored at a constant RPE. Eight cyclists participated in this study by cycling trials in a COOL (15°C), NORM (25° C), and HOT (35° C) environment anchored at a RPE of 16. The results showed an initial decrease in power outputs (P) at all conditions before the body temperature was abnormally elevated suggesting that the anticipatory regulation of exercise intensity via a feed-forward mechanism occurs. They also reported that P was reduced at a greater rate in HOT (2.35±0.73 W/min) than COOL (1.63±0.70 W/min) and NORM (1.61±0.80 W/min) during the trials suggesting that afferent feedback from skin temperatures and higher rate of heat storage in the hot environment led to this alteration. However, after 5min, there were no differences in the rates of heat storage until completion of the trials because the RPE must be constantly maintained in the RPE clamp protocol, the P was reduced more rapidly in HOT than COOL and NORM conditions. It was concluded that the regulation of exercise intensity in the hot environment is obtained through a cooperation of anticipatory feed-forward mechanism and afferent feedback mechanism to maintain thermal homeostasis by decreasing the exercise work rate to prevent excessive heat accumulation.

2.3.2 Afferent Feedback model

Kaufman et al., 2002

The purpose of this study was to describe the metabolic and mechanical stimuli that discharge the thin-fiber group III and IV muscle afferents. Some of important characteristics of the group III afferents have been suggested that 1) they are thinly myelinated and conduct impulses between 2.5 and 30 meters per second, 2) they respond to intermittent isometric or sustained isometric contraction, 3) they also respond to both mechanical and metabolic stimuli; group III afferents respond vigorously at the beginning of isometric contraction, with the first impulse from the start of task (i.e., mechanical); and also they are stimulated by bradykinin, potassium, and/or lactic acid when the working muscle is fatiguing (i.e., metabolic). On the other hand, it has been demonstrated that 1) group IV afferents are unmyelinated and conduct impulse at less than 2.5 meters per second, 2) they obviously respond to isometric contraction while muscles are ischemic rather than while the muscles are perfused, 3) group IV afferents also respond to the metabolic substance (i.e., bradykinin, potassium, lactic acid). For both group III and IV muscle afferents, it has been identified that they appear to be stimulated by low to moderate levels of exercise as well as severe or painful levels of exercise.

2.3.3 Corollary discharge model (feedforward mechanism)

Marcora 2009

The purpose of this study was to suggest that perception of effort during dynamic whole-body exercise is independent of afferent feedback mechanism from skeletal muscles. It has been suggested that group III and IV fibers innervate many skeletal muscles via afferent feedback associated with metabolic, biochemical, and mechanical stress, which indicated that the sense of effort is dependent of sensory inputs from muscle spindles and Golgi tendon organs in fatigued muscle. Marcora argued that there was a different response between alterations in afferent feedback from the fatigued locomotor muscles and a significant increase in perceive exertion during a high intensity cycling test. The author proposed that the sense of effort is centrally generated by forwarding neural signals via corollary discharge pathway, from motor (i.e., central command) to somatosensory areas (i.e., sense of effort). Marcora also suggested that corollary discharge pathways have been demonstrated as a single interneuron forwarding inhibitory signals from motor to sensory areas in the nervous system.

2.3.4 Sensory Tolerance Limit Theory

Hureau et al., 2018

The purpose of this study was to investigate the role of neural feedback and feedforward mechanisms in regulating exercise performance. It was suggested that afferent feedback pathway is from working muscles to the central nervous system, the related activation of sensory areas within the brain, thereby resulting in facilitation of perceptual effort and central fatigue. It was also suggested that corollary discharges activate sensory areas within the cortex, thus affect perception of effort and contribute to central fatigue during exercise. The authors proposed the ‘sensory tolerance limit’ model indicating a combination between the sum of afferent feedbacks (e.g., locomotor muscles, respiratory muscles, organs, or even remote muscles not directly involved in the exercise) and the corollary discharges related to central command are integrated within the brain, and ultimately regulate the work rate or the magnitude of central motor drive to ensure that voluntary activity remains tolerable. It is concluded that the sensory tolerance limit is described as a global negative feedback loop leading to task failure via both afferent feedback and feedforward pathways.

2.3.5 Performance Fatigability

Tomas et al., 2018

The purpose of this study was to propose that performance fatigability (i.e., a reduction in an objective measure of performance such as a production of maximal voluntary force, the ability to provide sufficient signal to voluntary activated muscle) is not constrained to a task-specific, critical peripheral threshold (i.e., metabolite-regulated afferent discharge in mediating central motor command during exercise), but rather is dependent on the muscle mass recruited and exercise intensity during an exercise, and the related disruption to homeostasis in multiple physiological systems. The authors have been suggested that the muscle mass engaged during an exercise depends on the intensity and mode of the specific task, and these two factors (i.e., intensity, mode) will determine the magnitude of performance fatigability. For example, when a task required a smaller active muscle mass, the degree of performance fatigability was larger than requiring a stimulation of double-limb or whole-body muscle. They argued that this was because the sensory input is confined to a small muscle mass, thus disruptions to other physiological systems are also smaller. In contrast, it has been suggested that as the active muscle mass increases during exercise, the degree of performance fatigability in the involved muscle was lower because other adjustments (e.g., cardiovascular, respiratory) collectively modulate the symptoms of fatigue. Also, it has been proposed that within the same exercise mode, increasing in an exercise intensity can result in greater development of performance fatigability for locomotor exercise by increasing in the recruitment and subsequent stress of a greater volume of muscle.

Summary

Understanding physio-psychological mechanisms during fatiguing exercise is important to identify why, when, and how people feel fatigue, and what factors regulate an exercise performance during an exercise. The mechanisms of fatigue during an exercise anchored by RPE can be explained by different perspectives. The RPE clamp protocol has been introduced to examine how the conscious perception of effort may play a regulatory role to ensure a steady work rate at an intensity that can be safely maintained for the anticipated duration of an exercise (Tucker et al. 2006). During a fatiguing exercise, a force or power output can be altered to maintain a constant RPE (Tucker et al. 2006). Two different mechanisms regulating an exercise intensity have been suggested that explain an initial reduced power output as a result of anticipatory regulation of exercise intensity via a feedforward mechanism (Tucker et al. 2006, Marcora 2009), and as exercise continues, afferent feedback from group III and IV fibers is stimulated to maintain a certain exercise intensity (Tucker et al. 2006, Kaufman et al. 2002). Specifically, different characteristics of group III and IV have been identified; even though group III and IV respond to isometric fatiguing muscle contractions and to metabolic stimuli when the recruited muscle is fatiguing, group III respond to at the beginning of isometric contraction with the first impulse from the start of task (i.e., mechanical), on the other hand, the group IV respond to isometric contractions while muscles are in ischemic conditions (i.e., metabolic conditions) (Kaufman et al. 2002). However, it has been argued that perception of effort during exercise is independent of afferent feedback mechanism from skeletal muscles, rather the sense of effort is centrally generated within the cortex, which forwards inhibitory neural signals via corollary discharge pathway from motor to sensory areas (Marcora

2009). A further investigation of these two mechanisms has been conducted and integrated into a “sensory tolerance limit theory”, a combination between the sum of afferent feedbacks (e.g., engaged muscles, cardiovascular and/or respiratory muscles, organs, and muscles indirectly involved in the task) and corollary discharges associated with to central command are integrated within the brain (Hureau et al. 2018). Thus, it has been proposed that this integrated, global negative feedback loop leads to central fatigue during exercise and thus regulates the magnitude of central motor drive to ensure that voluntary muscle activities remain tolerable and steady (Hureau et al. 2018). A recent study, however, has examined performance fatigability (i.e., a decrease in a voluntary force produced by recruited muscle) and argued that the performance fatigability is dependent on the muscle mass engaged, exercise intensity, and associated disruption to homeostasis in multiple physiological systems, rather than afferent feedback and/or feedforward mechanisms (Thomas et al. 2018). For example, when an exercise activates a double-limb or whole-body muscle, the degree of performance fatigability of the involved muscle was smaller than an exercise requiring a recruitment of small muscle mass because other physiological systems (e.g., cardiovascular, respiratory) collectively modulate the symptoms of fatigue (Thomas et al. 2018). It has been also suggested that increased exercise intensity contributes to greater recruitment and subsequent stress of a greater muscle volume of muscle, leading to greater development of performance fatigability in the involved muscle (Thomas et al. 2018). In conclusion, during a fatiguing exercise, the regulation of required force to maintain a specific task can be accomplished by complex physiological mechanisms. Previous studies have not examined the time courses of patterns of physiological responses during isometric, sustained handgrip exercises anchored at different RPE levels ranging 0 to 10. Therefore, further studies should be investigated to determine the unique mechanisms of fatigue during an isometric, fatiguing handgrip exercise anchored to different RPE levels.

2.4 Physiological responses during isometric fatiguing exercises

2.4.1 The use of Electromyography and Mechanomyography

Beck et al., 2004

The purpose of this study was to determine the mechanomyographic (MMG) amplitude (AMP) and mean power frequency (MPF) versus torque (or force) relationships during isometric muscle contractions of the forearm flexors. Following determination of isometric maximum voluntary contraction (MVC), the subjects performed submaximal muscle contractions in 10% increments from 10% to 90% MVC. The results indicated MMG AMP increased linearly with torque but appeared to plateau from 80% to 100% of isometric MVC. Considering that the MMG AMP reflects motor unit recruitment, the authors suggested that the plateau in MMG AMP from last 20% may be due to muscle stiffness, intramuscular fluid pressure (IMFP), and/or fusion of motor unit twitches at high firing rates. It was also reported that MMG MPF remained steady from 10% to 50% MVC, increased from 50% to 80% MVC, and reduced from 80% to 100% MVC. The MMG MPF reflects the global motor unit firing rate of the activated muscle. The relatively stable MMG MPF from 10% to 50% MVC may be due to the recruitment of additional slow-twitch motor units, thus leading to little alteration in the global motor unit firing rate of the activated muscle. The increase from 50% to 80% MVC may be explained by both the recruitment of fast twitch motor units with higher firing rates in addition to the increase in firing rates of earlier-recruited slow-twitch motor units. In addition, the reduction of MMG MPF from 80% to 100% may be due to similar physiological mechanisms (i.e., muscle stiffness, IMFP, fusion of motor unit twitches). It is concluded that the time and frequency domains of MMG signal may be useful for describing unique motor control strategies during isometric exercise.

Coburn et al., 2005

The purpose of this study was to examine the responses for mechanomyographic (MMG) and electromyographic (EMG) amplitude (AMP) and mean power frequency (MPF) versus torque relationships during submaximal to maximal isometric muscle contractions for leg extensor muscles, especially for the vastus medialis. Seven subjects performed isometric leg extension at 20, 40, 60, 80, and 100% of maximal voluntary contraction (MVC) for 6 seconds. The results indicated that EMG AMP (r^2 =0.999) and MMG MPF (r^2=0.946) increased to MVC, mean MMG AMP increased to 80% MVC, and then plateaued, and mean EMG MPF did was not altered across torque levels. It was suggested that a curvilinear increase in EMG AMP with isometric torque may be due to progressive recruitment of large-diameter fast twitch muscle fibers with greater action potential amplitudes and increase in the firing rates of motor units with fused twitches. During isometric muscle actions, the EMG MPF reflects the average action potential conduction velocity, which is associated with the number and type of the activated motor units. However, it was reported that there was no change in EMG MPF across percentage of MVC values. Considering the fact that MMG AMP reflects the summation of the twitch oscillations of the activated motor units, the increase in MMG AMP to 80% MVC was consistent with isometric torque-related increases in motor unit recruitment and firing rates. It was suggested that the plateau in MMG AMP from 80 to 100% MVC may be due to high motor unit firing rates that resulted in fusion of motor unit twitches and limited the oscillations of some muscle fibers. In addition, they reported that an increase in MMG MPF may be due to the global firing rate of unfused activated motor units. It was concluded that isometric torque production was modulated by different motor control strategies.

Smith et al., 2016

The purpose of this study was to determine the time course of changes in electromyographic (EMG) and mechanomyographic (MMG) time and frequency domain parameters during a fatiguing isometric leg extension exercise at 50% of maximal voluntary isometric contraction (MVIC). Eleven healthy people (22.5 ± 2.1 years) participated in this study. They performed pre-MVICs of leg extension, followed by a sustained isometric muscle action to exhaustion at 50% MVIC. EMG electrodes and an MMG accelerometer were placed on the vastus lateralis. The results showed that the EMG amplitude (i.e., muscle excitation) versus time to exhaustion had a positive linear relationship (r^2=0.77), and the EMG frequency (i.e., motor unit action potential conduction velocity) and the MMG frequency (i.e., global motor unit firing rate) had negative quadratic relationship (r^2=0.99; r^2=0.94, respectively) that began to decrease at 30% of the time to exhaustion. Also, the MMG amplitude (i.e., motor unit recruitment) showed a cubic relationship (r^2=0.94); increased from 10 to 30% and then decreased from 40 to 70% of the time to exhaustion and increased from 70% to failure. It was suggested that the increase in EMG and MMG amplitude from 10 to 30% was because an increase in muscle excitation and motor unit recruitment were primary contributors to sustain the required force production; and increases in EMG and MMG amplitude despite the decrease in EMG and MMG frequency from 30% to time to exhaustion, reflect the buildup of metabolic by-products related to occlusion of muscle blood flow, which alter muscle contractility and thus result in greater muscle activation to sustain a constant force. The authors also presented a possibility that the decrease in MMG amplitude from 40 to 70% of the time to exhaustion was due to the influence of intramuscular fluid pressure on the MMG signal which was greater than the increase in motor unit recruitment; the increase MMG amplitude from 70% to task failure was because of an increase in motor unit recruitment and a plateau in intramuscular fluid pressure. It was concluded that motor unit activation strategies are altered throughout the fatiguing isometric leg extension exercise at 50% MVIC to sustain the required force production.

De Luca & Contessa, 2015

The purpose of this study was to propose a novel model of muscle force generation, the Onion-Skin scheme. Muscle force is mediated by varying the number of recruited motor units and their firing rates. There has been an acceptance that higher-threshold motoneurons have greater firing rates than lower-threshold motoneurons because higher-threshold motoneurons exhibit a shorter after-hyperpolarization (AHP) and greater firing rates than lower-threshold motoneurons. However, this study showed that during voluntary constant-force muscle contractions, earlier-recruited motor units sustain higher firing rates than later-recruited ones. Specifically, in the Onion-Skin scheme, the lower-threshold motor units produce more force at lower input excitation levels, thus maintain force production for a relatively long time; at this level, the higher-threshold motor units are not yet engaged to produce force, which provides an economy of force generation at low force levels. It has been also suggested that the later-recruited, higher-threshold motor units maintain a reserve capacity and are recruited in situations requiring high firing rates at high force levels.

Summary

Two neuromuscular parameters, electromyography (EMG) and mechanomyography (MMG) have been used to examine the motor unit activation strategies (Beck et al. 2004, Coburn et al. 2005, Smith et al. 2016). EMG measures the motor unit electrical activity of working muscle, and MMG quantifies the low-frequency lateral oscillations of active skeletal muscle fibers and MMG has been considered as a mechanical counterpart of electrical activity of motor unit obtained by EMG (Beck et al. 2004, Coburn et al. 2005, Smith et al. 2016). It has been suggested the measurements of amplitude and frequency of EMG and MMG can be used to determine motor control strategies during various muscle actions (e.g., isometric, isokinetic, dynamic muscle contractions) (Beck et al. 2004, Coburn et al. 2005, Smith et al. 2016). Specifically, it has been identified that the amplitude of EMG (EMG AMP) is related to muscle excitation (i.e., motor unit recruitment, firing rate, synchronization) and the mean power frequency of EMG (EMG MPF) is associated with action potential conduction velocity of activated motor units (Beck et al. 2004, Coburn et al. 2005, Smith et al. 2016). It has been also demonstrated that the amplitude of MMG (MMG AMP) reflects motor unit recruitment and the mean power frequency of MMG (MMG MPF) is associated with global firing rates of the unfused, active motor units (Beck et al. 2004, Coburn et al. 2005, Smith et al. 2016). Therefore, the simultaneous measurements of EMG AMP and MPF, and MMG AMP and MPF have been enabled to monitor the dissociation between the electrical and mechanical events that occurs with fatigue (Beck et al. 2004, Coburn et al. 2005, Smith et al. 2016). The examination on time course of changes in these two neuromuscular parameters (i.e., EMG, MMG) during fatiguing isometric muscle actions have enabled the determination of when changes in specific aspects of motor unit activation strategies begin (initiation of a task to exhaustion) and the patterns of changes (e.g., linear, quadratic, or cubic) (Smith et al. 2016). The typical neuromuscular patterns of responses during a submaximal, fatiguing, isometric muscle action have been shown that the muscle excitation (EMG AMP) and motor unit recruitment (MMG AMP) continuously increased to produce the required force, despite the fatigue-induced decreases in motor unit action potential conduction velocity (EMG MPF) and global motor unit firing rate (MMG MPF) (Smith et al. 2016). A novel perspective (i.e., Onion-Skin scheme) on motor unit behavior has been proposed that earlier- recruited motor units sustain higher firing rates than later-engaged ones, providing an inverse orderly hierarchy of nested firing rate curves resembling the layers of the skin onion (De Luca and Contessa 2015). Overall, the articles in this section highlight that it is necessary to examine the time course of changes in neuromuscular responses during fatiguing exercises to identify the process of fatigue with unique motor unit activation strategies that are task dependent.

2.4.2 The use of Near-Infrared Spectroscopy

Barstow, 2019

The purpose of this review study was to understand the method, limitation, and best practices of near infrared spectroscopy (NIRS) to apply to skeletal muscle research. It has been a general agreement that sufficient delivery of oxygen to meet the metabolic demands in a tissue undergoing aerobic metabolism is important for long-term viability of that tissue. In this regard, it has been suggested that determining a global tissue oxygenation would be invaluable, and NIRS provides a noninvasive method to examine the muscle tissue oxygenation. It was proposed that the primary sources of the NIRS signals are hemoglobin (Hb) and myoglobin (Mb) heme, and the muscle tissue oxygen saturation (SmO_2) is calculated by an equation, $SmO2 = \frac{\text{oxy[heme]}}{\text{oxy[heme]} + \text{deoxy [heme]}} \cdot 100$. This study introduced an application of NIRS to track tissue/muscle oxygenation during exercise. For example, a study described the changes in deoxygenation (Hb+Mb) and muscle tissue oxygen saturation (SmO_2) during discontinuous incremental handgrip exercise; both signals linearly increased from 20% to 50% MVC, with a slight upward trend at the highest work rate (~70% MVC). It was concluded that even though there are several challenges, such as the presence of tissues (e.g., skin, adipose tissue) which lie between the surface and muscle tissue, the NIRS can be a useful tool in exercise science and/or clinical research field due to its benefits of the estimate of muscle oxidative capacity during exercise.

Mantooth et al., 2018

The purpose of this study was to investigate task and sex differences in muscle oxygenation measured by near infrared spectroscopy (NIRS) during a handgrip fatiguing exercise. 48 adults (24 males and 24 females) visited the laboratory on four separate days to complete submaximal fatiguing handgrip exercises at one of the four contraction intensities of 20, 40, 60 and 80% of maximum voluntary contraction (MVC). The NIRS sensors were placed on the extensor carpi radialis (ECR) and flexor carpi radialis (FCR). During these four tests, the force fluctuation and muscle tissue oxygenation index data of ECR and FCR were averaged over 10 seconds in three-time phases: early (1-10s), middle (5s around 50% sustaining time), and late (last 10s to exhaustion). It was reported that 1) force fluctuation patterns during fatiguing exercises at 20% MVC and 80% MVC were similar, 2) at higher exercise intensities (i.e., 40,60 and 80% MVC), there were greater decreases in muscle oxygenation in both ECR and FCR over time, but it remained unchanged overtime during at the lowest intensity (i.e., 20% MVC), 3) males and females showed different rates of oxygenation alterations as fatigue progressed in spite of indicating similar levels of relative fatigability. It was concluded that males exhibited greater desaturation than females because of potential, greater increase in intramuscular pressure based on sex differences in muscle morphology and mass at higher exercise intensities.

Keller and Kennedy, 2021

The purpose of this study was to investigate the effects of sex and fatigue on the early phase of skeletal muscle tissue oxygen saturation (SmO_2) desaturation rate during handgrip isometric muscle action. Twenty-four subjects completed the vascular occlusion test (VOT) to quantify the early phase of desaturation in a resting state. For the experimental visit, the subjects performed a sustained handgrip trial at 25% of MVC until to exhaustion, followed by post-fatigue VOT. The near-infrared spectroscopy device assessed the muscle desaturation which was defined as SmO_2. The SmO_2 was measured in standardized segments of 5% of time to failure yielding 20 time points across time during the sustained handgrip exercise. The rates of desaturation were quantified by using linear regression during both the VOTs and the hold to failure handgrip task. During the sustained handgrip trial, the transformed SmO_2 values indicated that males (b= -0.070, r^2=0.95) showed a significant faster rate of decrease than the females (b= -0.015, r^2=0.53) even though the fatiguing handgrip task led to a deceleration of the rate of decrement in microvascular tissue O_2 saturation regardless of sex. It was concluded that differences in muscle mass, strength, and adipose tissue were not the primary reasons for observed sex differences. Instead, it was hypothesized that differences in fiber type and mitochondria between males and females may be primary mechanisms to explain the provoking the difference in muscle oxygenation. It was also reported that the males and females resulted in similar time to exhaustion in the fatiguing handgrip task despite the sex difference in rate of reduction in SmO_2, which can be interpreted that muscle desaturation is not the main factor contributing to volitional fatigue during a sustained exercise task. factor contributing to volitional fatigue during a sustained exercise task.

Summary

During a sustained exercise, it is important to identify how muscle fatigue progresses to predict and thus improve an exercise performance. In addition to the neuromuscular measurements (i.e., EMG, MMG), near infrared spectroscopy (NIRS) has been developed in skeletal muscle research (Barstow 2019, Mantooth et al. 2018, Keller and Kennedy 2021). It has been suggested that the NIRS examines the muscle tissue oxygen saturation (SmO_2), which is calculated via spatially resolved spectroscopy using the equation, $SmO2 = \frac{\text{oxygenated hemoglobin}}{\text{oxyenated hemogloblin } + \text{deoxygenated hemoglobin}} * 100$. The primary sources of the NIRS signals are hemoglobin (Hb) and myoglobin (Mb) heme (Barstow 2019, Mantooth et al. 2018, Keller and Kennedy 2021). Several NIRS studies to investigate the SmO_2 responses during isometric, fatiguing handgrip exercise have been conducted (Mantooth et al. 2018, Keller and Kennedy 2021). For example, a study examined the task and sex differences in muscle oxygenation using the NIRS during a sustained a handgrip exercise performed at each of 20, 40, 60 and 80% of MVIC (Mantooth et al. 2018). The SmO_2 responses was measured three time points (e.g., start, middle, and end) (Mantooth et al. 2018). It was reported that males exhibited greater desaturation than females due to potential, greater increase in intramuscular pressure based on sex differences in muscle morphology and mass at higher exercise intensities (i.e., 40,60 and 80% MVC) (Mantooth et al. 2018). A further investigation of effects of sex and fatigue on the SmO_2 desaturation rate during handgrip isometric muscle action reported similar results but presented an alternative interpretation (Keller and Kennedy 2021). This study (Keller and Kennedy 2021) measured SmO_2 in standardized segments of 5% of time to failure yielding 20 time points across time and suggested that sex differences in fiber type and mitochondria may be primary mechanisms to explain the differences in muscle oxygenation, rather than the differences in muscle mass, strength, and adipose tissue (Mantooth et al. 2018, Keller and Kennedy 2021). Moreover, it was indicated that despite the sex difference in rate of decrease in SmO_2, there was no sex difference in time to exhaustion during the sustained handgrip exercise, which means that muscle desaturation could be not a primary reason eliciting volitional fatigue (Keller and Kennedy 2021). In conclusion, it is expected that simultaneous, combined assessments of fatiguing responses (e.g., neuromuscular, muscle oxygen saturation) will provide better understandings of time course of local muscle fatigue during a sustained isometric exercise.

CHAPTER 3. METHODS

3.1 Research Design

This study consisted of 8 total visits separated by a minimum of 24 hours. During the familiarization visit (Visit 1), prior to the maximum voluntary isometric contraction (MVIC) trial, a warm-up was performed with 3-5, 6-s holds at a perceived effort of 30-80% of maximum. After three minutes of rest from the last warm-up, the subjects performed MVICs for the dominant hand, each consisting of a 3-s contraction at 90° forearm flexion, with the hand in the neutral position. At visits 2-5, the subjects performed the MVICs (pre-MVIC) for the dominant hand, followed by a submaximal continuous isometric contraction to task failure (i.e., inability to maintain required force) at one of the four randomly determined percentages of MVIC (30, 40, 50 and 60%) for the dominant hand. Immediately following the completion of the holds to failure, the subjects performed another handgrip MVIC (post-MVIC). At each subsequent visit (6-8), the subjects performed a continuous isometric handgrip hold anchored by a rating of perceived exertion (RPE) at one of the three randomly ordered RPE levels (RPE = 3, 5, or 7) to task failure (i.e., force = 0). The holds to failure at visit 6-8 were performed on the dominant hand and pre- and post-MVICs were performed.

During visit 1, skinfold measurements were performed on the subject's brachioradialis and flexor digitorum superficialis of the dominant arm to estimate the layer of subcutaneous adipose tissue. During all handgrip exercises, neuromuscular responses including electromyography (EMG) and mechanomyography (MMG) were measured from the brachioradialis of the dominant limb. In addition, muscle oxygen saturation (%SmO_2) assessments were recorded from the flexor digitorum superficialis of the dominant arm.

3.2 Subjects

Subject characteristics included 12 men between 18 and 35 years of age of any racial/ethnic background. Inclusion in the study comprised subjects who were free of musculoskeletal injuries and neuromuscular diseases, currently were participating in resistance training (for at least 6 months, 1 time per week), demonstrated readiness for physical activity, had no medical contraindications as determined via health history form, and females who were not pregnant. The subjects were asked to maintain their current level of physical activity, but to abstain from upper body resistance training exercise at least 24 hours and from consuming caffeine within 3 hours prior to their testing session. All of the subjects completed a healthy history form and sign a written informed consent document approved by the University Kentucky Institutional Review Board.

3.3 Determination of Critical Force

Critical force (CF) was determined by completing randomly ordered sustained, handgrip exercises at four percentages of MVIC (30, 40, 50, and 60%) on separate days. The subjects maintained each force until the task failure to determine time to exhaustion (T_{lim}), which was defined as an inability to sustain the assigned percentage of MVIC (≥ 5% reduction in force for three consecutive seconds). During each trial, the subjects were given strong verbal encouragement and were able to track force production via visual feedback on a computer monitor. The amount of work performed (W_{lim}) was obtained by multiplying the force produced during a trial by the corresponding T_{lim}. The four W_{lim}

values were plotted as a linear function of the T_{lim} values, and the CF was defined as the slope coefficient of the W_{lim} versus T_{lim} relationship.

3.4 Determination of force value corresponding to an anchored rating of perceived exertions

During the testing visits, the subjects performed a continuous isometric hold exercise anchored by RPE at one of the three randomly ordered RPE levels (RPE = 3, 5 or 7). The subjects were blinded to force output to mitigate any potential pacing strategies during a trial. In other words, the subjects did not receive visual feedback associated to force production, so that the perception of exertion would not be confounded with a visual information of force. The subjects were instructed to adjust force production to maintain a predetermined level of exertion equivalent to each RPE = 3, 5, or 7. Task failure was determined as a timepoint at which subjects indicated that they would no longer sustain the assigned RPE (i.e., increase in perceived exertion) despite continued reductions in force (i.e., zero force production). The changes in force over time for each RPE were examined in standardized segments every 5% of time to exhaustion to examine the changes of time. During the familiarization visit, the following instructions which were modified from Keller et al. (2019) were read to subjects; “You will be asked to set an anchor point for both the lowest and highest value on the RPE scale. To determine the lowest anchor, you will be asked to sit quietly and relax your whole body without contracting your forearm muscles to familiarize yourself with a zero. You will be then asked to perform two maximal voluntary isometric contractions to familiarize yourself with a 10. When instructed to perform the handgrip task corresponding to this scale, perceived exertion at a given RPE level should be relative to these defined anchors”.

3.5 Determination of performance fatigability

The absolute MVIC force (kg) was examined for pre- and post-fatigue. For descriptive purposes, performance fatigability was calculated as the percent change in MVIC value from pre-MVIC to post-MVIC $[(\frac{(\text{pre}-\text{MVIC})-(\text{post}-\text{MVIC})}{Pre-MVIC}) * 100]$ within the dominant hand.

3.6 Electromyography and Mechanomyography Measurements

During the pre- and post-MVICs and hold to failure trials of experimental visits 2-8, pre-gelled surface electromyography (EMG) electrodes were placed in a bipolar arrangement (20mm center-to-center) on the brachioradialis of dominant arm. Prior to electrode placement, the site on the skin was shaved, carefully abraded, and cleaned with isopropyl alcohol. According to recommendations from Barbero et al. (2012), a line from the styloid process of radius to a midpoint on the line between the lateral and medial epicondyles were indicated. One electrode was then placed 75% of this line (i.e., proximal part of the muscle belly), and another electrode was placed 2 cm distally from the attached electrode on the same line. The mechanomyographic (MMG) signals were detected with an accelerometer placed 20mm below the bipolar surface EMG electrode arrangements using double-sided adhesive tape.

3.7 Muscle Oxygen Saturation

During hold to failure trials in visits 2-8, the NIRS device (MOXY, Fortiori Design LLC, Hutchinson, MN) was placed on the flexor digitorum superficialis 2cm distal to the medial epicondyle of dominant arm. The MOXY device reported muscle oxygen saturation (i.e., $\mathrm{SmO2} = \frac{\text{oxygenated hemoglobin}}{\text{oxyenated hemogloblin } + \text{deoxygenated hemoglobin}}$ *100). The time courses of patterns of responses of muscle oxygen saturation were recorded in standardized segments of 5% of time to exhaustion yielding 20 time points across time. Each 20 value was calculated by average values of each 5% T_{lim} (e.g., SmO_2 value at 5% T_{lim} = average values from 0% T_{lim} to 5% T_{lim}). During the testing sessions, the system was connected to a personal computer using the manufacturer's software program (Peripedal ©) to provide a graphic display of the data. Data was acquired at 2 Hz and obtained from the sensor's internal memory.

3.8 Signal Processing

The raw EMG and MMG signals were digitized at 2000 Hz and stored in a personal computer for analysis. The recorded signals were processed with a custom program written in MATLAB programming software. The EMG and MMG signals were differently amplified and bandpass-filtered (fourth-order Butterworth) at 10-500 Hz for EMG and 5 – 100 Hz for MMG, respectively. The EMG and MMG, AMP and MPF were recorded in standardized segments of 5% of time to task failure during fatiguing testing sessions and normalized to the respective values at the pre-MVIC. A 1-sec epoch at the beginning and end (0% and 100% T_{lim}) of each hold to failure and 500 ms before and after each 5% of

T_{lim} (1-second epoch from the center of each 5% segment) were used to calculate the AMP (root mean square) for EMG (μVrms) and MMG ($m \cdot s^{-2}$) and the mean power frequency (Hz) for both signals. For the MPF analysis, each data segment was processed with a Hamming window and a discrete Fourier transform (DFT) algorithm. The MPF was selected to represent the power spectrum based on the recommendations of Hermens et al. (1999) and was calculated as described by Kwatny et al. (1970). In addition, neuromuscular efficiency was calculated for each 5% segment by determining the ratio of the normalized force to normalized EMG AMP (Jones et al. 2016).

3.9 Data Analyses

Anthropometric data (age, height, weight, adipose tissue thickness for sites on the dominant arm) was used for descriptive purposes. Analyses were performed to examine performance fatigability (MVIC kg) and T_{lim} and as well as the patterns of responses and time course of changes in force, neuromuscular (EMG AMP, EMG MPF, MMG AMP, and MMG MPF), and muscle oxygen saturation (%SmO_2) responses. Based on the force and EMG AMP values, the neuromuscular efficiency (normalized force/ normalized EMG AMP) response was also analyzed. T_{lim} were analyzed using a 1(Time) x 3(RPE: 3, 5, and 7) repeated measure ANOVA and post-hoc t-tests with a Bonferroni corrected alpha level ($p<0.017$). The performance fatigability (% change) was analyzed using a 1(percent decline %) x 3(RPE: 3, 5, and 7) repeated measure ANOVA and post-hoc t-tests with a Bonferroni corrected alpha level ($p<0.017$). For the performance fatigability (absolute values) of pre- and post-MVICs, a 2(Time: pre- vs post-hold) x 3(RPE: 3, 5, and 7) repeated measure ANOVA and post-hoc t-tests with a Bonferroni corrected alpha level ($p<0.017$) was used. Since each subject had a different time to task failure (T_{lim}), time was normalized as a percentage T_{lim} and 21 timepoints (5% segments, initial -100%T_{lim}) were used for the analyses of force, EMG, and MMG responses. Specifically, the time course of changes in force, EMG AMP, EMG MPF, MMG AMP, MMG MPF, and neuromuscular efficiency were examined using separate, 3(RPE:3, 5, and 7) x 21(time:0-100% T_{lim}) repeated measures ANOVAs, with follow up one-way repeated measures ANOVAs and post-hoc t-tests with Bonferroni corrected alpha level for comparisons across time ($p<0.0025$) and between RPE levels ($p<0.017$). For SmO_2 response, a 3(RPE: 3, 5, and 7) x 20(time: 5-100% MVIC) repeated measures ANOVA, with follow up one-way ANOVA and post-hoc t-tests with Bonferroni corrected alpha level for comparisons across time ($p<0.0026$) and between RPE levels ($p<0.017$). An alpha level of $p \leq 0.05$ was used to determine statistical significance for all ANOVAs. Measures of effect size included partial eta square (η_p^2) and Cohen's d (ES). All statistical analyses were conducted using the Statistical Package for Social Sciences software (v.28.0 IBM SPSS Inc., Chicago, Illinois, USA).

CHAPTER 4. RESULTS

4.1 Subject Descriptive Characteristics

Table 1 indicates the subjects descriptive characteristics including age (yrs), height (cm), weight (cm), and adipose tissue thickness (cm) obtained by skinfold measurements.

4.2 Time to Task Failure

The time to task failure (T_{lim}) for each RPE hold was 478.7±196.6sec (RPE 3), 512.4±245.9sec (RPE 5), and 495.8±173.8sec (RPE 7). A one-way repeated measure ANOVA ($F=0.210$, $p=0.812$, $\eta_p^2=0.019$) and post-hoc t-tests with a Bonferroni corrected alpha level ($p<0.017$) indicated that there were no differences in T_{lim} among RPE 3, 5, and 7 ($p=0.569$-0.744) (Figure 1).

4.3 Time course of changes in force

All subjects reached the 0 kg in the last milliseconds during the all handgrip holds at respective RPE 3,5, and 7. A 3(RPE: 3, 5, and 7) x 21(time: 0-100% MVIC) repeated measures ANOVA indicated that there was a RPE x time ($F=2.805$, $p<0.001$, $\eta_p^2=0.203$) interaction for the relative force responses (% MVIC) during the fatiguing, isometric handgrip holds to task failure. The follow-up one-way repeated measures ANOVA for each of the three RPE holds (RPE 3, $F=36.205$, $p<0.001$, $\eta_p^2=0.767$; RPE 5, $F=24.754$, $p<0.001$, $\eta_p^2=0.692$; RPE 7, $F=44.247$, $p<0.001$, $\eta_p^2=0.801$) and post-hoc t-tests with Bonferroni corrected alpha level ($p<0.0025$) indicated that there were decreases in force, relative to the initial value (0% T_{lim}), from 20% to 100% T_{lim} for RPE 3, from 45% to 100% T_{lim} for

RPE 5, and from 15% to 100% T_{lim} for RPE 7 (Figure 2). The results of the 21, separate, follow-up 1 (time) X 3 (RPE) repeated-measures ANOVAs and post-hoc t-tests with a Bonferroni corrected alpha level ($p<0.017$) are indicated in Table 2.

4.4 Critical force (CF) and time to CF

The absolute (kg) and relative (% MVIC) CF values were 9.0±2.3kg, and 19.4±3.8% MVIC, respectively. The times to CF (sec, % T_{lim}) at RPE 3, 5, and 7 for each subject are indicated in Table 3.

4.5 Performance Fatigability

The performance fatigability values were 30.0±14.5%, 38.2±11.5%, and 37.9±12.9% for the RPE 3, 5, and 7, respectively. A one-way repeated measures ANOVA ($F=5.196$, $p=0.014$, $\eta_p^2=0.321$) and post-hoc t-tests with a Bonferroni corrected alpha ($p<0.017$) indicated that performance fatigability for RPE 5 was greater than RPE 3 ($p=0.015$, mean diff= 8.158, 95% CI= 0.219 – 16.098, and Cohen's d= 0.837), but there was no difference between RPE 7 and RPE 3 ($p=0.036$, mean diff= 7.842, 95% CI= -1.433 – 17.116, and Cohen's d= 0.688), and RPE 5 and RPE 7 ($p=0.899$, mean diff= 0.317, 95% CI= -6.545 – 7.178, and Cohen's d = 0.038) (Figure 3). The absolute values of pre- and post- MVIC (kg) are indicated in Table 4. For the absolute pre- and post- MVIC values, 3 (RPE: 3, 5, and 7) x 2 (Time: pre- and post) repeated measures ANOVA indicated that there was a RPE x time interaction ($F=4.777$, $p=0.019$, $\eta_p^2=0.303$). The post-hoc t-tests ($p<0.017$) indicated that there was no difference in pre-MVIC ($p=0.494$-0.894) among RPE

3, 5, and 7. However, the post-MVIC value of RPE 3 was greater than RPE 5 ($p=0.008$), but not RPE 7 ($p=0.024$), and there was no difference in RPE 5 and 7 ($p=0.924$) (Figure 4). In addition, there were significant decreases from pre- to post-MVIC at RPE 3, 5, and 7 ($p<0.001$).

4.6 Electromyographic and Mechanomyographic responses

A 3(RPE: 3, 5, and 7) x 21(time: 0-100% MVIC) repeated measures ANOVA indicated that there was a RPE x time ($F=1.766$, $p=0.003$, $\eta_p^2=0.138$) interaction for the EMG AMP. The follow-up one-way repeated measures ANOVA for each of the three RPE holds (RPE 3, $F=16.447$, $p<0.001$, $\eta_p^2=0.599$; RPE 5, $F=4.605$, $p<0.001$, $\eta_p^2=0.444$; RPE 7, $F=12.331$, $p<0.001$, $\eta_p^2=0.529$) and post-hoc t-tests with Bonferroni corrected alpha level ($p<0.0025$) indicated that there were decreases in EMG AMP, relative to the initial value (0% T_{lim}), at 20% and 25%, and from 35% to 100% T_{lim} at RPE 3, at 30%,55%,60%, and 100% T_{lim} at RPE 5, and at 30% and from 40% to 100% T_{lim} at RPE 7 (Figure 5). The results of the 21, separate, follow-up 1 (time) X 3 (RPE) repeated-measures ANOVAs and post-hoc t-tests with a Bonferroni corrected alpha level ($p< 0.017$) are indicated in Table 5.

A 3(RPE: 3, 5, and 7) x 21(time: 0-100% MVIC) repeated measures ANOVA indicated that there was no RPE x time ($F=1.309$, $p=0.104$, $\eta_p^2=0.106$) interaction or main effect for RPE ($F=1.313$, $p=0.289$, $\eta_p^2=0.107$) for EMG MPF. There was, however, a significant main effect for time ($F=7.439$, $p<0.001$, $\eta_p^2=0.403$). The follow-up one-way repeated measures ANOVA for time ($F=1.784$, $p=0.024$, $\eta_p^2=0.140$), collapsed across RPE, and post-hoc t-tests with a Bonferroni corrected alpha level ($p<0.0025$) showed that there were decreases in the EMG MPF (% MVIC), relative to the initial value (0% T_{lim}), at 15%,25%,30%, and from 45% to 95% T_{lim} (Figure 6).

A 3(RPE: 3, 5, and 7) x 21(time: 0-100% MVIC) repeated measures ANOVA indicated that there was no RPE x time ($F=0.924$, $p=0.607$, $\eta_p^2=0.077$) interaction for MMG AMP. There was, however, a significant main effect for time ($F=6.906$, $p<0.001$, $\eta_p^2=0.386$), collapsed across RPE, and a main effort for RPE ($F=6.386$, $p=0.007$, $\eta_p^2=0.367$), collapsed across time. The post-hoc t-tests with a Bonferroni corrected alpha level ($p<0.0025$) showed that there were no significant changes in the MMG AMP (% MVIC), relative to the initial value (0% T_{lim}), at any time points ($p=0.005$-0.036) (Figure 7). The post-hoc t-tests with a Bonferroni corrected alpha level ($p<0.017$) indicated that there was no significant difference in MMG AMP between RPE 3 and 5 ($p=0.411$), but RPE 7 was greater than RPE 3 ($p=0.013$) and RPE 5 ($p=0.001$), collapsed across time (Figure 8).

A 3(RPE: 3, 5, and 7) x 21(time: 0-100% MVIC) repeated measures ANOVAs indicated that there was no RPE x time ($F=1.129$, $p=0.276$, $\eta_p^2=0.093$) interaction or main effect for RPE ($F=2.142$, $p=0.141$, $\eta_p^2=0.163$) for MMG MPF. There was, however, a significant main effect for time ($F=2.743$, $p<0.001$, $\eta_p^2=0.200$). The post-hoc t-tests with a Bonferroni corrected alpha level ($p<0.0025$) showed that there were no significant changes in the MMG MPF (% MVIC), relative to the initial value (0% T_{lim}), at any time points ($p=0.027$-0.920) (Figure 9).

4.7 Neuromuscular Efficiency

A 3(RPE: 3, 5, and 7) x 21(time: 0-100% MVIC) repeated measures ANOVAs indicated that there was a RPE X time (F=1.498, p=0.029, η_p^2=0.120) interaction for neuromuscular efficiency (normalized force/normalized EMG AMP). The follow-up one-way repeated measures ANOVA for each of the three RPE holds (RPE 3, F=11.410, p<0.001, η_p^2=0.509; RPE 5, F=20.704, p<0.001, η_p^2=0.0.653; RPE 7, F=14.828, p<0.001, η_p^2=0.574) and post-hoc t-tests with a Bonferroni corrected alpha level (p<0.0025) indicated there were no differences in the neuromuscular efficiency, relative to the initial value (0% T_{lim}), at any time points (p=0.004-0.780) for RPE 3. There was, however, significant decreases in the neuromuscular efficiency, relative to the initial value (0% T_{lim}), from 50% to 65%, and from 80% to 100% for RPE 5. For the RPE 7 hold, there was a significant decrease in the neuromuscular efficiency, relative to the initial time point of 0% T_{lim}, at the last time point (100% T_{lim}) (Figure 10). The results of the 21, separate, follow-up 1 (time) X 3 (RPE) repeated-measures ANOVAs and post-hoc t-tests with a Bonferroni corrected alpha (p<0.017) are indicated in Table 6.

4.8 Muscle Oxygen Saturation responses

A 3(RPE: 3,5, and 7) x 20(time: 5-100% MVIC) repeated measures ANOVA indicated that there was a RPE X time (F=2.060, p<0.001, η_p^2=0.158) interaction for SmO_2 responses. The follow-up one-way repeated measures ANOVA for each of the three RPE holds (RPE 3, F=0.655, p=0.860, η_p^2=0.056; RPE 5, F=2.462, p<0.001, η_p^2=0.183; RPE 7, F=4.963, p<0.001, η_p^2=0.311) and post-hoc t-tests with Bonferroni corrected alpha level (p<0.0026) indicated that there was no significant differences in SmO_2, relative to the initial value (5% T_{lim}), at any time point at RPE 3 (p=0.094-0.774), RPE 5 (p=0.074-0.543), and RPE 7 (p=0.017-0.632) (Figure 11). The results of the 20, separate, follow-up 1 (time) X 3 (RPE) repeated-measures ANOVAs and post-hoc t-tests with a Bonferroni corrected alpha (p<0.017) are indicated in Table 7. There were no significant differences across time for any of the RPE holds (Table 7).

Table 1. Individual descriptive data including age, height weight, and adipose tissue thickness.

Subject	Age (yrs)	Height (cm)	Weight (kg)	Adipose tissue thickness (cm)
1	27	179.8	67.8	5
2	26	163.2	70.5	5
3	29	174.4	61.33	2
4	23	178.1	99.7	29
5	26	180.5	90.5	2
6	33	188.7	115.6	13
7	31	179	64.2	4
8	32	191.4	99.07	7
9	32	178.8	87.9	5
10	32	176.5	67.4	6
11	23	179	71.7	8
12	24	181.2	94.3	4
Mean	28.2	179.2	82.5	7.5
SD	3.8	7.0	17.5	7.4

Table 2. The results of the 21, separate, follow up one-way repeated-measures ANOVAs and post-hoc t-tests with a Bonferroni corrected alpha ($p<0.017$) for the changes in force values across time.

Time	Force (% MVIC)			Follow up one-way ANOVA			Post Hoc comparison		
	RPE 3	RPE 5	RPE 7	F value	Sig.	Effect size ($\eta_{p}2$)	RPE 3 and 5	RPE 3 and 7	RPE 5 and 7
0%	21.159 ± 4.274	26.250 ± 7.640	37.370 ± 5.793	12.889	<0.001	0.540	0.230	*<0.001	* 0.005
5%	19.951 ± 3.093	24.624 ± 3.971	29.577 ± 4.230	7.782	0.003	0.414	0.038	*0.002	0.106
10%	14.661 ± 2.674	19.343 ± 2.394	22.825 ± 3.714	11.861	<0.001	0.519	*0.006	*0.002	0.051
15%	12.303 ± 2.510	16.122 ± 2.675	19.886 ± 3.524	15.985	<0.001	0.592	*0.004	*<0.001	0.027
20%	10.207 ± 2.050	14.176 ± 2.277	18.498 ± 2.949	21.935	<0.001	0.666	*0.012	*<0.001	*0.003
25%	10.187 ± 1.924	12.604 ± 2.064	15.042 ± 2.981	6.722	0.005	0.379	0.101	*0.002	0.104
30%	8.495 ± 1.707	10.323 ± 1.861	14.430 ± 2.826	10.059	<0.001	0.478	0.140	*0.002	0.017
35%	7.392 ± 1.132	9.821 ± 1.698	14.041 ± 3.059	9.399	0.001	0.461	0.089	*0.001	0.038
40%	6.802 ± 1.360	8.803 ± 1.854	10.580 ± 2.117	3.717	0.041	0.253	0.195	0.029	0.165
45%	6.481 ± 0.894	7.844 ± 1.886	9.528 ± 2.224	2.468	0.108	0.183	0.363	0.050	0.233
50%	6.041 ± 0.743	6.915 ± 1.542	9.635 ± 1.948	5.617	0.110	0.338	0.456	*0.006	0.051
55%	5.270 ± 0.661	6.382 ± 1.630	7.378 ± 1.525	2.033	0.155	0.156	0.315	0.026	0.419
60%	4.933 ± 0.826	5.708 ± 1.507	8.419 ± 1.770	5.117	0.150	0.317	0.516	*0.005	0.067
65%	4.726 ± 1.179	5.818 ± 1.415	7.139 ± 1.176	2.730	0.087	0.199	0.430	*0.015	0.186
70%	4.132 ± 0.895	6.237 ± 1.510	6.807 ± 1.857	3.688	0.042	0.251	0.046	*0.013	0.615
75%	4.075 ± 0.638	5.664 ± 1.318	6.451 ± 1.138	3.858	0.037	0.260	0.117	*0.004	0.417
80%	3.910 ± 0.327	5.014 ± 1.009	4.686 ± 0.918	1.627	0.219	0.129	0.155	0.218	0.608
85%	3.591 ± 0.425	4.731 ± 1.277	5.621 ± 0.777	4.437	0.024	0.287	0.189	*0.005	0.194
90%	2.821 ± 0.476	4.332 ± 1.195	3.747 ± 0.924	2.011	0.158	0.155	0.092	0.133	0.528
95%	2.571 ± 0.326	2.584 ± 0.407	3.038 ± 0.421	1.395	0.269	0.113	0.953	0.102	0.232
100%	1.319 ± 0.135	1.300 ± 0.128	1.330 ± 0.159	0.118	0.889	0.011	0.669	0.954	0.579

*Indicates significant differences between force values for the RPE holds ($p<0.017$).

Table 3. The CF (kg, % maximal voluntary isometric contraction [MVIC]) and time to CF (sec, % of time to task failure) at RPE 3, 5, and 7 for each subject.

Subject	CF		Time to CF (sec)			Time to CF (%)		
	kg	% MVIC	RPE 3	RPE 5	RPE 7	RPE 3	RPE 5	RPE 7
1	10.2	19.2	3.2	18.2	49.4	0.7	3.5	8.1
2	5.8	12.7	13.2	25.7	88.4	6.9	16.4	37.4
3	11.2	20.1	64.2	48.7	108.7	9.5	8.6	17.3
4	7.2	19.6	6.7	25.8	55.1	2.6	7.4	10.1
5	13.0	19.5	18.9	4.2	17.4	5.4	0.5	4.4
6	6.2	15.4	8.3	17.8	46.3	1.5	5.0	13.5
7	9.0	22.2	33.7	26.5	102.6	7.5	10.4	29.7
8	10.3	25.5	23.6	81.1	89.1	4.0	16.4	23.7
9	6.9	17.9	12.0	62.6	48.5	3.5	16.4	9.5
10	11.4	25.0	17.7	49.6	34.1	2.1	4.8	3.8
11	7.7	20.4	0.0	5.3	19.6	0.0	0.9	3.6
12	8.7	15.3	22.2	2.7	120.8	3.1	0.4	23.1
Mean	9.0	19.4	18.6	30.7	65.0	3.9	7.6	15.5
SD	2.3	3.8	17.2	24.8	35.4	2.9	6.2	11.0

Table 4. The absolute pre- and post- maximal voluntary isometric contraction values (kg) at each rating of perceived exertion (RPE).

Subject	RPE 3		RPE 5		RPE 7	
	pre (kg)	post (kg)	pre (kg)	post (kg)	pre (kg)	post (kg)
1	52.0	46.6	55.4	44.2	54.3	40.9
2	44.0	27.0	43.4	24.0	44.4	28.7
3	56.7	45.7	53.5	34.5	51.8	34.5
4	38.4	22.4	36.4	20.8	36.1	14.5
5	65.3	56.6	68.2	54.9	67.5	49.0
6	39.7	26.3	39.8	23.8	39.7	28.7
7	41.6	33.9	44.8	24.2	40.8	26.2
8	43.6	16.8	38.2	19.3	43.2	22.8
9	41.5	30.6	42.6	28.0	40.8	26.4
10	45.2	27.0	44.1	21.9	46.5	20.4
11	36.4	28.0	35.5	26.9	35.8	28.7
12	57.7	38.4	53.0	26.0	60.2	29.0
Mean	46.8	33.3	46.2	29.0	46.8	29.1
SD	9.0	11.5	9.6	10.6	9.8	9.1

Table 5. The results of the 21, separate, follow up one-way repeated-measures ANOVAs and post-hoc t-tests with a Bonferroni corrected alpha ($p<0.017$) for the changes in electromyographic amplitude (EMG AMP) (%MVIC) across time.

Time	EMG AMP (% MVIC)			Follow up one-way ANOVA			Post Hoc comparison		
	RPE 3	RPE 5	RPE 7	F value	Sig.	Effect size (η_p2)	RPE 3 and 5	RPE 3 and 7	RPE 5 and 7
0%	23.253 ± 11.715	22.871 ± 11.505	32.937 ± 15.693	4.810	0.018	0.304	0.900	0.068	* 0.006
5%	15.364 ± 6.117	20.788 ± 12.109	25.950 ± 9.569	5.198	0.014	0.321	0.071	* 0.002	0.252
10%	12.558 ± 3.511	16.127 ± 6.448	23.920 ± 9.436	21.018	<0.001	0.656	0.018	* <0.001	* 0.002
15%	11.164 ± 3.710	15.107 ± 7.219	19.761 ± 6.901	10.726	<0.001	0.494	0.035	* <0.001	0.059
20%	10.094 ± 2.972	14.559 ± 7.032	17.448 ± 7.019	11.484	<0.001	0.511	0.018	* <0.001	0.096
25%	10.965 ± 3.537	11.987 ± 4.476	16.688 ± 6.345	10.997	<0.001	0.500	0.314	* 0.002	* 0.010
30%	10.135 ± 3.828	10.791 ± 4.416	15.399 ± 5.682	14.294	<0.001	0.565	0.430	* <0.001	* 0.003
35%	8.920 ± 3.133	12.809 ± 5.577	16.516 ± 7.737	9.640	<0.001	0.467	* 0.007	* <0.001	0.123
40%	9.341 ± 4.112	11.991 ± 5.843	13.823 ± 4.599	5.103	0.015	0.317	0.056	* 0.014	0.228
45%	8.694 ± 2.630	11.051 ± 5.616	14.182 ± 5.320	8.423	0.002	0.434	0.093	*0.004	0.027
50%	9.220 ± 3.006	11.357 ± 5.279	15.062 ± 5.877	16.383	<0.001	0.598	0.047	* <0.001	* 0.003
55%	9.444 ± 3.801	10.660 ± 5.719	13.056 ± 5.973	4.459	0.024	0.288	0.318	0.031	0.040
60%	8.382 ± 2.609	9.252 ± 4.730	13.810 ± 5.479	14.061	<0.001	0.561	0.391	* <0.001	* 0.002
65%	8.158 ± 3.114	11.137 ± 5.456	13.587 ± 7.855	6.920	0.005	0.386	0.036	*0.008	0.110
70%	8.388 ± 2.787	11.570 ± 6.176	14.860 ± 8.853	7.270	0.004	0.398	0.035	0.017	0.023
75%	8.931 ± 3.473	11.135 ± 19.763	14.089 ± 7.675	1.253	0.305	0.102	0.142	0.031	0.105
80%	9.092 ± 3.209	11.800 ± 7.196	12.538 ± 7.219	4.254	0.027	0.279	0.063	0.058	0.287
85%	8.512 ± 3.110	11.583 ± 10.044	12.177 ± 4.768	3.084	0.066	0.219	0.022	* 0.008	0.547
90%	7.793 ± 2.284	11.997 ± 6.254	11.831 ± 6.374	5.541	0.011	0.335	0.020	* 0.012	0.907
95%	8.031 ± 2.590	10.397 ± 4.752	11.326 ± 6.979	2.062	0.151	0.158	0.087	0.045	0.676
100%	4.856 ± 2.018	8.862 ± 4.361	8.915 ± 3.820	10.012	<0.001	0.476	* 0.006	* 0.007	0.926

*Indicates significant differences in normalized EMG AMP between the RPE holds ($p<0.017$).

Table 6. The results of the 21, separate, follow up one-way repeated-measures ANOVAs and post-hoc t-tests with a Bonferroni corrected alpha ($p<0.017$) for the changes in neuromuscular efficiency values (%) across time.

Time	Neuromuscular efficiency (%)			Follow up one-way ANOVA			Post Hoc comparison		
	RPE 3	RPE 5	RPE 7	F value	Sig.	Effect size ($\eta_p 2$)	RPE 3 and 5	RPE 3 and 7	RPE 5 and 7
0%	0.509 ± 0. 344	0.566 ± 0.277	0.707 ± 0.554	1.971	0.163	0.152	0.395	0.139	0.225
5%	0.662 ± 0.264	0.673 ± 0.337	0.567 ± 0.177	1.975	0.163	0.152	0.874	0.018	0.164
10%	0.583 ± 0.266	0.625 ± 0.246	0.482 ± 0.149	6.005	0.008	0.353	0.182	0.068	* 0.009
15%	0.548 ± 0.263	0.565 ± 0.219	0.481 ± 0.130	1.327	0.286	0.108	0.684	0.341	0.137
20%	0.491 ± 0.226	0.507 ± 0.187	0.539 ± 0.222	0.481	0.625	0.042	0.711	0.313	0.604
25%	0.461 ± 0.222	0.508 ± 0.145	0.444 ± 0.189	1.168	0.330	0.096	0.293	0.725	0.144
30%	0.415 ± 0.200	0.466 ± 0.165	0.459 ± 0.169	1.168	0.329	0.096	0.183	0.282	0.826
35%	0.424 ± 0.195	0.376 ± 0.092	0.418 ± 0.194	0.634	0.540	0.054	0.378	0.889	0.351
40%	0.462 ± 0.422	0.373 ± 0.124	0.375 ± 0.153	0.683	0.515	0.058	0.414	0.428	0.924
45%	0.375 ± 0.139	0.361 ± 0.147	0.326 ± 0.159	0.889	0.425	0.075	0.750	0.195	0.318
50%	0.340 ± 0.157	0.317 ± 0.150	0.319 ± 0.133	0.239	0.789	0.021	0.456	0.626	0.956
55%	0.291 ± 0.107	0.309 ± 0.153	0.295 ± 0.147	0.167	0.847	0.015	0.589	0.893	0.718
60%	0.301 ± 0.137	0.326 ± 0.198	0.301 ± 0.124	0.180	0.837	0.016	0.507	0.994	0.697
65%	0.346 ± 0.328	0.263 ± 0.128	0.280 ± 0.123	0.747	0.486	0.064	0.395	0.378	0.681
70%	0.253 ± 0.123	0.278 ± 0.165	0.256 ± 0.162	0.258	0.775	0.023	0.570	0.893	0.620
75%	0.234 ± 0.081	0.261 ± 0.130	0.256 ± 0.125	0.397	0.677	0.035	0.506	0.445	0.883
80%	0.231 ± 0.106	0.229 ± 0.113	0.209 ± 0.103	1.008	0.381	0.084	0.912	0.143	0.277
85%	0.227 ± 0.115	0.210 ± 0.142	0.243 ± 0.098	0.504	0.611	0.044	0.551	0.649	0.387
90%	0.180 ± 0.076	0.179 ± 0.096	0.167 ± 0.104	0.140	0.870	0.013	0.988	0.652	0.630
95%	0.162 ± 0.057	0.142 ± 0.090	0.152 ± 0.065	0.586	0.565	0.051	0.346	0.467	0.638
100%	0.159 ± 0.095	0.082 ± 0.040	0.077 ± 0.025	10.757	<0.001	0.494	* 0.004	* 0.008	0.629

*Indicates a significant difference in neuromuscular efficiency between RPE holds ($p<0.017$).

Table 7. The results of the 20, separate, follow up one-way repeated-measures ANOVAs and post-hoc t-tests with a Bonferroni corrected alpha ($p<0.017$) for the changes in muscle oxygen saturation (SmO_2 [%]) across time.

Time	Muscle Oxygenation (%)			Follow up one-way ANOVA			Post Hoc comparison		
	RPE 3	RPE 5	RPE 7	F value	Sig.	Effect size ($\eta_p 2$)	RPE 3 and 5	RPE 3 and 7	RPE 5 and 7
5%	52.8 ± 9.9	45.6 ± 16.1	46.0 ± 13.2	1.641	0.217	0.130	0.135	0.179	0.939
10%	54.1 ± 9.1	46.9 ± 12.7	45.0 ± 9.5	3.492	0.048	0.241	0.067	0.025	0.632
15%	55.8 ± 8.4	52.0 ± 8.5	49.5 ± 7.0	2.399	0.114	0.179	0.206	0.076	0.366
20%	55.7 ± 8.7	53.6 ± 6.9	52.0 ± 6.4	0.907	0.418	0.076	0.444	0.299	0.454
25%	55.5 ± 8.7	53.6 ± 7.8	52.9 ± 6.7	0.562	0.578	0.049	0.462	0.421	0.703
30%	55.1 ± 8.7	54.5 ± 8.2	53.8 ± 7.1	0.130	0.879	0.012	0.800	0.685	0.736
35%	55.5 ± 8.4	54.4 ± 7.0	54.1 ± 7.3	0.157	0.885	0.014	0.686	0.675	0.870
40%	54.7 ± 8.2	54.3 ± 7.6	54.2 ± 7.0	0.021	0.979	0.002	0.885	0.866	0.962
45%	54.3 ± 8.2	54.1 ± 8.0	54.8 ± 6.1	0.037	0.964	0.003	0.948	0.862	0.760
50%	53.7 ± 7.9	53.9 ± 8.2	53.9 ± 4.9	0.006	0.994	0.001	0.942	0.924	0.980
55%	54.3 ± 6.6	54.1 ± 8.1	54.0 ± 5.4	0.011	0.989	0.001	0.935	0.885	0.954
60%	54.0 ± 6.5	54.2 ± 8.9	54.5 ± 5.6	0.021	0.979	0.002	0.939	0.837	0.894
65%	53.7 ± 7.1	54.7 ± 7.7	54.6 ± 5.4	0.100	0.905	0.009	0.726	0.735	0.989
70%	54.1 ± 6.7	54.9 ± 7.6	55.1 ± 4.7	0.118	0.889	0.011	0.774	0.674	0.859
75%	54.3 ± 6.7	55.2 ± 9.0	54.8 ± 5.4	0.085	0.919	0.008	0.736	0.816	0.826
80%	54.0 ± 8.3	54.8 ± 8.7	53.9 ± 6.2	0.081	0.923	0.007	0.779	0.983	0.580
85%	53.8 ± 7.5	54.6 ± 7.8	54.0 ± 6.1	0.052	0.949	0.005	0.804	0.958	0.701
90%	53.5 ± 6.3	55.2 ± 8.4	53.5 ± 5.6	0.359	0.702	0.032	0.535	0.997	0.329
95%	54.0 ± 6.2	55.0 ± 8.3	53.6 ± 6.1	0.204	0.817	0.018	0.703	0.904	0.317
100%	53.7 ± 7.6	54.9 ± 8.1	54.4 ± 7.8	0.124	0.884	0.011	0.671	0.831	0.691

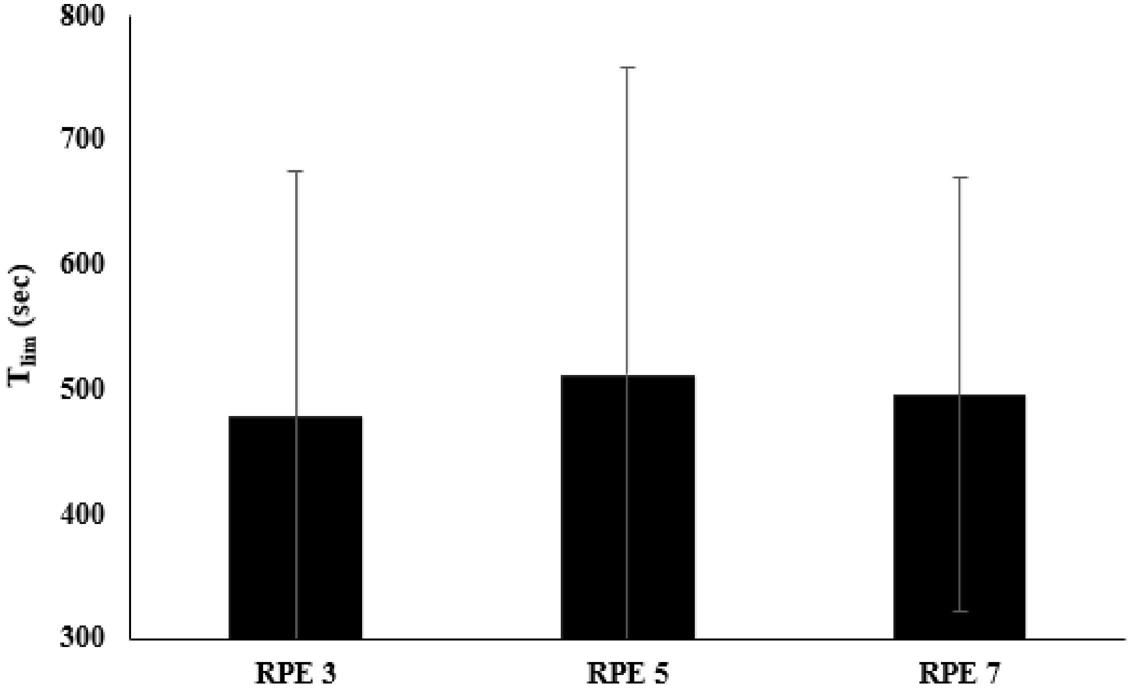

Figure 1 The comparison of time to task failure (T_{lim}) during the sustained, isometric, fatiguing handgrips holds anchored to rating of perceived exertion (RPE) 3, 5, and 7 ($p<0.05$).

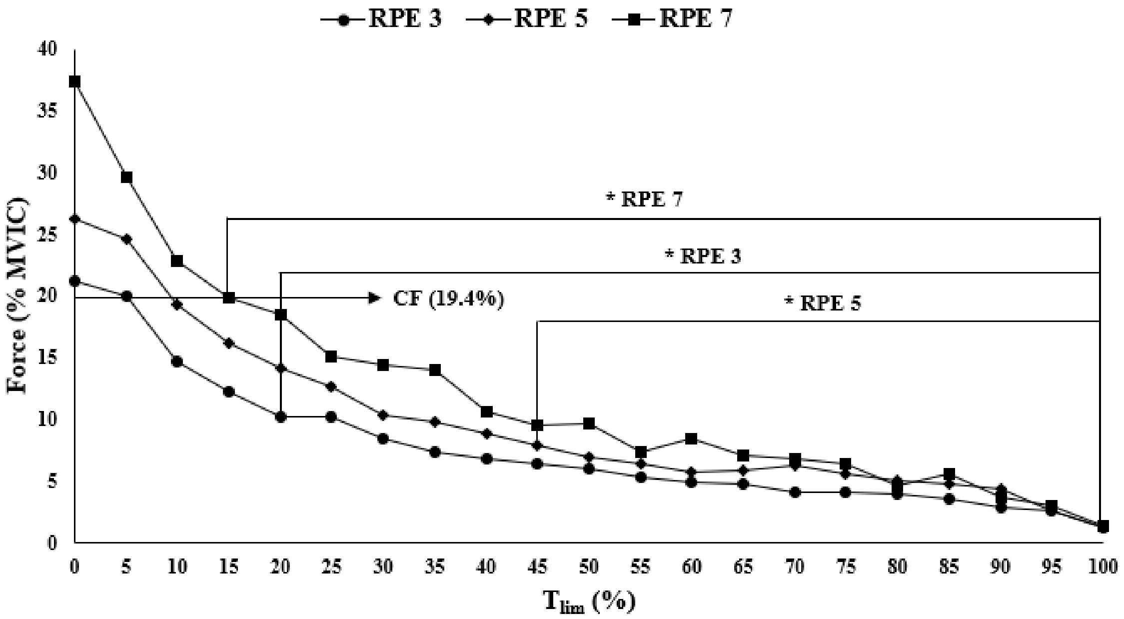

Figure 2. Time course of changes in the relative force (% pre-MVIC) during the fatiguing, isometric handgrip holds anchored to rating of perceived exertion (RPE) 3, 5, and 7.

* Indicates a significant ($p<0.0025$) decrease in force, relative to the initial time point (0% T_{lim}).

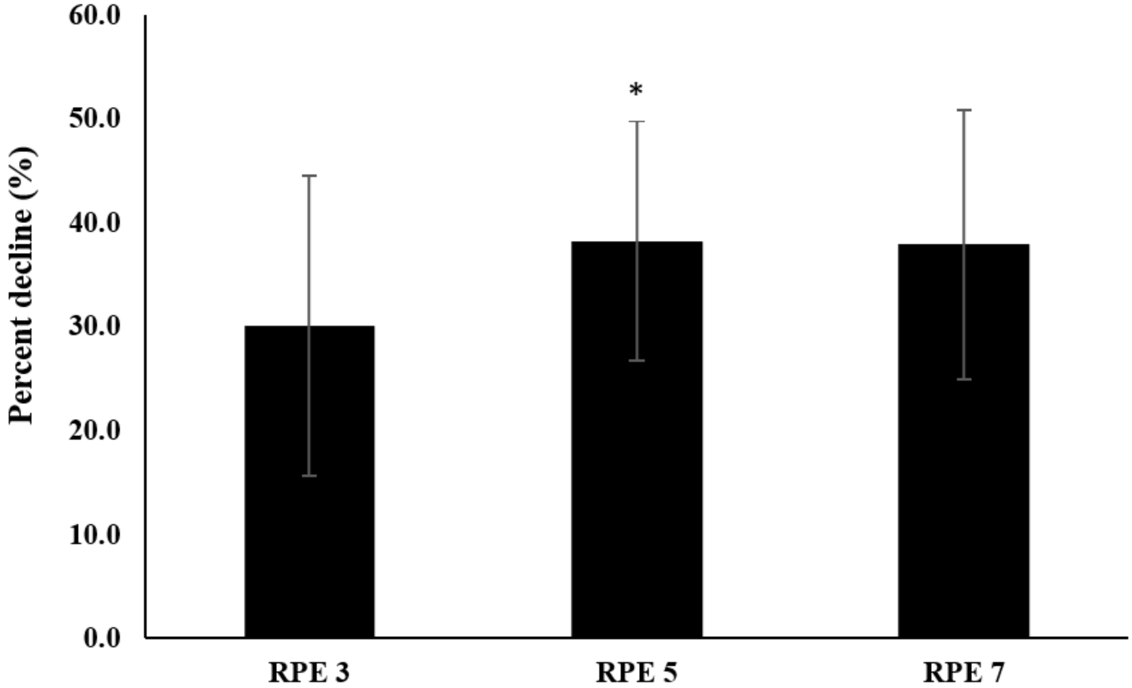

Figure 3. The performance fatigability values (%) for rating of perceived exertion (RPE) holds at 3, 5, and 7. * Indicates significantly greater than RPE 3 ($p<0.017$).

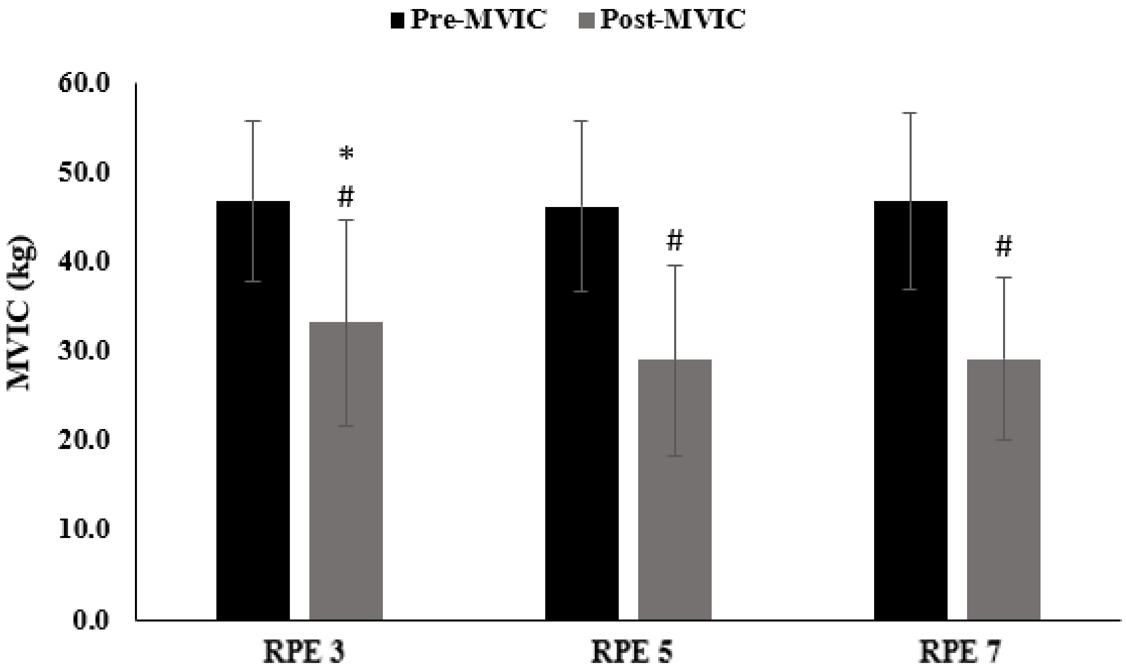

Figure 4. The pre- and post- maximal voluntary isometric contraction (MVIC) values at each rating of perceived exertion (RPE) 3, 5, and 7. * Indicates significantly greater post-MVIC value at RPE 3 than RPE 5 ($p<0.017$). # Indicates a significant decrease from pre- to post-MVIC for the respective RPE.

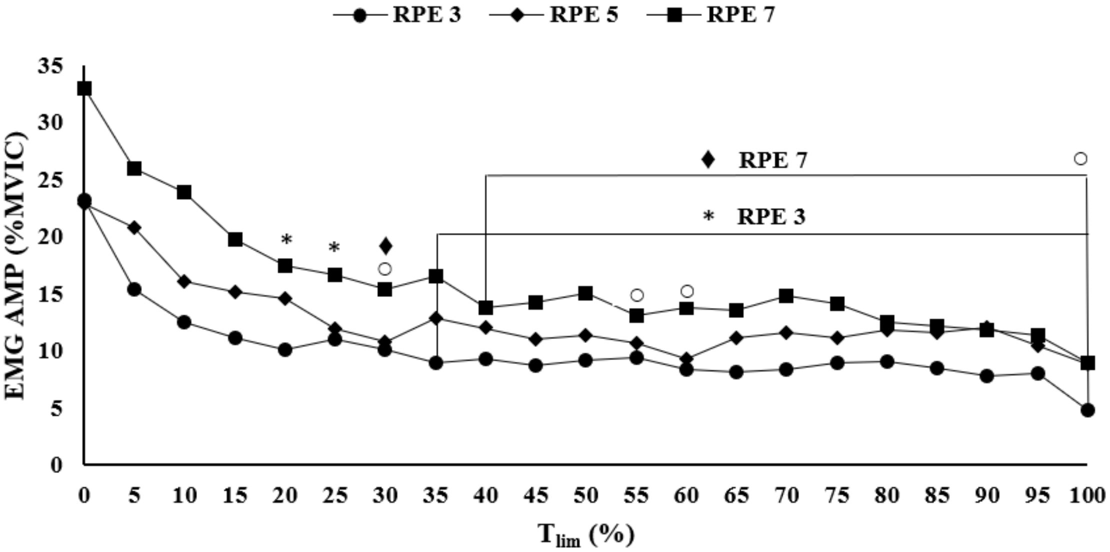

Figure 5. Time course of changes in the normalized electromyographic amplitude (EMG AMP) values (% pre-maximal voluntary isometric contraction [MVIC]) during the fatiguing, isometric handgrip holds anchored at RPE 3, 5, and 7. * Indicates a significant ($p<0.0025$) decrease in EMG AMP, relative to the initial time point (0% T_{lim}) for the rating of perceived exertion (RPE) 3 trial. ○ Indicates a significant ($p<0.0025$) decrease in EMG AMP, relative to the initial time point (0% T_{lim}) for the RPE 5 trial. ♦ Indicates a significant ($p<0.0025$) decrease in EMG AMP, relative to the initial time point (0% T_{lim}) for the RPE 7 trial.

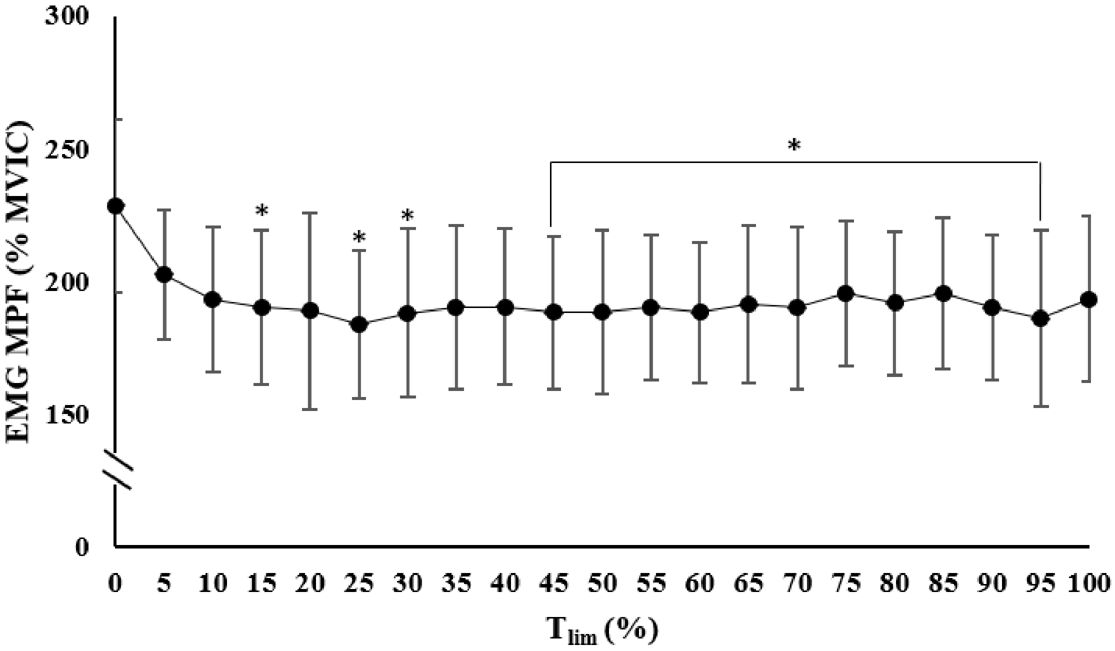

Figure 6. Time course of changes in normalized electromyographic mean power frequency (EMG MPF) (% pre- maximal voluntary isometric contraction [MVIC]), collapsed across rating of perceived exertion (RPE), during the fatiguing, isometric handgrip holds anchored to RPE 3, 5, and 7. * Indicates a significant ($p<0.0025$) decrease in EMG MPF, relative to the initial time point (0% T_{lim}).

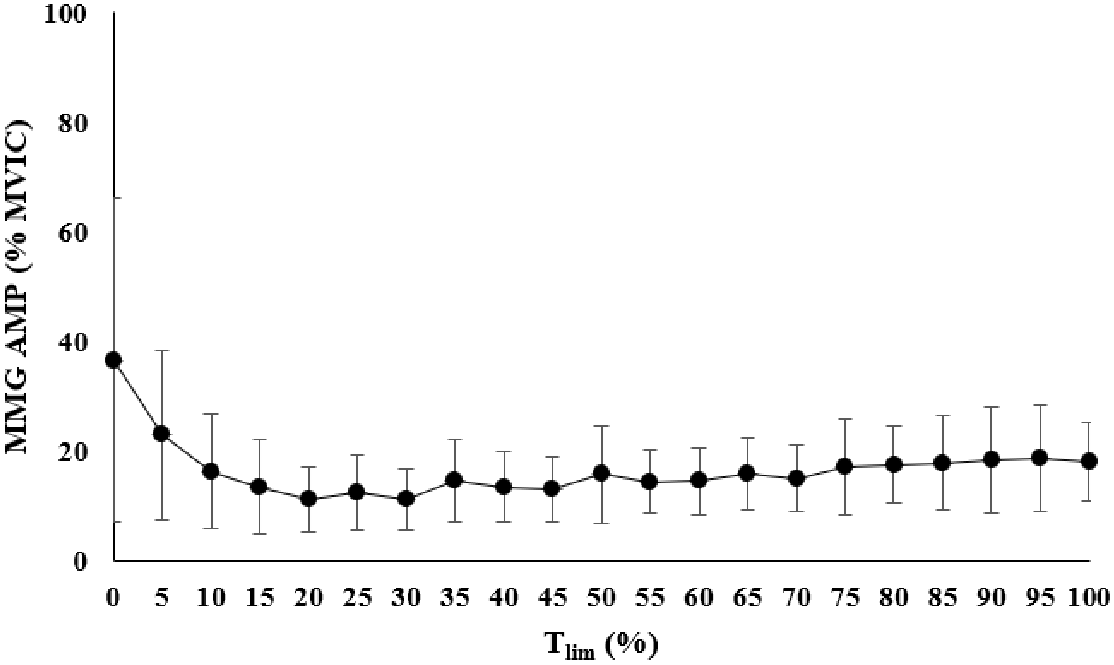

Figure 7. Time course of changes in normalized mechanomyographic amplitude (MMG AMP) (% pre- maximal voluntary isometric contraction [MVIC]), collapsed across rating of perceived exertion (RPE), during the fatiguing, isometric handgrip holds anchored to RPE 3, 5, and 7.

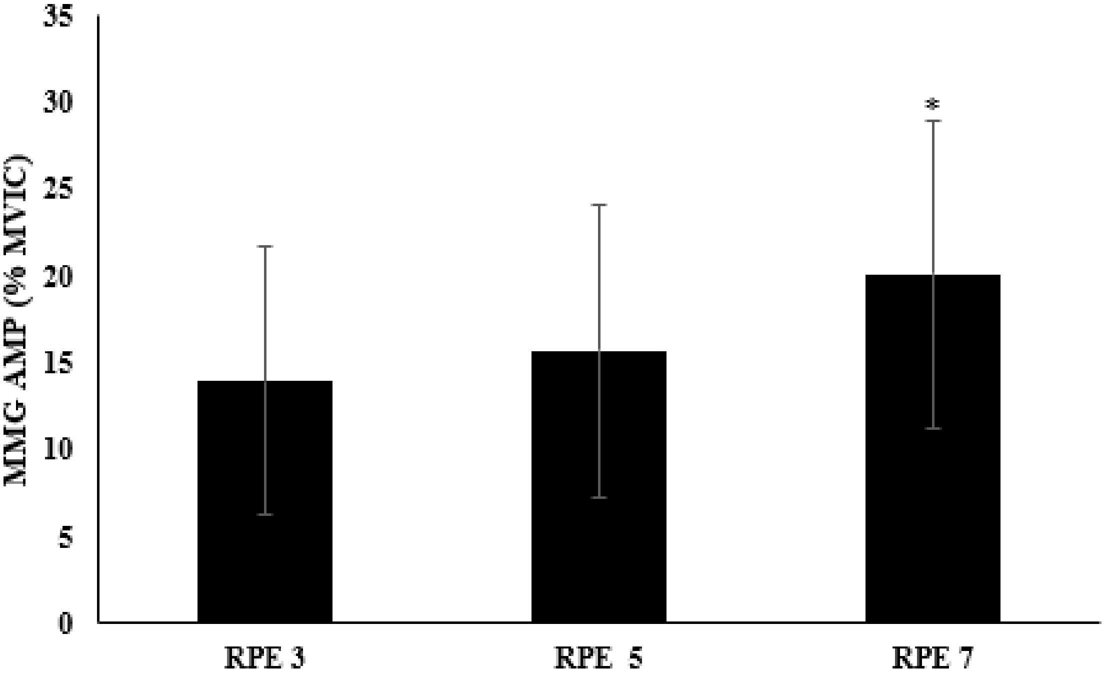

Figure 8. The comparison of mechanomyographic amplitude (MMG AMP) values (% pre- maximal voluntary isometric contraction [MVIC]), collapsed across 21 time points, among ratings of perceived exertion (RPE) 3, 5, and 7. * Indicates a significantly ($p<0.017$) greater MMG AMP at RPE 7 than RPE 3 and RPE 5.

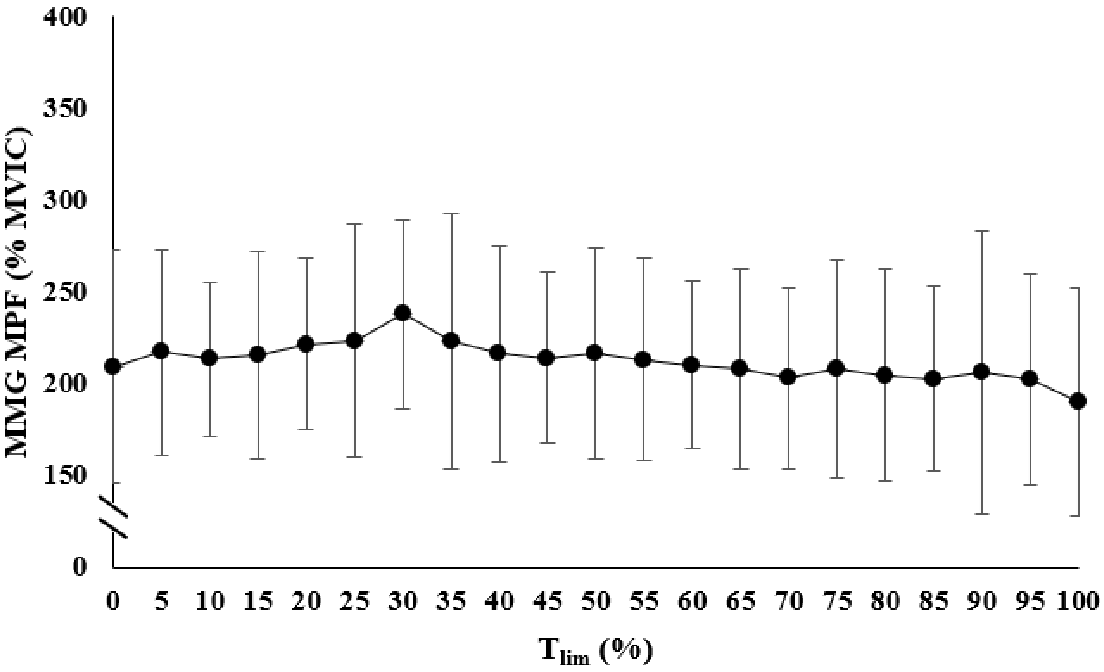

Figure 9. Time course of changes in normalized mechanomyographic mean power frequency (MMG MPF) (% pre- maximal voluntary isometric contraction [MVIC]), collapsed across RPE, during the fatiguing, isometric handgrip holds anchored to ratings of perceived exertion (RPE) 3, 5, and 7.

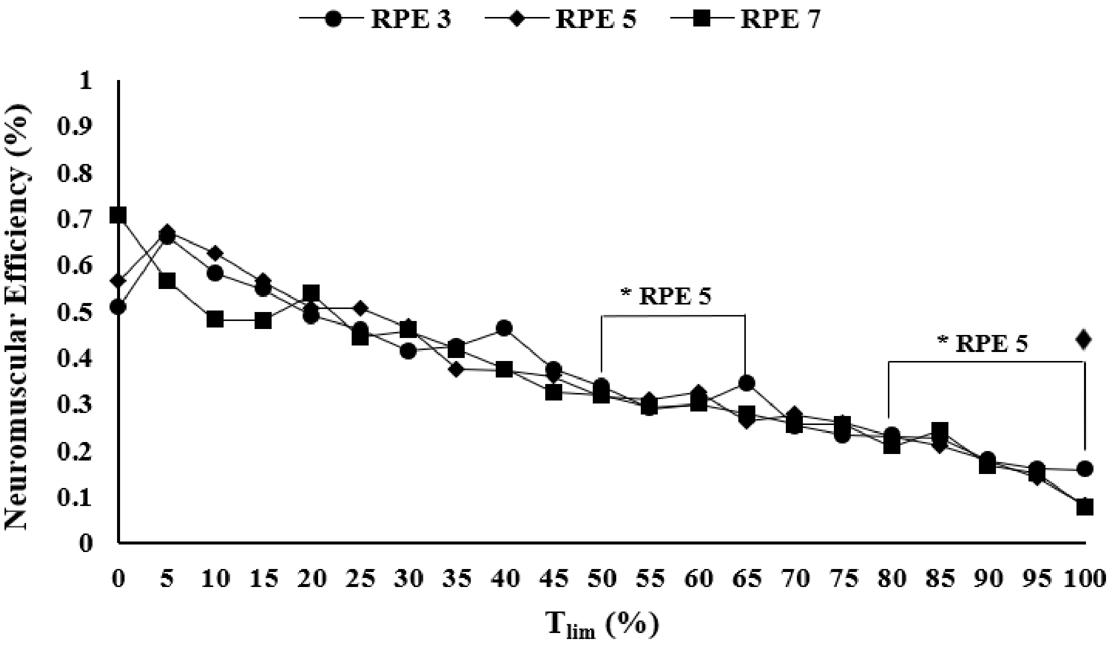

Figure 10. Time course of changes in the neuromuscular efficiency (normalized force/ normalized electromyographic amplitude) during the fatiguing, isometric handgrip holds anchored to ratings of perceived exertion (RPE) 3, 5, and 7. * Indicates a significant ($p<0.0025$) decrease in neuromuscular efficiency, relative to the initial time point (0% T_{lim}) for the RPE 5 hold. ♦ Indicates a significant ($p<0.0025$) decrease in neuromuscular efficiency value, relative to the initial time point (0% T_{lim}) for the RPE 7 hold.

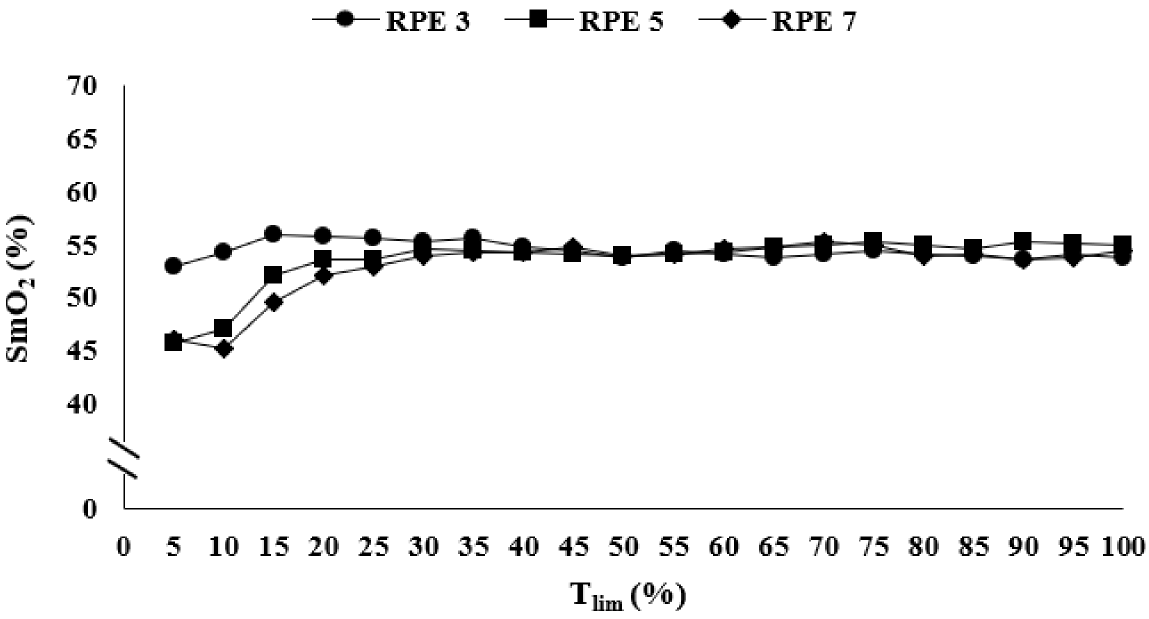

Figure 11. Time course of changes in muscle oxygen saturation (%SmO_2) responses during the fatiguing, isometric handgrip holds anchored to ratings of perceived exertion (RPE) 3, 5, and 7.

CHAPTER 5. DISCUSSION

5.1 Overview of Discussion

This study investigated the time to failure (T_{lim}), force alterations, neuromuscular responses (i.e., EMG, MMG), performance fatigability, and SmO_2 across time during fatiguing, isometric handgrip holds to failure anchored to RPE 3, 5, and 7. There were no significant differences in T_{lim} between RPE 3, 5, and 7 (p=0.569-0.744) (Figure 1), however, the patterns of changes in force, EMG AMP, EMG MPF, MMG AMP, MMG MPF, and SmO_2 within and between each RPE hold across time varied depending on three different time phases: initial (0-15%), mid (20-85%), and end (90-100%) phase. The time to CF during each RPE hold (RPE 3: 3.9±2.9% T_{lim}; RPE 5: 7.6±6.2% T_{lim}; RPE 7: 15.4±11.0% T_{lim}) was approximately at or below 15% T_{lim}, thus the initial phase (phase 1) was determined as 0-15% T_{lim} to examine the responses from the onset of exercise (0% T_{lim}) to the time point where there was an initial steep decline in force and force crossed CF. The end phase (phase 3) was determined as 90-100% T_{lim} because 90% T_{lim} was the time point where the force outputs from RPE 3, 5, and 7 converged and these patterns continued to 100% T_{lim}, the point where all of the subjects reached to 0kg force (at or around the last milliseconds of the task). The mid-phase (phase 2) was defined as the time periods after the CF (20% T_{lim}) and before the end phase (85% T_{lim}) where there were varying response among RPE 3, 5, and 7.

5.2 Force alterations and underlying mechanisms

5.2.1 Phase 1 (0% to 15 T_{lim})

In the current study, the initial forces at each RPE hold (RPE 3: 21.16±4.27%; RPE 5: 26.25±7.64%; RPE 7: 37.37±5.79%) were underestimated relative to the expected forces (% MVIC) corresponding to RPE 3, 5, and 7 (RPE 3: 30% MVIC, RPE 5: 50% MVIC, RPE 7: 70% MVIC) (Keller et al. 2022, Smith et al. 2021, West et al. 2005). The initial force values were consistent with or slightly lower than the initial relative force values reported in previous studies that have examined responses to RPE-clamp exercise (Smith et al. 2021, Keller et al. 2022). Specifically, the initial force values (% MVIC) were 59.7±15.0% anchored to RPE 7 during an isometric forearm flexion task (Smith et al. 2021), and 55.5%±10.0% during an isometric leg extension task anchored to RPE 8 (Keller et al. 2022). These previous findings (Keller et al. 2022, Smith et al. 2021) and those in the present study were supported by an RPE-clamp study by Tucker (2009), where it was suggested that there is an anticipatory or feedforward component that integrates previous experience and training, motivation, expected exercise duration, and physiological inputs prior to exercise (e.g., muscle glycogen, skin temperature), and these physio-psychological factors allow subjects to self-select an initial exercise intensity, which is expected to be optimal for the anticipated duration of exercise. At the onset of exercise, subjects in this study could perceive the sensations of tensions from handgrip-involved muscles (Pageaux 2016), and consciously adjust the forces to maintain the anticipated duration of exercise at each prescribed RPE. These reductions in force were associated with conscious decreases in central motor command, which are descending neural signals (i.e., efferent copy) from higher brain centers including primary motor- and pre-motor areas (Smith et al. 2022).

These initial responses (the first 5-10% of T_{lim}) may also be influenced by inhibitory feedback from mechanosensitive neurons (i.e., group III afferent neurons). Amann et al. (2020) suggested that primarily the group III afferent neurons detect mechanical alterations (e.g., stretch and the intensity of contraction) within the muscle and provide feedback to reduce central motor command. In the current study, although there were no significant changes across time for EMG or MMG AMP in the initial phase, qualitatively, the patterns of responses demonstrated ~52%, 34%, and 40% decreases in muscle excitation (EMG AMP) from 0 to 15% T_{lim} for RPE 3, 5, and 7, respectively (Table 5), and decrease from ~37% to 13% MVIC (64% change) for MMG AMP (motor unit recruitment) for each RPE (Figure 7). Together, these responses likely reflected the derecruitment of activated motor units (Amann et al. 2020, Tucker 2009). Thus, in the current study, as the exercise started, the integrated process of anticipatory regulation and group III afferent neurons may have resulted in the subjects' voluntary reduction in central motor command (Figure 5), which resulted in the derecruitment of motor units and voluntary decrease in force output during phase 1 (Figures 2,5,7).

Interestingly, although CF theoretically represents the highest force that can be maintained for a very long time without fatigue, subjects in the current study reached the CF at or before 15% of T_{lim} (~19 to 65 sec) during each RPE hold (RPE 3: 3.9±2.9% T_{lim}; RPE 5: 7.6±6.2% T_{lim}; RPE 7: 15.4±11.0% T_{lim}) (Table 3) and the subjects did not sustain the relative forces near the CF level, but instead demonstrated continuous decreases in force, relative to the initial value, for the majority of time points from 15% T_{lim} through phase 2 and phase 3 (Figure 2). After the initial adjustments (~5%-10% of T_{lim}) in phase 1 from the anticipatory overestimation and mechanosensitive neural feedback (group III afferents), it is possible that metabosensitive neurons (group IV afferents) provided additional feedback, whereby subjects continued to reduce force (Tucker 2009). Theoretically, exercise above CF or ~20-22% MVIC (Bonde-Peterson et al. 1975) results in alterations in the circulatory conditions in the muscle including reductions in blood flow and oxygen availability for energy metabolism that leads to the production of metabolic byproducts (e.g., inorganic phosphate and hydrogen ions). The buildup of metabolic byproducts has been shown to impact excitation-contraction coupling and reduce force generating capacity (Broman et al. 1985, Smith et al. 2022). Previous studies reported that blood flow started to decrease at forces higher than 20% MVIC (Barnes 1980) due to an increase in intramuscular pressure and occlusion of vascular beds (Thompson et al. 2007). In the present study, subjects started the handgrip holds above 20% MVIC for each RPE hold (RPE 3: 21.16±4.27%; RPE 5: 26.25±7.64%; RPE 7: 37.37±5.79%). Thus, it is possible that there were alterations in blood flow during the initial phase that resulted in metabolic byproducts and feedback, primarily from group IV afferents. Therefore, to maintain a constant RPE, the subjects continued to reduce the force to allow for sufficient oxygen availability without restriction of blood flow. The SmO_2 pattern of responses may partially support this mechanism (Figure 11). Although there were no significant differences in SmO_2 responses for any RPE hold across time, qualitatively, the patterns of responses for each RPE demonstrated an increase in SmO_2 from ~46 to 52% (13% change) for RPE 5, from ~46 to 50% (9% change) for RPE 7, and ~53 to 56% (6% change) for RPE 3, that corresponded with the phases of the most rapid force adjustments (phase 1 and early phase 2). This response was more pronounced at RPE 5 and 7 where the initial forces were higher and force adjustments were greater than at RPE 3. The SmO_2 responses then stabilized at ~55% for the remainder of the holds, which may have indicated that any initial reductions in blood flow to the active muscle were eliminated during the phase 1 force adjustments.

The EMG MPF responses in the present study may also support the hypothesis that metabolic byproducts (i.e. potassium, hydrogen ions) were generated during this initial phase. The EMG MPF is an indirect indicator of muscle fiber action potential conduction velocity (APCV) (Beck et al. 2004), and in this study, the EMG MPF significantly decreased at 15% T_{lim}, relative to the initial time point (0% T_{lim}) (Figure 6). Previous studies (Enoka and Duchateau 2008, Fortune and Lowery 2007, Keller et al. 2022) have suggested that the decrease in APCV is associated with increases in extracellular potassium and decreases in intracellular pH, and these metabolic perturbations lead to a loss of membrane excitability, resulting in slower conduction velocities of active muscle fibers (i.e., peripheral fatigue). Therefore, it is possible that the decrease in EMG MPF was to some degree affected by the generation and clearance of the metabolic byproducts occurred during phase 1. It is also possible that decreases in EMG MPF reflected derecruitment of motor units with higher APCV (Coburn et al. 2005). It is also important to note that there were no significant changes relative to the initial value (0% T_{lim}) in neuromuscular efficiency (NME) during the first phase (0-15% T_{lim}) for any RPE hold. Jones et al. (2016) suggested that NME (force/EMG AMP) is expected to decrease in fatigue-induced conditions during submaximal levels of muscle contraction. Thus, it is hypothesized that group III mechanosensitive afferent neurons were primarily responsible for the decrease in force during phase 1 but is likely that some degree of metabolic perturbation also began during phase I that were not sufficient to affect NME but may have contributed to the decrease in force during phase 2 via group IV afferent feedback.

There were different responses in force across RPE 3, 5, and 7. The patterns of force production between each RPE hold was hierarchical, such that RPE 7>5>3 during the phase 1 (Figure 2). The initial force (0% T_{lim}) for RPE 7 was greater than RPE 5 and RPE 3, the magnitude of decrease in force for RPE 7 (-17.4 kg; 47% change) was greater than RPE 5 (-10.1 kg; 39% change) and RPE 3 (-8.9 kg, 42% change) from 0% to 15% T_{lim}, and the forces for RPE 7 were greater than RPE 3 at all-time points in phase 1 (0-15% T_{lim}) (Table 2). During this time, muscle excitation (EMG AMP) for RPE 7 was greater than RPE 5 at 0% and 10% T_{lim}, and RPE 3 from 5% to 15% T_{lim} (Table 5). Interestingly, the NME of RPE 7 was lower than RPE 5 at 10% T_{lim} (Table 6). Therefore, we hypothesize that greater afferent feedbacks from group III/IV neurons and anticipatory regulation for RPE 7 led to a greater amount of force reduction and decrease in the efficiency of neuromuscular system compared to RPE 3 and RPE 5 during phase 1. Between RPE 5 and RPE 3, the forces for RPE 5 were greater than RPE 3 at 10% and 15% T_{lim} (Table 2), however, there was no differences between RPE 5 and RPE 3 in EMG AMP at any time point (0 to 15% T_{lim}) (Table 5). Moreover, there was no significant difference in NME between RPE 5 and RPE 3 (Table 6). Therefore, these findings may suggest that during the phase 1, even though subjects produced more force at RPE 5 than RPE 3, the fatigue-related differences and changes (i.e., muscle excitation and neuromuscular efficiency) were minimal between each RPE, which may indicate that subjects were similarly affected by the afferent feedbacks from group III/IV neurons and anticipatory regulation for RPE 5 and RPE 3.

5.2.2 Phase 2 (20% to 85 T_{lim})

In the current study, the forces gradually decreased from 20% to 85% T_{lim} (Figure 2). Specifically, from the end time point of phase 1 (15% T_{lim}), the forces continuously decreased, relative to 0% T_{lim}, from 15%, 45%, and 20% T_{lim} for RPE 7, RPE 5, and RPE 3, respectively (Figure 2). Importantly, 40% T_{lim} was the first time point where the forces were not significantly different from each other for RPE 3, 5, and 7 (Figure 2). From this point, RPE 5 and 7 continued to demonstrate similar levels of force, although the force at RPE 7 was greater than at RPE 3 for the majority of timepoints in phase 2. There were no noticeable differences between RPE 3 and 5. Smith et al. (2022) used a similar time period of phase 2 (5% to 95% T_{lim}) to explain the patterns of changes in force that reflect unique mechanism of fatigue relative to the initial and final phases, during sustained, isometric forearm flexion to task failure at three different elbow joint angles of 75˚,100˚, and 125˚. Smith et al. (2022) reported that the gradual force reduction during the phase 2 was mainly affected by an accumulation of metabolites caused by a metabosensitive group IV afferent neurons with a small amount of group III feedback (Tucker 2009), because the force values across the majority of phase 2 were related to the intensity (> 22% MVIC) of the onset of blood flow restriction (Bonde-Peterson et al. 1975) which are associated with intramuscular metabolic perturbations. In the present study, however, the forces across the phase 2 were below CF and were less than 20% MVIC at all-time points from 20% to 85% T_{lim} for RPE 3, 5, and 7 (Figure 2). Moreover, the SmO_2 responses were not significantly different, relative 0% T_{lim}, from 20% to 85% T_{lim} (Figure 11), which may indicate that the active muscles were working with sufficient oxygen availability without a restriction of blood flow during the phase 2. Thus, despite differences in force levels for RPE 7 and 3, the mechanism regulating RPE may be similar due to the fact that exercise was performed below CF for all three RPEs. In the present study, there were significant decreases in EMG MPF, relative to 0% T_{lim}, across the majority of phase 2 (25%, 30% and from 45% to 85%) for each RPE, and there were significant decreases in NME for RPE 5, with overlapping patterns of responses with RPE 3 and 7. These findings may suggest that there were still metabolic perturbations that remained from phase 1, leading to a loss of membrane excitability and, thus, slowing conduction velocity (Fortune and Lowery 2007, Enoka and Duchateau 2008, Keller et al. 2022) even if the production and clearance of the metabolic byproducts could continuously occur during phase 2. Therefore, it is plausible that the force reductions during phase 2 were affected by an integration of intramuscular metabolic disturbances from metabosensitive and mechanosensitive group IV and III afferent neurons. It is also possible that the corollary discharge model may partially explain the force reductions in phase 2. Previous authors (Marcora 2009, Pageaux 2016) have described that, according to the corollary discharge model, the perception of effort is regulated by a neuronal process of an efferent copy of internal signals derived from the centrifugal motor commands (i.e., activity of premotor and motor areas of brain regulating voluntary muscle contractions) that impact perception. Marcora (2009) reported that when muscle fatigue is generated independently from exercise-induced metabolites, the perception of effort would result from the efferent copy of central motor command. Pageaux (2016) also noted that according to the corollary discharge model, afferent feedback is not considered to be a sensory signal influencing the perception of effort. In this study, the relatively low force levels during phase 2 (< 20% MVIC) suggested that it was unlikely there was continued production of metabolic byproducts and, thus, the corollary discharge model may, in part, explain continued force reductions. However, the decreases in EMG MPF and NME during this phase indicated that there may have been residual effects of metabolic perturbations from the time spent above CF in phase 1, particularly for RPE 5 and 7, that carried over into phase 2 and provided continued group IV/III neural afferent feedback. Thus, it seems plausible that force regulation during phase 2 may be explained by a combination of the corollary discharge model and afferent feedback.

5.2.3 Phase 3 (90% to 100 T_{lim})

The current study showed that the patterns of gradual force reductions from phase 2 resulted in convergence of forces for RPE 3, 5, and 7 at 90% of T_{lim} that was carried through task failure in phase 3. Specifically, the forces for each RPE 3, 5, and 7 significantly decreased, relative to 0% T_{lim}, from 90% T_{lim} to the task failure (100% T_{lim}) (Figure 2). Moreover, there were no significant differences between forces for any of the RPEs during phase 3 (Table 2), which demonstrated that the gradually decreased forces for each RPE hold converged prior to task failure which occurred at a relatively low level of force for the last time point average (~1.32% MVIC, collapsed across RPEs). Importantly, the T_{lim} was not different for any of the RPE holds (Figure 1). This finding may be best explained by the sensory tolerance limit, whereby each subject continuously reduced force to reach task failure at similar times for each RPE hold (Hureau et al. 2018, Keller et al. 2021).

The integration of efferent and afferent signals in regulating the perception of effort is explained by the sensory tolerance limit. Hureau et al. (2018) proposed the sensory tolerance limit model, suggesting that a combination between the sum of afferent feedbacks (e.g., active muscles, respiratory muscles, and indirectly involved muscles and organs) the corollary discharges associated with central command are integrated within the brain, and ultimately regulate work rate or the magnitude of central motor drive to enable the voluntary muscle actions to be tolerable. In other words, the sensory tolerance limit is described as a global negative feedback loop resulting in a task failure via both afferent feedback and feedforward (i.e., anticipatory) pathways (Hureau et al. 2018). Specifically, in this study the central motor commands (i.e. feedforward) via corollary discharge pathways may have provided information to regulate force to maintain the constant RPEs, and all afferent feedback, mainly from the metabosensitive group IV and III afferent neurons, would require that subjects continuously adjust the magnitude of central motor drive, and ultimately lead to the zero force output at task failure (Hureau et al. 2018) (note: all subjects reached 0kg force in the last millisecond of the tasks).

In the present study, and NME patterns demonstrated a continuous pattern of decrease that was most pronounced for RPE 5, relative to the initial value, and the EMG MPF remained lower than the initial value through 95% of T_{lim} during phase 3 (Figure 6 and 10). Based on the SmO_2 response which remained unchanged (Figure 11), it appears that the RPE holds were not affected by a restriction of blood flow and because the intensity of muscle contractions was very low (<5% MVIC) during the phase 3 (Table 2). It is possible that, in response to afferent feedback from the metabolic perturbations from phase 1 (i.e. increases in extracellular potassium and decreases in intracellular pH), the subjects continued to voluntarily reduce force until force reached 0kg. Like phase 2, it is also possible that voluntary reduction in force to maintain the required RPE was the result of efferent copies of central motor command. Robertson and Marino (2016) suggested that the lateral prefrontal cortex (LPFC) is where the conscious decision to continue or terminate an exercise occurs because LPFC can integrate physiological (i.e. afferent feedback) and psychological (e.g. motivational and emotional) responses during exercise. Robertson and Marino (2016) proposed that once LPFC receives this physio-psychological information, the decision to adjust the exercise intensity or terminate a task is sent to the premotor area and the basal ganglia via feedforward pathways. Therefore, during phase 3, the subjects in the present study would be affected by their individual sensory tolerance limits from the cumulative effects of phase 1 and 2 that caused them to continuously reduce force and finally reach zero force output at a similar time to task failure in phase 3. Interestingly, in the current study, the researcher stopped exercise when the subjects reached zero force output for each RPE hold. At this point, all subjects perceived that they were still producing force, which means that subjects did not give up or terminate the exercise by themselves. This finding suggested that there were dissociations in actual force production versus perceptual responses at the end moment of task failure.

5.3 Performance Fatigability

The performance fatigability in the current study was characterized as global fatigue [i.e., decrease in absolute force (kg) or percent (%) from pre- to post-MVIC force]. Previous studies (Enoka and Duchateau 2016, Keller et al. 2021) have cautioned against dichotomizing global fatigue into peripheral and central fatigue, and rather argued that examinations of performance fatigability should be characterized as “real-world performance” including T_{lim}, RPE, and changes in MVIC forces. In the present study, performance fatigability [percent decline (%)] for RPE 5 was greater than RPE 3, and there was no significant difference between RPE 5 and 7 (Figure 3). It should be noted that performance fatigability for RPE 3 and 7 were not significantly different using a conservative post-hoc test, however, the magnitude of performance fatigability between 5 and 7 (38.2% and 37.9%) differed by <0.5%, and both reflect a % decline that was ~8% greater than at RPE 3. Thus, these findings were interpreted as reflecting similar levels of performance fatigability at RPE 5 and 7 that were relatively greater than RPE 3. Thomas et al. (2018) proposed that performance fatigability is related to the exercise intensity since greater exercise intensities will result in the greater recruitment and concomitant stress of a greater volume of active muscle and that exercise performed above the CF results in a similar magnitude of performance fatigability that is greater than the performance fatigability for exercise preformed below the CF. Burnley et al. (2012) suggested that below CF, peripheral fatigue would develop due to a reduction in muscle glycogen and Ca^{2+} sensitivity, not metabolic byproducts (i.e. hydrogen ions, inorganic phosphate), while fatigue for exercise performed above CF results from a combination of peripheral (metabolic byproducts) and central factors (reduced central command). In the current study, subjects sustained each RPE hold below CF for the majority of the T_{lim}, or ~7 to 8 min (Figure 2), thus it seems likely that factors influencing peripheral fatigue occurred, independent of the production of metabolic byproducts (Burnley et al. 2012). However, the time spent above CF likely influenced the mechanisms and magnitude of fatigue at each RPE. The time spent above CF was intensity dependent such that RPE 3 spent the least amount of the total T_{lim} (~19 sec) above CF, while subjects were above CF for an average of 65 sec at RPE 7 and 31 sec at RPE 5. It has been well established that the adenosine triphosphate (ATP) and creatine phosphate (CP) system (i.e., ATP-PCr system) provides the immediate and primary source of energy for the force development for ~10s (Knuttgen and Komi 2003). Depending on the intensity and duration of exercise, anaerobic glycolysis provides energy for resynthesis of ATP thereafter, and in events that last at least 60s, the aerobic metabolism will begin to more fully contribute energy reconstitution (Knuttgen and Komi 2003). Theoretically, CF reflects the intensity where blood flow and oxygen availability is reduced from increased intramuscular pressure during contractions (Bonde-Peterson et al. 1975, Thompson et al. 2007, Hendrix et al. 2009). Thus, above this point, after the intial contributions of the ATP-PCr system, anaerobic glycolysis would continue to be the primary activated energy system beyond the first minute (~3min), until metabolic byproduct accumulation limits force production (e.g. reduction in excitation-contraction coupling) or force is reduced sufficiently (below CF) where aerobic energy production is used for continued exercise. Therefore, based on the relative intensity and duration, it is likely that the metabolic perturbations above CF for each RPE hold mainly came from reliance on the ATP-PCr (i.e., inorganic phosphate) and anaerobic glycolysis (i.e., hydrogen ions) systems in phase 1 and early in phase 2. As previously noted, the metabolic perturbations in phase 1 (and portions of phase 2 for RPE 3 and 5) may have contributed to continuous reductions in APCV for each RPE hold (Figure 6) and decreases in NME in phases 2 (Figure 10) (Broman et al. 1985, Fortune and Lowery 2007, Enoka and Duchateau 2008, Keller et al. 2022).

There were RPE dependent responses in the magnitude of changes in force, muscle excitation, and motor unit recruitment during the holds that may have differentially affected the degree of performance fatigability. Across phases 1 and 2, force production and muscle excitation (EMG AMP) for RPE 7 were generally greater than for RPE 3, with few differences between RPE 5 and 7, or 5 and 3, and MMG AMP (motor unit recruitment) was greater, collapsed across time, for the hold at RPE 7 compared to RPE 5 and 3 (Figure 8). These greater levels force and muscle excitation for RPE 5 and 7, compared to RPE 3 likely resulted in fatigue to a larger portion of the motor unit pool. Thus, compared to RPE 3, the greater amount of time spent above CF in phase 1 for RPE 5 and 7, the greater sustained forces in phase 1 for RPE 5, and in phase 1 and 2 for RPE 7, may explain the differences in performance fatigability. Specifically, a combination of peripheral fatigue (i.e lower NME leading to excitation-contraction coupling failure and significant reductions in APCV) in response to metabolic byproducts as well as decreases in central motor drive from afferent feedback and/or corollary discharge may explain the ~38% decline in force from pre- to post-MVIC measures for RPE 5 and 7, while the decline in force capacity for RPE 3 may have resulted from peripheral factors, independent of metabolic byproducts. Taken together, despite similar times to task failure among the three RPE holds, performance fatigability for RPE 5 and 7 were similar and 8% (~38% vs 30%) greater than RPE 3, which was likely a result of the time spent above CF during phase 1 and early phase 2 of the RPE holds and the relatively higher force levels for RPE 5 (phase 1) and 7 (phase 1 and 2), compared to RPE 3.

5.4 Neuromuscular Responses (Motor Unit Activation Strategies)

The neuromuscular responses (EMG AMP, MMG AMP, MMG MPF) during the phase 1 did not exhibit the typical fatigue-related changes demonstrated for constant force exercise [i.e., increases in muscle excitation (EMG AMP) and motor unit recruitment (MMG AMP), and decreases in global, firing rate of the unfused, active motor units (MMG

MPF)] (Keller et al. 2022) (Figure 5,7, and 9). Specifically, although there was no significant difference in phase 1 from 5% to 15% T_{lim}, relative to 0% T_{lim} for EMG AMP (Figure 5), MMG AMP (Figure 7), and MMG MPF (Figure 9), qualitatively, there were decreased patterns of response for EMG AMP (42% change, collapsed across RPEs) and MMG AMP (63% change, collapsed across RPEs), while MMG MPF remained relatively constant. These changes in EMG and MMG AMP indicated that there was likely a derecruitment of motor units that tracked the voluntary reductions in force as subjects were able to freely reduce force to maintain the required RPE. The lack of change in MMG MPF (firing rate) may have reflected the relatively low intensity (% MVIC) of the RPE holds. Beck et al. (2004) have suggested that during low intensity isometric muscle actions (approximately 10% to 50%), MMG MPF remains relatively steady since the force production is mainly from the recruitment of slow-twitch motor units with the accompanied firing rates, not from fast-twitch motor units and therefore, there would be little change in the global motor unit firing rate of active motor units. In the current study, the forces for each RPE hold during the phase 1 were approximately 10% to 40%. Thus, it is possible that slow-twitch motor units were primarily recruited to meet the relatively lower intensity of the initial forces and the force production did not rely on the recruitment of fast-twitch motor units with accompanied higher firing rates, which resulted in no differences in global, unfused firing rates of muscle fibers (MMG MPF). Thus, the motor unit activation strategy in phase 1 likely reflected the derecruitment of motor units and the maintenance of the global, firing rate of the unfused, active motor units of the as force was reduced.

During phase 2 and 3, EMG AMP decreased, relative to 0% T_{lim}, for the holds at RPE 3, 5, and 7 (Figure 5), which suggested that muscle excitation continuously decreased as the subjects voluntarily reduced the force outputs (Smith et al. 2022). However, this was not accompanied by any further quantitative decreases in MMG AMP. Although there is conflicting evidence (Perry et al. 2003), it has been suggested that during fatiguing contractions there is a decrease in muscular compliance due to increased muscle thickness, fluid content, and intra-muscle pressure and this decrease in muscular compliance may attenuate the MMG amplitude (Perry et al. 2002, Perry et al. 2003, Beck et al. 2005). Thus, the lack of changes in MMG AMP may have reflected the competing influences of derecruitment (which decreases in MMG AMP) and decreases intramuscular pressures (which tends to increase MMG AMP) as force was reduced (Perry et al. 2003). Moreover, MMG MPF (i.e., global, firing rate of unfused, active motor units) did not change at any time points from 20% to 100% $T_{lim,}$ collapsed across RPEs (Figure 9). This finding suggested that like the phase 1, during the phase 2 and 3, the slow-twitch motor units with its low firing rates were primarily recruited without engaging fast-twitch motor units, and thus resulted in no differences in the global firing rate of the unfused, activated motor units during phase 2 and 3.

5.5 Summary

The present study demonstrated that complex physio-psychological factors regulated the force and the magnitude of central motor drive throughout the isometric, fatiguing, handgrip holds anchored to three RPE 3, 5, and 7. It is likely that the force alterations, the accompanying metabolic and/or neuromuscular responses, and performance fatigability were affected by different mechanisms depending on the phase (1 vs. 2 and 3) and/or RPE (3 vs. 5 vs. 7).

During phase 1, the integrated process of anticipatory (i.e. feedforward) regulation and mechanosensitive, group III afferent neurons (i.e. inhibitory feedback) was likely primarily responsible for the decrease in force. However, based on the relative intensities (>20% MVIC; above CF) of muscle contractions and the decrease in EMG MPF (reduced APCV) responses, it is possible that metabolic perturbation also began during phase 1, and feedback primarily from metabosensitive, group IV afferents would lead to continuous force reductions after the initial adjustments of phase 1 and carried over into phase 2. The relatively lower SmO_2 responses that qualitatively increased during phase 1 for RPE 5 and 7, but to a much lesser degree for RPE 3 suggested that there may have been some restriction in local muscle blood flow. These findings may demonstrate that the subjects continued to freely reduce the force to allow for sufficient oxygen availability without restriction of blood flow. Thus, it is likely that the generation and clearance of the metabolic byproducts occurred during phase 1 and those effects were carried into phase 2 and 3. Between the three RPE holds during phase 1, the greater afferent feedbacks from group III/IV neurons and anticipatory regulation for RPE 7 would lead to a greater amount of force reduction and decrease in NME compared to RPE 3 and RPE 5. Moreover, no differences in EMG MPF and NME responses between RPE 5 and 3 may indicate that subjects were similarly affected by the afferent feedback from group III/IV neurons and anticipatory regulation for RPE 5 and 3.

The continued force reductions during phase 2 may have been driven by continued afferent feedback as well as feedforward mechanisms. In phase 2, the forces were below CF (< 20% MVIC), there continued to be reduced for each RPE hold. During this phase, the SmO_2 responses were stable. These responses, along with the relative force levels suggested that this phase was not likely associated with continued generation of significant intramuscular metabolic byproducts. However, it is likely that the perturbations from phase I continued to alter cellular environments which may explain the continued decrease in EMG MPF and NME during phase 2. These effects were particularly apparent for RPE 5 and 7 and may have provided continued group III/IV afferent feedback during phase 2. The decision to reduce forces may also be affected by feedforward pathways via corollary discharges (i.e., brain activity of premotor and motor areas regulating voluntary muscle contractions) that is independent from exercise-induced metabolites. During phase 2, the sum of afferent feedback and the corollary discharges would be integrated within the brain and regulate the magnitude of central motor drive (i.e., force reduction). The integration of feedback and feedforward mechanism likely continued into phase 3 and are used to describe the sensory tolerance limit.

During phase 3, the subjects would be affected by their individual sensory tolerance limit from the cumulative effects of phase 1 and 2 that resulted in continuously decrease forces and finally reach zero force output (i.e., task failure) at a similar time between each RPE hold. It is likely that throughout the holds, the central motor command via corollary discharge pathways would continuously be facilitated, and LPFC may have received and integrated all physio-psychological, afferent feedback, and informed the decision to continuously reduce force. Interestingly, in the present study, subjects did not decide to terminate the exercise since all subjects perceived that they were still producing force when the researcher stopped the exercise at zero force output. This finding suggested that there were dissociations in actual force production versus perceptual responses at the end moment of task failure.

The performance fatigability in this study would be affected by a combination of peripheral and central factors that developed throughout the task depending on time (phase 1-3), force intensity (below or above CF), and RPE (RPE 3,5, and 7). During the time spent above CF, it is possible that both peripheral (i.e., metabolic byproducts-induced excitation-contraction coupling failure and slow APCV) and central factors (i.e., reduced central command from afferent feedback and corollary discharge); in contrast, during the time spent below CF, it is likely that peripheral fatigue (i.e. reduction in muscle glycogen and Ca^{2+} sensitivity) occurred. Therefore, the relatively greater levels of performance fatigability at RPE 5 and 7 than RPE 3 may have resulted from a greater amount of time spent above CF in phase 1 for RPE 5 and 7, the greater sustained forces in phase 1 for RPE 5, and in phase 1 and 2 for RPE 7 compared to RPE 3.

For the neuromuscular responses (EMG AMP, MMG AMP, MMG MPF), it is possible that the decreased EMG and MMG AMP (i.e., derecruitment of motor units) tracked the voluntary reduction in force as subjects were able to freely reduce force to maintain the predetermined RPEs during phase 1. Moreover, the lack of change in MMG MPF may be due to the recruitment of slow-twitch motor units with the accompanied firing rates, without a significant contribution from fast-twitch motor units, thus there would be little change in the global motor unit firing rate of active muscle fibers. During phase 2 and 3, the decreases in patterns of responses for EMG AMP and the lack of change in MMG MPF continued to task failure. Therefore, it is likely that the underlying motor unit activation strategies of EMG AMP and MMG MPF that started in phase 1 were similarly applied into phase 2 and 3. However, the lack of changes in MMG AMP during 2 and 3 may reflect that there would be competing impacts of derecruitment of motor units and increased muscular compliance, potential due to decreased intramuscular pressures as force was reduced in the active muscle.

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PUBLICATIONS

1. Benitez, B., Dinyer-McNeely, T.K., McCallum, L., **Kwak, M**., Succi, P.J., & Bergstrom, H.C. Electromyographic and Mechanomyographic Responses of the Biceps Brachii During Concentric and Eccentric Muscle Actions to Failure at High and Low Relative Loads. *European Journal of Applied Physiology*, March 2023.

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HONORS AND AWARDS

2023 Spring	John Edwin Partington and Gwendolyn Gray Partington Scholarship
2023 Spring	College of Education Scholarship
2023 Spring	Kinesiology and Health Promotion Research Award
2022 Fall	Kinesiology and Health Promotion Research Award
2022 Spring	Kinesiology and Health Promotion Research Award