THE INFLUENCE OF OXYGEN DELIVERY AND OXYGEN UTILIZATION ON THE DETERMINANTS OF EXERCISE TOLERANCE

by

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B.A., Washburn University, 2009
M.S., Kansas State University, 2011

AN ABSTRACT OF A DISSERTATION

submitted in partial fulfillment of the requirements for the degree

DOCTOR OF PHILOSOPHY

Department of Anatomy and Physiology
College of Veterinary Medicine

KANSAS STATE UNIVERSITY
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Abstract

The physiological mechanisms determining the tolerable duration of exercise dictate human physical accomplishments across all spectrums of life. Despite extensive study, these specific mechanisms, and their dependence on oxygen delivery and oxygen utilization, remain, to a certain extent, undefined. The purpose of this dissertation was to test the overarching hypothesis that muscle contraction characteristics (i.e., intensity of contraction, muscle contraction-relaxation duty cycle, etc.) alter oxygen delivery and oxygen utilization, which directly influence the power-duration relationship and fatigue development, and therefore, exercise tolerance. To accomplish this, specific interventions of altered muscle contraction-relaxation duty cycle and blood flow occlusion were utilized. In the first investigation (Chapter 2), we utilized low and high muscle contraction-relaxation duty cycles to alter blood flow to the active skeletal muscle, demonstrating that critical power (CP) was reduced with the high muscle contraction-relaxation duty cycle due to a reduction in blood flow, while the curvature constant (W’) was not altered. The second investigation (Chapter 3) utilized blood flow occlusion to show that CP was reduced and W’ increased for blood flow occlusion exercise conditions compared to control blood flow exercise conditions. The final investigation (Chapter 4) utilized periods of blood flow occlusion during and post-exercise to reveal greater magnitudes of peripheral and central fatigue development during blood flow occlusion exercise compared to control blood flow exercise. Moreover, this investigation demonstrated that W’ was significantly related to the magnitude of fatigue development. Collectively, alterations in oxygen delivery and oxygen utilization via muscle contraction characteristics and blood flow occlusion directly influence CP and the magnitude of fatigue development. However, W’ does not appear to be influenced by manipulations in oxygen delivery and oxygen utilization, per se. Rather, W’ may be determined by the magnitude of fatigue accrued during exercise, which is dependent upon oxygen delivery and oxygen utilization. The novel findings of the investigations presented in this dissertation highlight important physiological mechanisms that determine exercise tolerance and demonstrate the need for interventions that improve oxygen delivery and oxygen utilization in specific populations, such as those with chronic heart failure or chronic obstructive pulmonary disease, to improve exercise tolerance.
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Approved by:

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Dr. Thomas J. Barstow
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Preface

Chapters 2–4 of this dissertation represent original research articles that have been published following or are currently in the peer-review process (citations may be found below). They are reproduced here with permission from the publishers.

**Broxterman RM, Ade CJ, Wilcox SL, Schlup SJ, Craig JC, and Barstow TJ.**

**Broxterman RM, Ade CJ, Craig JC, Wilcox SL, Schlup SJ, and Barstow TJ.**

**Broxterman RM, Craig JC, Smith JR, Wilcox SL, Jia C, Warren S, and Barstow TJ.**
Chapter 1 - Introduction

The physiological mechanisms determining the tolerable duration of activity have dictated human physical accomplishments throughout history. The notion of a relationship between the intensity of an exercise and the tolerable duration of that exercise dates back as early as the fourth century (59, 60). This relationship constrains human performance across all spectrums of life, from elite athletes to disease populations (such as those with chronic heart failure or chronic obstructive pulmonary disease) where activities of daily living and the quality of life are contingent upon the tolerable intensities of exercise.

The relationship between progressively increasing power outputs and decreasing exercise duration was first described by A.V. Hill in the early 1900s (25, 26) and formally characterized in 1965 by Monod and Scherrer (41). This robust power-duration relationship is now commonly characterized using a two-parameter hyperbolic mathematical model to obtain the asymptote (critical power (CP)) and the curvature constant (W’) (27, 31, 58). CP represents the highest attainable steady-state for energy production without continually drawing upon W’ (13, 15, 41, 42, 45, 55), while W’ has been purported to be determined by intramuscular energy stores (38-40), the accumulation of fatigue inducing metabolites (12, 19, 21, 33), and/or the magnitude of the severe-intensity exercise domain (9, 55).

Furthermore, CP is the highest intensity in which a physiological steady-state can be achieved for oxygen uptake ($\dot{V}_{O_2}$), blood flow, intramuscular concentrations of phosphocreatine ([PCr]), inorganic phosphate ([Pi]), and hydrogen ions ([H$^+$]) (14, 33, 46). As such, CP demarcates the boundary between the heavy- and severe-intensity exercise domains, distinguishing sustainable and unsustainable intensities of exercise (45).

Elucidating the mechanisms of fatigue has been a primary focal point for understanding the physiological determinants of exercise tolerance. Fatigue is defined as a reversible decrease in the
ability to produce voluntary maximal force (2, 17, 24) and can be quantified as peripheral or central in origin. Peripheral fatigue occurs at or distal to the neuromuscular junction, while central fatigue occurs proximal to the neuromuscular junction (2, 24). Accumulating evidence suggests that exercise tolerance above CP is limited by the development of fatigue (3, 4, 10, 16, 23, 49, 50, 53). Amann et al. (7) merged the concepts of a “critical threshold” of muscle fatigue, a “sensory tolerance limit” of group III/IV muscle afferent feedback, and central motor drive into a paradigm describing the mechanisms determining exercise tolerance. This integrative paradigm highlights the importance of feedback from group III/IV muscle afferent fibers to the central nervous system regarding the physiological state of the working skeletal muscle (1, 34, 35) in determining the “critical threshold” of fatigue (6, 24) and the point where central motor drive becomes limited or limiting (54). This physiological paradigm is purported to limit the magnitude of fatigue developed during exercise as a component of homeostasis (5, 7, 50). Recently, Pethick et al. (44) demonstrated, that beyond a decrease in torque-generating capacity, fatigue also limits the ability of the neuromuscular system to adapt to external perturbation. Thus, the magnitude of fatigue developed during exercise dictates the exercise tolerance.

Oxygen delivery and oxygen utilization are important determinants of the power-duration relationship and the development of fatigue during exercise. CP has been demonstrated to be aerobic in nature and influenced by alterations in the fraction of inspired oxygen content (15, 42, 55). Although it has been demonstrated that blood flow can be impeded or occluded due to the increased intramuscular pressure accompanying muscle contraction (28, 36, 48, 52) and that rhythmic alterations in blood flow occur throughout the muscle contraction-relaxation cycle (8, 20, 48, 57), the influence of muscle contraction-relaxation alterations in blood flow on CP has not been investigated. Less is understood regarding the influence of oxygen delivery and oxygen utilization on W’, but this parameter has traditionally been associated with anaerobic energy production due to early findings that interventions
affecting anaerobic energy production altered $W'$ (18, 19, 30, 38, 39) and interventions affecting oxygen delivery and oxygen utilization did not alter $W'$ (22, 29, 41, 42, 47). Moreover, these lines of thinking were greatly influenced by Monod and Scherrer (41) who in originally characterizing the power-duration relationship speculated on the influence of blood flow occlusion by stating, “Factor b [CP] is linked to circulatory conditions in the muscle. For when the dynamic work is performed under arterial cuff, the maximum work becomes constant whatever be the time after which exhaustion occurs. The maximum work is then equal to factor a [$W'$]…” However, this speculation remains to be empirically tested and more recent evidence suggests that $W'$ may be associated with the severe-intensity exercise domain (9, 55) and the $\dot{V}O_2$ slow component (19, 32, 43, 56). Moreover, $W'$ has been shown to be decreased during hyperoxia compared to normoxia (55). The magnitude of peripheral fatigue developed during exercise has been demonstrated to be independent of alterations in oxygen delivery and oxygen utilization for large muscle mass activity (4, 49), but not for small muscle mass activity (11, 37, 51). Collectively, these findings suggest that oxygen delivery and oxygen utilization influence CP, while the influence on $W'$ and the magnitude of fatigue development is equivocal.

The findings of Burnley et al. (10) that peripheral fatigue development occurs above CP, in combination with the fatigue paradigm of Amann et al. (7), suggest that CP may represent the exercise intensity above which exercise tolerance is limited by the attainment of the “sensory tolerance limit”. Therefore, the mechanisms determining $W'$ may be related to the magnitude of fatigue developed during severe-intensity exercise. In addition, a constant “sensory tolerance limit” for a given exercise condition would constrain the amount of work that could be performed above CP and the degree of intramuscular metabolic perturbation, which may explain the consistency in these variables associated with the complete utilization of $W'$ (33, 41, 42, 46, 55).
There are currently no investigations that have altered the muscle contraction-relaxation duty cycle or utilized blood flow occlusion to examine the influence of oxygen delivery and oxygen utilization on the power-duration relationship and the magnitude of fatigue development. The purpose of this dissertation was to test the overarching hypothesis that muscle contraction characteristics (i.e., intensity of contraction, muscle contraction-relaxation duty cycle, etc.) alter oxygen delivery and oxygen utilization, which directly influence the power-duration relationship and fatigue development, and therefore, exercise tolerance.
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Chapter 2 - Influence of duty cycle on the power-duration relationship for handgrip exercise: observations and potential mechanisms
Summary

The highest sustainable rate of aerobic metabolism [critical power (CP)] and the finite amount of work that can be performed above CP (W’) were determined under two muscle contraction duty cycles. Eight men completed at least three constant-power handgrip tests to exhaustion to determine CP and W’ for 50% and 20% duty cycles, while brachial artery blood flow (\(\dot{Q}_{\text{BA}}\)) and deoxygenated-[hemoglobin+myoglobin] (deoxy-[Hb+Mb]) were measured. CP was lower for the 50% duty cycle (3.9 ± 0.9 W) than the 20% duty cycle (5.1 ± 0.8 W; p < 0.001), while W’ was not significantly different (50% duty cycle: 452 ± 141 J vs. 20% duty cycle: 432 ± 130 J; p > 0.05). At the same power output, \(\dot{Q}_{\text{BA}}\) and deoxy-[Hb+Mb] achieved higher end-exercise values for the 20% duty cycle (9.87 ± 1.73 ml·s\(^{-1}\); 51.7 ± 4.7 μM) than the 50% duty cycle (7.37 ± 1.76 ml·s\(^{-1}\), p < 0.001; 44.3 ± 2.4 μM, p < 0.03). These findings indicate that blood flow influences CP, but not W’.
Introduction

The notion of an increase in exercise duration with progressively decreasing power outputs dates back at least to the early 20th century (34, 35) and potentially as early as the 4th century (81, 82). This robust power-duration relationship is now commonly characterized using a hyperbolic mathematical model to obtain the asymptote (critical power, CP) and the curvature constant (W’) (36, 43, 80). CP demarcates the boundary between the heavy- and severe-exercise intensity domains, as it is the highest intensity in which a physiological steady-state can be achieved [i.e., for oxygen uptake (\(\dot{V}_{O_2}\)) (60), blood flow (inferred from (14)), intramuscular concentrations of phosphocreatine [PCr], inorganic phosphate [Pi], and hydrogen ion [H\(^+\)] (45)]. W’ represents a finite work capacity that can be performed above CP and has traditionally been associated with ‘anaerobic’ metabolism (13, 21, 26, 50, 51, 53). This interpretation is supported by [Pi], [H\(^+\)], and [PCr] consistently achieving ‘critical levels’ upon exhaustion (12, 45, 60, 75). Alternatively, W’ may be determined by the magnitude of the severe-domain (i.e., the range between CP and \(\dot{V}_{O_2\text{max}}\)) (8, 75) and has been associated with the \(\dot{V}_{O_2\text{slow}}\) component (21, 44, 55, 76). This interpretation is supported by several studies that demonstrated a decrease in W’ with interventions that increased CP (40, 74, 75). It has been speculated that these decreases in W’ were a result of the interventions increasing CP disproportionately to \(\dot{V}_{O_2\text{max}}\) and therefore decreasing the magnitude of the severe-domain (8, 75). Although the mechanism(s) determining W’ are not fully understood, it is clear that exercise tolerance for any activity performed at an intensity above CP is limited by the magnitude of W’ with exhaustion ensuing upon complete utilization of W’ if the power output is not lowered to an intensity equal to or below CP.

Monod and Scherrer (1965), in originally characterizing the power-duration relationship, suggested that CP is dependent upon the circulatory conditions in the muscle, while W’ is determined by intramuscular ‘anaerobic’ (with the exception of O\(_2\) stores) mechanisms. Subsequent experiments have
revealed that CP is dependent upon the rate of aerobic ATP production (i.e., O_2 delivery and O_2 utilization) (18, 36, 43, 54, 75), while W’ (at least in part) is dependent upon ‘anaerobic’ ATP production (33, 41, 50, 51, 72). Thus, any intervention altering O_2 delivery (i.e., reduced blood flow) to the active skeletal muscle would be expected to alter CP, with presumably no (or little) affect on W’.

The increased intramuscular pressure accompanying muscle contraction can exhibit a profound influence on blood flow as a result of blood vessel compression, increased impedance to blood flow, and possible occlusion of blood flow (38, 47, 64, 68). The muscle contraction-relaxation cycle yields rhythmic alterations in intramuscular pressure, and therefore blood flow, with the majority of blood flow occurring during the relaxation period when intramuscular pressure is low (4, 25, 64, 79). Robergs et al. (1997) suggested that the relaxation period blood flow may be important in determining the attainment of a steady-state metabolic rate. The muscle contraction duty cycle (time under tension/total contraction time) directly impacts blood flow, such that with high duty cycles (high time under tension relative to total contraction time) blood flow to the active skeletal muscle becomes limited (6, 7), while blood flow is not compromised at low duty cycles (low time under tension relative to total contraction time) even with increased contraction frequencies (23, 56, 71). Collectively, these results demonstrate that the muscle contraction duty cycle directly influences blood flow to the active skeletal muscle.

We are aware of no study to date that has examined the influence of alterations in blood flow due to the muscle contraction-relaxation cycle on the parameters of the power-duration relationship. Therefore, the aim of the current study was to manipulate blood flow using muscle contraction duty cycles in order to assess the dependence of CP and W’ on blood flow. We hypothesized that 1) CP would be higher for the 20% duty cycle compared to the 50% duty cycle, while W’ would remain unchanged. Further, when the same power output was repeated at both duty cycles, 2) blood flow would
be higher for the 20% duty cycle than the 50% duty cycle, but 3) deoxy-[Hb+Mb] and EMG measurements would achieve similar end-exercise values for both duty cycles.
Methods

Subjects

Eight healthy men (age: 24.8 ± 2.5 yrs, height: 173.7 ± 4.6 cm; weight: 77.1 ± 14.6 kg) volunteered to participate in this study. Subjects reported to the Human Exercise Physiology Laboratory with at least 24 h between testing sessions and having abstained from vigorous activity within that 24 h period. All experimental procedures in the present study were approved by the Institutional Review Board of Kansas State University and conformed to the standards set forth by the Declaration of Helsinki. Prior to testing, each subject was informed of the overall protocol along with the potential risks involved. Each subject then provided written informed consent and completed a health history evaluation.

Experimental Protocol

All testing was performed on a custom-built handgrip ergometer. The handrail of the ergometer was attached to a pneumatic cylinder by means of a cable-pulley system and provided a fixed linear displacement of 4 cm. Resistance was set by pressurizing the pneumatic cylinder and work was accomplished by compressing the air within the cylinder when the handrail was moved. Power output was calculated as 

\[ P = R d f \cdot k^{-1} \]

where \( P \) is power in Watts (W), \( R \) is resistance in kg, \( d \) is displacement in meters, \( f \) is contraction frequency, and \( k \) is the constant 6.12 for the conversion of kg·m·min\(^{-1}\) to W. When seated at the ergometer the subject grasped the handrail so that the forearms were at approximately heart level and the elbows were slightly bent. A contraction frequency of 20 contractions·min\(^{-1}\) was utilized for both duty cycles so that each total contraction cycle duration was maintained at 3.0 s. Thus any set resistance would produce the same power output for both duty cycles. The 50% duty cycle consisted of a 1.5 s contraction period (in which the handrail was raised with concentric muscle contraction and lowered with eccentric muscle contraction) followed by a 1.5 s
relaxation period. The 20% duty cycle consisted of a 0.6 s contraction period (in which the handrail was raised with concentric muscle contraction and then immediately released) followed by a 2.4 s relaxation period (Figure 2.1). Both duty cycles had the same duration of concentric contraction and total contraction cycle, while the 20% duty cycle had no eccentric contraction period and therefore a longer duration of time without muscle tension. The eccentric contraction period duration was altered specifically to minimize any metabolic differences between duty cycles, while emphasizing blood flow differences (see Discussion). Audio recordings set with the specific timing for each duty cycle were used along with feedback provided by an investigator monitoring the tests to ensure correct timing. Subjects completed three familiarization trials per duty cycle prior to data collection to aid in correct, consistent production of the contraction-relaxation timing. All testing sessions were continued until exhaustion, determined as the inability to complete three consecutive contraction cycles.

A peak incremental test for each duty cycle was completed in a randomized order during the initial two testing sessions. These tests were initiated at 1.0 W and the power output was increased by 0.5 W·min\(^{-1}\) until exhaustion. The peak power (P\(_{\text{peak}}\)) was recorded as the highest power output for which at least 30 s of the stage was completed. The P\(_{\text{peak}}\) was utilized to determine the power outputs for the subsequent constant-power testing sessions that would elicit exhaustion between 2-15 min. Subjects completed a minimum of three randomly ordered constant-power tests per duty cycle in which the time-to-exhaustion (T\(_{\text{lim}}\)) was recorded. After the initial three constant-power tests, the data were fit with the two-parameter hyperbolic model and the goodness-of-fit was analyzed. If the goodness-of-fit data did not meet the a priori criteria (see Data Analysis) a fourth testing session was conducted in an attempt to lower the parameter standard error values. A power output that elicited exhaustion between 2-5 min for the 50% duty cycle was repeated for the 20% duty cycle, such that any differences in the physiologic
responses between duty cycles could be examined without the confounding influence of different power outputs (i.e., metabolic rates).

**Measurements**

**Doppler ultrasound**

The raw blood velocity profiles were measured using Doppler ultrasound (Vivid 3, GE Medical Systems, Milwaukee, WI, USA) operating in pulse wave mode at a Doppler frequency of 4.0 MHz with a phased linear array transducer probe operating at an imaging frequency of 6.7 MHz, and were stored for post-hoc analysis. For all testing sessions the Doppler gate was set to the full width of the brachial artery to ensure complete insonation and all Doppler velocity measurements were corrected for the angle of insonation, which was adjusted to be less than 60 degrees. Measurements were made 2-5 cm above the antecubital fossa to avoid the bifurcation of the brachial artery. A bifurcation was not seen in the two-dimensional image, suggesting that all Doppler measurements were made greater than 1 cm from the bifurcation, as previously utilized in our laboratory (2). Brachial artery diameters were measured in the transverse axis using two-dimensional sonography.

**Near-infrared spectroscopy**

The oxygenation characteristics of the flexor digitorum superficialis were determined using a frequency-domain multi-distance NIRS system (Oxiplex TS, ISS, Champaign, IL, USA). The principles and algorithms of the NIRS technology were reviewed by Gratton (29) and have previously been described by Ferreira et al. (23). Briefly, this device consists of eight light-emitting diodes (LED) operating at wavelengths of 690 and 830 nm (four LEDs per wavelength) with one detector fiber bundle and LED-detector separation distances of 2.0, 2.5, 3.0, and 3.5 cm. The NIRS data were collected at 50
Hz and stored for post-hoc analysis. After locating the flexor digitorum superficialis of the right arm using EMG and palpation, the NIRS probe was secured longitudinally along the belly of the muscle. The position of the probe was then marked with indelible ink for reproducible placement throughout the study. The NIRS probe was calibrated prior to each test according to the manufacturer’s recommendations using a calibration block with known absorption and scattering coefficients. Calibration was confirmed on a separate block with different absorption and scattering coefficients.

*Electromyography*

Surface electromyography (EMG) measurements were obtained from the flexor digitorum superficialis in the left forearm. The single differential EMG electrode (Trigno EMG, Delsys Inc., Boston, MA, USA) consists of four silver contact bars (5 x 1 mm) arranged in a 2 x 2 orientation. The electrode was positioned over the belly of the muscle, as determined by palpation and strong electrical activity when the fingers were flexed, but not with ulnar or radial deviation. This site was then marked with indelible ink for reproducible placement of the electrode throughout the study. The EMG data were sampled at 1000 Hz and stored for post-hoc analysis.

*Data Analysis*

*Determination of the power-duration relationship*

The parameters of the power-duration relationship (CP and W’) were determined with the two-parameter hyperbolic model \( t = \frac{W'}{P - CP} \), where \( t \) is time in s, \( W' \) is the finite work capacity in Joules (J), \( P \) is power in W, and \( CP \) is critical power in W. The data from the initial three constant-power tests were fit with the hyperbolic model and the goodness-of-fit was assessed. A fourth constant-power test was conducted if the parameter standard error (SE) was greater than 10% of the parameter.
value for either CP or W’. When applied to whole-body exercise (i.e., cycling) this ‘acceptable’ margin of error allows for the anaerobic work capacity to be accurately estimated by W’ (36). There has been no established margin of error for small muscle mass exercise (i.e., handgrip) and therefore we chose to use the 10% cutoff.

**Doppler Ultrasound**

Mean blood velocity ($V_{\text{mean}}$, cm·s$^{-1}$) was defined as the time-averaged mean velocity over each 3 s contraction cycle. Brachial artery blood flow ($Q_{BA}$) was calculated using the product of $V_{\text{mean}}$ and vessel cross-sectional area (CSA). Brachial artery diameters were measured every minute throughout each test and were used to calculate vessel CSA in cm$^2$ (CSA = πr$^2$). The $Q_{BA}$ data were analyzed using one contraction cycle (i.e., 3 s) at the time points 0 s, 46.5 s, 91.5 s, while three consecutive contraction cycles (i.e., 9 s) were utilized for the end of each subsequent minute, at the equivalent time within the 20% duty cycle to the time of end-exercise for the 50% duty cycle (matched-time), and at end-exercise. $Q_{BA}$ data were also measured 9 s post-exercise using a 3 s average.

**NIRS**

The NIRS data were processed using 3 s averages throughout each testing session. During the first minute of exercise and at 91.5 s the NIRS data were analyzed for each contraction cycle, while 3 consecutive contraction cycles were used for each subsequent minute, at 50% matched-time, and at end-exercise. At 9 s post-exercise the NIRS data were analyzed using a 3 s average. The deoxy-[hemoglobin+myoglobin] (deoxy-[Hb+Mb]) is relatively insensitive to changes in blood-volume (16, 22, 28) and has been used to reliably estimate the fractional oxygen extraction (17, 19, 22, 23, 28). The device used in the present study provides absolute concentrations (μM) for deoxy-[Hb+Mb] and
oxygenated-[hemoglobin+myoglobin] (oxy-[Hb+Mb]), which may be combined to provide total-[hemoglobin+myoglobin] (total-[Hb+Mb]). The dynamic reduced scattering coefficients were measured throughout the tests and were incorporated in all of the NIRS data calculations.

**EMG**

The raw EMG data were processed with a band-pass filter (30-300 Hz) and each electrical burst corresponding to a muscle contraction was detected using a custom-designed computer program. The EMG signal amplitude characteristics were analyzed via integrated EMG (iEMG), a measure of motor unit recruitment and motoneuron firing rate, which typically increases as the muscle fatigues (20, 27). The EMG signal frequency characteristics were analyzed via mean power frequency (MPF), a measure of the muscle action potential conduction velocity, which typically shifts to lower frequencies as the muscle fatigues (31). During the first minute of exercise and at 91.5 s the EMG data were analyzed for each contraction cycle, after which the end of each subsequent minute, 50% matched-time, and end-exercise were analyzed using three consecutive contraction cycles.

**Estimation of oxygen consumption**

To investigate the relationship between O$_2$ delivery and O$_2$ extraction across duty cycles we used the model put forth by Wagner and colleagues (65, 77, 78) which integrates perfusive O$_2$ delivery [Fick Principle, $\dot{V}_{O_2} = Q(\text{arterial-venous O}_2 \text{ content difference})$, where $Q$ is blood flow] and diffusive O$_2$ capacity [Fick’s Law of Diffusion, $\dot{V}_{O_2} = D_{O_2}(P_{\text{cap}O_2} - P_{\text{mit}O_2})$, where $D_{O_2}$ is the oxygen diffusing capacity of the muscle, $P_{\text{cap}O_2}$ is the partial pressure of oxygen within the microcirculation, and $P_{\text{mit}O_2}$ is the partial pressure of oxygen within the mitochondria]. The intersection of these two relationships yields the $\dot{V}_{O_2\text{peak}}$ for those conditions. The mechanisms for the discrepancy in CP between duty cycles
in the current study can be further explored using this model under a few assumptions. The assumptions were held constant between duty cycles to reduce systematic error, so that any differences in the model would be attributable to differences in the deoxy-[Hb+Mb] and $Q_{BA}$ values. It was assumed that the deoxy-[Hb+Mb] signal reflects only deoxy-[Hb] [n.b., we are aware that the signal contains deoxy-[Mb] as well (15)] and that the entire signal arises solely from the muscle (i.e., not from any intervening adipose or skin tissue). With these assumptions the deoxy-[Hb] may be converted into an estimated $\dot{V}_{O_2}$. The deoxy-[Hb] values are in units of μmole heme/l tissue, where the tissue is assumed to be muscle. These deoxy-[Hb] units can be converted into μmole heme/l blood using the conversion 1.36% capillary blood volume/muscle volume [derived from 400 cap/mm$^2$, 28.3 μm$^2$ CSA, and a coefficient of 1.2 correcting for tortuosity and branching of the capillaries (63)]. These units can then be converted into mole O$_2$/l blood assuming 1 mole O$_2$/mole heme and further to l O$_2$/l blood using the conversion 22.4 l O$_2$/mole O$_2$. $\dot{V}_{O_2}$ values in l O$_2$/min may then be obtained by multiplying this value by the measured $Q_{BA}$ values. The $Q_{BA}$ and deoxy-[Hb+Mb] responses for each duty cycle (Figures 3 and 4) were fit with exponential models which were then integrated to provide the $\dot{V}_{O_2}$ response throughout each duty cycle.

**Statistical analysis**

$P_{peak}$, CP, and W’ were compared across duty cycles using paired t-tests. Main effects for $Q_{BA}$, deoxy-[Hb+Mb], total-[Hb+Mb], $\dot{V}_{O_2}$, iEMG, and MPF were tested using two-way ANOVA with repeated measures (duty cycle x time) for the same power output constant-power tests for each duty cycle. When a significant main effect was detected, a Tukey’s post-hoc analysis was conducted.
Differences were considered statistically significant when $p < 0.05$ and all data are presented as mean ± SD unless otherwise noted.
Results

Power-duration relationship

As determined from the a priori goodness-of-fit criteria, the power-duration relationships were determined using four constant-power tests in all of the subjects for the 50% duty cycle and in four of the subjects for the 20% duty cycle. The resulting SE values as a percent of the parameter value were 4.6 ± 6.1% for CP and 12.7 ± 8.7% for W’ with the 50% duty cycle and 1.6 ± 1.4% for CP and 10.8 ± 11.7% for W% with the 20% duty cycle. The coefficient of determination values for the 50% and 20% duty cycles were 0.98 ± 0.02 and 0.98 ± 0.02, respectively. CP was significantly lower for the 50% duty cycle (3.9 ± 0.9 W) than the 20% duty cycle (5.1 ± 0.8 W; p < 0.001), while W’ was not significantly different (50% duty cycle: 452 ± 141 J and 20% duty cycle: 432 ± 130 J; coefficient of variation = 13.9%) (Figure 2.2). There was a significant inverse correlation between the percent change in CP versus the percent change in W’ between the 50% and 20% duty cycles (r = -0.83, p = 0.01), but not for the absolute changes in CP versus W’ (r = -0.61, p = 0.11).

Equivalent power output tests

The $P_{\text{peak}}$ from the incremental test was significantly lower for the 50% duty cycle (5.7 ± 0.7 W) compared to the 20% duty cycle (6.7 ± 0.8 W; p < 0.001). The mean power output that was repeated for both duty cycles was 6.2 ± 0.8 W, which equated to a significantly higher relative power output for the 50% duty cycle (109 ± 8.4 %$P_{\text{peak}}$) compared to the 20% duty cycle (93.7 ± 7.5 %$P_{\text{peak}}$; p < 0.001). This power output was also significantly higher as a percentage of CP for the 50% duty cycle (165 ± 37.3 %) than the 20% duty cycle (125 ± 14.4%; p = 0.003). The $T_{\text{lim}}$ for the 50% duty cycle (201 ± 52.1 s) was significantly shorter than the 20% duty cycle (501 ± 314 s; p = 0.017).
The brachial artery diameter and $V_{\text{mean}}$ data are presented in Table 2.1. $Q_{BA}$ increased significantly between 91.5 s to end-exercise for the 20% duty cycle, while $Q_{BA}$ did not increase for the 50% duty cycle, such that at matched-time (50% duty cycle: $7.37 \pm 1.76$ ml·s$^{-1}$; 20% duty cycle: $9.26 \pm 1.99$ ml·s$^{-1}$; $p = 0.001$) and end-exercise (50% duty cycle: $7.37 \pm 1.76$ ml·s$^{-1}$; 20% duty cycle: $9.87 \pm 1.73$ ml·s$^{-1}$; $p < 0.001$) the 50% duty cycle $Q_{BA}$ was significantly lower than the 20% duty cycle (Figure 2.3A). At 9 s post-exercise $Q_{BA}$ was not significantly different from end-exercise within the 20% duty cycle, but had significantly increased above end-exercise within the 50% duty cycle ($p = 0.008$), such that $Q_{BA}$ was no longer significantly different between duty cycles (20% duty cycle: $11.3 \pm 2.8$ ml·s$^{-1}$; 50% duty cycle: $10.6 \pm 3.4$ ml·s$^{-1}$) (Figure 2.3B).

**NIRS**

The deoxy-[Hb+Mb] increased to a significantly higher value at end-exercise for the 20% duty cycle ($51.7 \pm 4.7$ μM) compared to the 50% duty cycle ($44.3 \pm 2.4$ μM; $p = 0.03$) (Figure 2.4A). At 9 s post-exercise there was no significant difference (albeit marginally) between duty cycles for the deoxy-[Hb+Mb] (20% duty cycle: $52.3. \pm 16.7$ μM; 50% duty cycle: $45.8 \pm 9.19$ μM; $p = 0.054$) (Figure 2.4B). Throughout exercise the total-[Hb+Mb] increased within each duty cycle and no significant difference was detected between duty cycles.

**EMG**

Within the 20% duty cycle, iEMG did not change significantly throughout the test (Figure 2.5A). During the 50% duty cycle, the iEMG progressively increased until end-exercise, resulting in significant differences between duty cycles at 120 s ($p = 0.017$), matched-time ($p < 0.001$), and end-exercise ($p = 0.002$). The MPF did not change significantly during the 20% duty cycle test, while it continually
decreased throughout the 50% duty cycle test (Figure 2.5B). This resulted in a significantly higher MPF for the 20% duty cycle at matched-time (p = 0.005) and end-exercise (p = 0.008).

\( \dot{V}_O_2 \)

The integration of the \( \dot{Q}_{BA} \) and deoxy-[Hb+Mb] values estimated \( \dot{V}_O_2 \) data that qualitatively increased with similar time courses and amplitudes for both duty cycles until approximately 90 s (as seen for \( \dot{Q}_{BA} \), Figure 2.3 and deoxy-[Hb+Mb], Figure 2.4), after which the 20% duty cycle \( \dot{V}_O_2 \) increased beyond that of the 50% duty cycle (Figure 2.6). \( \dot{V}_O_2 \) significantly increased between 91.5 s to end-exercise for the 20% duty cycle, while \( \dot{V}_O_2 \) did not increase for the 50% duty cycle, such that at matched-time (50% duty cycle: 32 ± 9 ml O₂·min⁻¹; 20% duty cycle: 43 ± 11 ml O₂·min⁻¹; p = 0.003) and end-exercise (50% duty cycle: 32 ± 9 ml O₂·min⁻¹; 20% duty cycle: 50 ± 11 ml O₂·min⁻¹; p < 0.001) the 50% duty cycle \( \dot{V}_O_2 \) was lower than the 20% duty cycle (Figure 2.7). The model analysis resulted in \( \dot{D}_O_2 \) values of 1.02 ml⁻¹·min⁻¹·mmHg⁻¹ for the 50% duty cycle and 1.72 ml⁻¹·min⁻¹·mmHg⁻¹ for the 20% duty cycle. At 9 s post-exercise the \( \dot{V}_O_2 \) values were not significantly different between duty cycles (50% duty cycle 50 ± 13 ml O₂·min⁻¹ and 20% duty cycle 53 ± 17 ml O₂·min⁻¹; p = 0.612).
Discussion

Consistent with our first hypothesis, CP was higher for the 20% duty cycle compared to the 50% duty cycle, while W’ was not different between duty cycles. When the same power output was completed for both duty cycles, $Q_{BA}$ was higher for the 20% duty cycle compared to the 50% duty cycle, consistent with our second hypothesis. In contrast to our third hypothesis, however, deoxy-$[Hb+Mb]$ achieved higher values for the 20% duty cycle, while the iEMG was lower and the MPF higher for the 20% duty cycle compared to the 50% duty cycle.

In characterizing the power-duration relationship, Monod and Scherrer (1965) considered CP to be dependent upon muscle blood flow (i.e., $O_2$ delivery). Since this seminal publication, CP has been demonstrated to be dependent upon $O_2$ delivery (blood flow x arterial $O_2$ content) by manipulating inspired $O_2$ concentrations to reveal that CP is lowered with hypoxia (18, 54) and elevated with hyperoxia (75). The current study has extended these findings by manipulating $O_2$ delivery via altered blood flow with the use of two different duty cycles for muscle contraction, demonstrating that CP is lower for the 50% duty cycle compared to the 20% duty cycle as a result of reduced blood flow. In addition, $O_2$ extraction was altered with duty cycle as the 50% duty cycle deoxy-$[Hb+Mb]$ was lower compared to the 20% duty cycle. These differences in blood flow and deoxy-$[Hb+Mb]$ measured between the duty cycles performed at the same power output, would be anticipated for the other exercise tests as well. Consistent with this, CP was lower for the 50% duty cycle compared to the 20% duty cycle. These findings support that CP reflects the highest rate of $O_2$ utilization which is matched by $O_2$ delivery, that the muscle contraction duty cycle directly influences CP.

The deterministic mechanisms of W’ have traditionally been associated with intramuscular ‘anaerobic’ energy production [depletion of the intramuscular energy stores (45, 50, 51, 53) and/or metabolite accumulation (13, 21, 26, 45)]. In the current study, muscle contraction duty cycle-induced alterations in $O_2$ delivery ($Q_{BA}$) and $O_2$ extraction (deoxy-$[Hb+Mb]$) did not alter W’. The findings of
the current study are consistent with hypoxia leading to a decrease in CP, while not altering $W'$ (18, 54). In contrast, hyperoxia led to an increase in CP and, interestingly, a decrease in $W'$ (75). A more recent definition of $W'$ as a work capacity that is determined by the magnitude of the severe-intensity domain has emerged in the literature (8, 75). This definition postulates that the parameters determining the severe-intensity domain ($\dot{V}_{O_2\text{max}}$ and CP) dictate $W'$.

It is worth noting that this definition implies $\dot{V}_{O_2\text{max}}$ is involved in determining $W'$, despite the power-duration relationship being determined by (and assumed to hold true for) work rates in the extreme-intensity domain where exhaustion ensues (and theoretically $W'$ is completely utilized) prior to the attainment of $\dot{V}_{O_2\text{max}}$. The magnitude of the severe-intensity domain was not determined in the current study, as the $\dot{V}_{O_2}$ at CP was not measured. However, implications may be drawn from examining the power outputs associated with the boundaries of the severe-intensity domain. $P_{\text{peak}}$ and CP were both approximately 1.0 W lower for the 50% duty cycle compared to the 20% duty cycle, which implies that the magnitude of the severe domain, and therefore $W'$, was unaltered. This is consistent with hypoxia resulting in a concomitant 29 W reduction in the power output at $\dot{V}_{O_2\text{peak}}$ with a 30 W reduction in CP and no change in $W'$ (Dekerle et al., 2012). An unaltered magnitude of $W'$ with a lower CP would necessitate a faster rate of $W'$ utilization at the same power output and a decrease in time-to-exhaustion (as seen in the present study), as ‘critical levels’ (60) of the ‘anaerobic’ substances associated with fatigue would be achieved earlier in the exercise bout. Collectively, these findings support that the magnitude of $W'$ is not dependent on $O_2$ delivery or $O_2$ extraction per se, rather these determine the rate at which $W'$ is utilized, via alterations in $\dot{V}_{O_2\text{max}}$ and CP.

The $\dot{V}_{O_2\text{peak}}$ values from the current study are similar to previously reported directly measured values for handgrip exercise of ~30-50 ml $O_2\cdot\text{min}^{-1}$ (62, 73). From the model analysis, it was found that the change in $\dot{D}_{O_2}$ (69 %) was double the change in $Q_{BA}$ (34 %) between duty cycles. The $\dot{D}_{O_2}/Q$ ratio is
indicative of $O_2$ extraction (59, 65), and therefore the increased $D_{O_2}/Q$ ratio for the 20% duty cycle in the current study would explain the increased deoxy-[Hb+Mb] compared to the 50% duty cycle. A possible mechanism for the increased diffusive $O_2$ capacity [$D_{O_2} = A/T \times (\text{solubility/} \sqrt{\text{molecular weight}})$, where $A$ is the surface area for diffusion and $T$ is the thickness of the membrane across which diffusion occurs] for the 20% duty cycle may be due to enhanced longitudinal recruitment of capillary surface area (59).

Increased red blood cell velocity and fractional $O_2$ extraction increase the length of a capillary involved in $O_2$ exchange (‘longitudinal recruitment’) (Poole et al. 2011), which may be a mechanism for increasing capillary surface area, and thus $D_{O_2}$, during exercise. In the current study, brachial artery blood velocity was significantly faster and brachial artery diameter was significantly larger for the 20% duty cycle compared to the 50% duty cycle (Table 2.1). Assuming that duty cycle did not alter the microvascular volume, the increased brachial artery blood flow ($\dot{V}_{\text{mean}} \times \text{CSA}$) for the 20% duty cycle evinces an increased red blood cell velocity in the capillaries, leading to increased longitudinal recruitment. The increased $O_2$ extraction despite the increased blood flow for the 20% duty cycle suggests that red blood cell transit time was not limiting [consistent with Richardson et al. (1993b)], but rather served to augment $O_2$ extraction. The surface area for gas exchange in the capillary is also determined by capillary hematocrit, which is approximately 33% of systemic values at rest and increases to systemic values at maximal exercise (46). However, total-[Hb+Mb] was not significantly different between duty cycles, suggesting that microvascular hematocrit was similar between conditions. Thus, both the increased $O_2$ delivery and $O_2$ extraction for the 20% duty cycle likely contributed to the higher CP and estimated $\dot{V}_{O_2 \text{peak}}$ compared to the 50% duty cycle.

The underlying end-exercise metabolic state of the muscle was examined by analyzing the data immediately in recovery to remove the influence of the muscle contraction. The increase in $Q_{BA}$ with no physiological change in deoxy-[Hb+Mb] (despite slight statistical differences) during recovery for the
50% duty cycle above the end-exercise value suggests that $Q_{BA}$ was limited during exercise (possibly due to the decreased relaxation time), while the lack of increase during recovery for the 20% duty cycle suggests that this contraction style was not limiting. Importantly, both duty cycles were performed at the same power output and therefore similar metabolic rates would be expected. However, the $\dot{V}_{O_2}$ model demonstrates that this was not the case, as the estimated $\dot{V}_{O_2peak}$ was lower for the 50% duty cycle. The fact that the 50% duty cycle $\dot{V}_{O_2}$ increased (as a result of the increase in $Q_{BA}$) in recovery to a value not different from the 20% duty cycle suggests that the same metabolic rate may have been ‘wanted’ by the muscles for both duty cycles, but the limitations imposed on $O_2$ delivery ($Q_{BA}$) and $O_2$ extraction (deoxy-[$Hb+Mb$]) for the 50% duty cycle prevented this metabolic rate from being achieved. As a result, the aerobic energy contribution would be diminished for the 50% duty cycle (reflecting a decreased CP) while requiring a greater anaerobic energy contribution for any power output above CP. This would result in the faster utilization of $W'$ and earlier occurrence of exhaustion, as seen in the present study.

Despite being performed at the same power output, the iEMG and MPF profiles differed between the 20% and 50% duty cycles. In contrast to the current study, Burnley et al. (9) reported that isometric knee-extension exercise at various intensities above CP yielded similar end-exercise EMG values. However, these findings may not directly relate to the current study due to differences in the mode of exercise (knee-extension versus handgrip), contraction style (isometric versus dynamic), and duty cycle (constant duty cycle versus altered duty cycle). The EMG profiles in the current study may have differed between duty cycles as a result of differences in the relative intensity and the duration of the tests, as these have been demonstrated to affect the EMG response (10, 57, 58). Amann (3) suggested that the accumulation of metabolites within the muscle may lead to increased firing rates of the group III/IV afferents, resulting in the inability to voluntarily produce the required force despite the muscle
being capable of generating it. In addition, exhaustion for supra-CP power outputs has been linked to the attainment of critical levels for intramuscular energy stores and metabolites ([PCr], [H⁺], and [Pi]) (75), which may directly impair force production (24). Therefore EMG differences between duty cycles in the current study may be a consequence of increased firing rates of the group III/IV afferents and/or the attainment of a critical level of intramuscular [PCr], [H⁺], and [Pi] at different levels of muscle activation. During handgrip exercise the *flexor digitorum superficialis* and *flexor digitorum profundus* are the primary muscles activated and used throughout the exercise test (52) and the fiber type composition of these muscles are ~50% Type I (39, 42). The EMG data from the current study suggest that the 50% duty cycle led to a greater recruitment of Type II fibers and/or induced more fatigue of these fibers than the 20% duty cycle. The limitation of O₂ delivery and O₂ extraction in the 50% duty cycle may have led to greater muscle fiber fatigue, thus requiring the recruitment of more muscle fibers to maintain the requisite power output. The current study demonstrated that at exhaustion the muscles were in different states of motor unit recruitment and action potential conduction velocities between the two duty cycles.

The findings of the present study have direct implications for past and future studies, as well as direct application for activities performed above CP. The different values for CP, \( Q_{BA}, \text{deoxy-[Hb+Mb]} \), and EMG between duty cycles emphasize that comparisons among different protocols need to be made with regard to the specific contraction protocol so as to prevent misinterpretation. In application, altering the biomechanics of locomotion to provide a shorter duty cycle may lead to higher levels of sustainable performance. In running, decreasing the ground-contact time (i.e., duty cycle) may permit higher blood flow and O₂ extraction values, leading to improved performance. In a clinical setting, a shorter duty cycle in ambulation may allow higher intensities of ‘exercise’ to be maintained, such that activities of daily living become less fatiguing, increasing the patient’s quality of life. For cycling, the
power output [but not the metabolic rate (5)] associated with CP has consistently been demonstrated to be lower with high pedal cadences (≥ 100 rpm) compared to low pedal cadences (≤ 60 rpm), while W’ has not been affected when fitting the data with the hyperbolic model used in the current study (5, 11, 37, 49). The pedal frequencies used in these studies would vary the time under tension for the muscle, as the force generation by the muscle decreases with increasing pedal cadences (48, 70), and therefore would alter $O_2$ delivery by producing less blood flow impedance (30). The finding that W’ was not altered by duty cycle in the current study is in line with the pedal cadence manipulation studies and cumulatively the data support that W’ is independent of $O_2$ delivery. Importantly, the subjects of the studies examining the effect of pedal cadence on the power-duration relationship were non-cyclists. As trained cyclists tend to select higher pedal cadences ((30, 61, 69) than non-cyclists (30), it is not known if experienced cyclists would demonstrate similar decreases in CP with high pedal cadences.

Several experimental limitations are pertinent when interpreting the findings from the current study. In order to vary the duty cycle while maintaining the 3 s contraction cycle duration, the eccentric contraction component was omitted for the 20% duty cycle. The additional eccentric contraction of the 50% duty cycle may have contributed to metabolic differences between duty cycles. However, this does not seem likely as the estimated $\dot{V}_{O_2\text{peak}}$ (along with peak $Q_{BA}$ and deoxy-[Hb+Mb]) was higher for the 20% duty cycle. In addition, eccentric contraction $O_2$ consumption is approximately 20% that of concentric contraction (1) and concentric contraction efficiency (measured as ATP/contraction) is ~15%, while eccentric efficiency is ~35% (67). Furthermore, the maintenance of tension by the muscle requires less energy than the development of tension (32, 66). Therefore, the major energy requiring component (concentric contraction) was the same between duty cycles, while the less energy demanding component (eccentric contraction) differed. Another limitation of the current study was that $\dot{V}_{O_2}$ was not directly measured. Rather it was estimated using the deoxy-[Hb+Mb] and $Q_{BA}$ values. We recognize
that these assumptions may have limited the accuracy of the absolute values. Nevertheless, any contribution of these assumptions to the detected differences was minimized by holding the assumptions constant between duty cycles. The integration of the deoxy-[Hb+Mb] and $\dot{Q}_{BA}$ responses allowed for the estimation of time course changes in $\dot{V}_{O_2}$ for both duty cycles. However, due to the limited number of deoxy-[Hb+Mb] and $\dot{Q}_{BA}$ data points for the exponential fits, no statistical kinetic analyses were conducted to prevent over interpretation of the data.

In conclusion, the current study reveals that a relatively long muscle contraction duty cycle imposes limitations on blood flow and $O_2$ extraction that ultimately leads to a decrease in exercise tolerance. CP was lower for the 50% duty cycle compared to the 20% duty cycle, while $W'$ was not different. The 20% duty cycle resulted in elevated $\dot{Q}_{BA}$ and deoxy-[Hb+Mb] compared to the 50% duty cycle and upon removal of the contraction impedance $\dot{Q}_{BA}$ and deoxy-[Hb+Mb] increased for the 50% duty cycle to values not different from those of the 20% duty cycle. These findings suggest that $O_2$ delivery and $O_2$ extraction were limited for the 50% duty cycle, possibly due to a decreased relaxation time and less longitudinal recruitment of the capillary surface area, respectively. The EMG values also differed between duty cycles, such that at exhaustion the muscles were in different states of motor unit recruitment and action potential conduction velocities. The 50% duty cycle appears to have limited the physiological determinants of CP, resulting in a greater utilization of $W'$ per contraction and less $W'$ restoration between contractions at the same power output. This resulted in a decreased exercise tolerance compared to the 20% duty cycle. The findings of the current study support the notion that CP is determined by the highest sustainable rate of aerobic ATP production, which in turn is influenced by $O_2$ delivery and $O_2$ extraction. In contrast, the magnitude of $W'$ appears to be determined (at least in part) by mechanisms that are independent of $O_2$ delivery and $O_2$ extraction, while the rate of $W'$ utilization is affected by $O_2$ delivery and $O_2$ extraction via alterations in CP.
Table 2.1 Brachial artery diameter and blood velocity data.

<table>
<thead>
<tr>
<th></th>
<th>50% duty cycle</th>
<th></th>
<th>20% duty cycle</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Diameter (cm)</td>
<td>( \bar{V}_{\text{mean}} ) (cm·s(^{-1}))</td>
<td>Diameter (cm)</td>
<td>( \bar{V}_{\text{mean}} ) (cm·s(^{-1}))</td>
</tr>
<tr>
<td>Baseline</td>
<td>0.45 ± 0.04</td>
<td>11.4 ± 4.56</td>
<td>0.46 ± 0.03</td>
<td>12.1 ± 6.85</td>
</tr>
<tr>
<td>46.5 s</td>
<td>0.46 ± 0.04</td>
<td>35.6 ± 10.6(^{b2})</td>
<td>0.46 ± 0.03</td>
<td>36.6 ± 6.56(^{b2})</td>
</tr>
<tr>
<td>91.5 s</td>
<td>0.46 ± 0.03</td>
<td>41.6 ± 9.62(^{b2})</td>
<td>0.47 ± 0.03</td>
<td>41.3 ± 7.62(^{b2})</td>
</tr>
<tr>
<td>Matched-time</td>
<td>—</td>
<td>—</td>
<td>0.48 ± 0.03</td>
<td>50.1 ± 11.7(^{a1,b2,c2,d1})</td>
</tr>
<tr>
<td>End-exercise</td>
<td>0.48 ± 0.03(^{b1,c1})</td>
<td>43.0 ± 6.88(^{b2})</td>
<td>0.51 ± 0.04(^{a2,b2,c2,d2})</td>
<td>49.1 ± 8.18(^{a1,b2,c2,d1})</td>
</tr>
</tbody>
</table>

\( \bar{V}_{\text{mean}} \), mean blood velocity; Matched-time, equivalent time-point within the 20% duty cycle test to that of end-exercise for the 50% duty cycle. \(^{a}\) significantly different from 50% duty cycle. \(^{b}\) significantly different from baseline within duty cycle. \(^{c}\) significantly different from 46.5 s within duty cycle. \(^{d}\) significantly different from 91.5 s within duty cycle. Level of significance: \(^{1}p < 0.05\) and \(^{2}p < 0.001\).
Figure 2.1 Displacement profiles for the 50% and 20% duty cycles.

Schematic representation of the specific contraction components for each duty cycle (Panel A). The 50% duty cycle consisted of a 0.6 s concentric contraction period, a 0.3 s isometric transition period, a 0.6 s eccentric contraction period, and a 1.5 s relaxation period. The 20% duty cycle consisted of a 0.6 s concentric contraction period and a 2.4 s relaxation period. A displacement profile for a representative subject throughout a contraction cycle for each duty cycle is shown in Panel B.
Figure 2.2 A representative subject’s power-duration relationship for the two duty cycles.

Two-parameter hyperbolic fits to the 50% duty cycle (solid line) and the 20% duty cycle (dashed line) data are shown. The asymptote of each model represents critical power (CP) and the curvature constant represents W’. 

- 50% Duty cycle
  - CP = 4.39 W
  - W’ = 324 J
- 20% Duty cycle
  - CP = 5.38 W
  - W’ = 394 J
Figure 2.3 Brachial artery blood flow responses for the two duty cycles at the same absolute power output.

Mean and standard error exercise brachial artery blood flow ($\dot{Q}_{BA}$) data (Panel A), and end-exercise and 9 s post-exercise (Panel B) for the 50% and 20% duty cycles. † significantly different from the 50% duty cycle end-exercise, $p < 0.001$. ‡ significantly different from the 50% end-exercise time, $p < 0.001$. * significantly different from 20% duty cycle at 91.5 s, $p < 0.001$. 
Figure 2.4 Deoxygenated-[hemoglobin + myoglobin] response for the two duty cycles at the same power output.

Mean and standard error deoxygenated-[hemoglobin+myoglobin] (deoxy-[Hb+Mb]) data (Panel A), and end-exercise and 9 s post-exercise (Panel B) for the 50% and 20% duty cycles. † significantly different from 50% end-exercise, p < 0.05. ‡ significantly different from the 50% duty cycle end-exercise time, p < 0.001.
Figure 2.5 Mean electromyography response for the two duty cycles at the same power output.

Group mean and standard error integrated electromyography (iEMG) (Panel A) and mean power frequency (MPF) (Panel B). † significantly different from the 50% duty cycle end-exercise, p < 0.01. ‡ significantly different from 50% end-exercise time, p < 0.001. * significantly different from the 50% duty cycle at the same time points, p < 0.05. # significantly different from the 50% duty cycle at 60s, p < 0.05. + significantly different from the 50% duty cycle at 90s and 120 s, p < 0.05.
Figure 2.6 Estimated oxygen uptake response for the two duty cycles at the same power output.

Mean and standard error exercise estimated oxygen uptake ($\dot{V}_O_2$; determined from brachial artery blood flow and deoxygenated-[hemoglobin+myoglobin]; see Methods for assumptions) (Panel A), and end-exercise and 9 s post-exercise (Panel B) for the 50% and 20% duty cycles. The integrated $\dot{V}_O_2$ response was determined from the integration of exponential model fits to the brachial artery blood flow and deoxygenated-[hemoglobin/myoglobin] data. † significantly different from the 50% duty cycle end-exercise, $p < 0.001$. ‡ significantly different from the 50% end-exercise time, $p < 0.001$. * significantly different from 20% duty cycle at 91.5 s, $p < 0.001$. 
Figure 2.7 Diagram of estimated oxygen uptake as a function of microvascular $P_{O_2}$ for each duty cycle.

The model integrates perfusive oxygen delivery (Fick Principle, curved lines) and diffusive oxygen delivery (Fick’s Law, straight lines from origin) to yield $\dot{V}_{O_2\text{peak}}$ values for the specific conditions of each duty cycle. Exercise was carried out to the limit of tolerance ($T_{\text{lim}}$) at the same absolute power output ($6.5 \pm 0.9$ W) for each duty cycle. $\dot{V}_{O_2}$ was estimated using brachial artery blood flow ($\dot{Q}_{BA}$) and the deoxygenated-[hemoglobin+myoglobin] (deoxy-[Hb+Mb]) (See Discussion for details). The percent change in $\dot{Q}_{BA}$ and the diffusive oxygen capacity ($\dot{D}_{O_2}$) from the 50% duty cycle to the 20% duty cycle was estimated to be 69 % and 34 %, respectively, which together predicted a 56 % higher $\dot{V}_{O_2\text{peak}}$ for the 20% duty cycle. The 20% duty cycle allowed for a higher $\dot{Q}_{BA}$ (possibly due to the longer relaxation time) and a higher $\dot{D}_{O_2}$ (possibly due to increased longitudinal capillary recruitment) compared to the 50% duty cycle.
References


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Chapter 3 - Influence of blood flow occlusion on muscle oxygenation characteristics and the parameters of the power-duration relationship
Summary

It was previously postulated that blood flow occlusion during exercise would reduce critical power (CP) to 0 Watts (W), while not altering the curvature constant (W’). We empirically assessed the influence of blood flow occlusion on CP, W’, and muscle oxygenation characteristics. Ten healthy men (age: 24.8 ± 2.6 yrs; height: 180 ± 5 cm; weight: 84.6 ± 10.1 kg) completed four constant-power handgrip exercise tests during both control blood flow (control) and blood flow occlusion (occlusion) for the determination of the power-duration relationship. Occlusion CP (-0.7 ± 0.4 W) was significantly (p < 0.001) lower than control CP (4.1 ± 0.7 W) and significantly (p < 0.001) lower than 0 W. Occlusion W’ (808 ± 155 J) was significantly (p < 0.001) different from control W’ (558 ± 129 J) and all ten subjects demonstrated an increased occlusion W’ with a mean increase of ~49%. The current findings support the aerobic nature of CP. The findings also demonstrate that the amount of work that can be performed above CP is constant for a given condition, but can vary across conditions. Moreover, this amount of work that can be performed above CP does not appear to be the determinant of W’, but rather a consequence of the depletion of intramuscular energy stores and/or the accumulation of fatigue inducing metabolites which limit exercise tolerance and determine W’.
Introduction

The robust nature of the power-duration relationship (and its equivalents for other modes of exercise) has been well established (26, 27, 52). Nevertheless, the precise physiological mechanisms of the curvature constant (W’), and to a lesser degree critical power (CP), have remained elusive. The growing body of evidence supports that CP represents the highest attainable steady-state for aerobic energy production without continually drawing on W’ and, as such, demarcates the boundary between the heavy- and severe-intensity exercise domains (4, 12, 38, 39, 42, 51). It is also evident that W’ is a constant term that determines \( T_{\text{lim}} \) for severe-intensity exercise (21, 55). Intramuscular energy stores (35, 36, 38), the accumulation of fatigue inducing metabolites (7, 18, 21, 28), and/or the magnitude of the severe-intensity domain (5, 51) have all been postulated to determine W’. Building evidence supports that complete utilization of W’ is associated with consistent muscle [PCr], [Pi], and [H+] perturbations, which may limit the amount of work performed above CP (28, 43, 51). Additionally, the rate of W’ utilization (but not the magnitude of W’) is influenced by manipulations in O\(_2\) delivery and O\(_2\) extraction via alterations in muscle contraction duty cycle (4). While much has been revealed regarding the mechanisms of CP and W’, it is not clear how blood flow occlusion influences each parameter.

In originally characterizing the power-duration relationship, Monod and Scherrer (38) speculated on the influence of blood flow occlusion by stating, “Factor b [CP] is linked to circulatory conditions in the muscle. For when the dynamic work is performed under arterial cuff, the maximum work becomes constant whatever be the time after which exhaustion occurs. The maximum work is then equal to factor a [W’]…” Implicit in this statement, is that CP must be 0 Watts (W) with blood flow occlusion for the maximum work performed to be equal to W’ and W’ to remain constant. This suggests that CP is independent of anaerobic energy production and that the O\(_2\) trapped in the arm with occlusion (i.e., bound to myoglobin and within the vasculature) is not sufficient to measurably contribute to CP.
Furthermore, this statement implies that $W'$ is not determined by aerobic energy production nor the clearance of $H^+$ from the muscle vascular space with perfusion (at least beyond the conditions of the occluded limb). A constant $W'$ also implies that intracellular pathways for energy production are unaltered, if indeed similar intramuscular metabolic perturbations do occur for the complete utilization of $W'$ across interventions. Thus, blood flow occlusion exercise is a unique model to empirically test the statement of Monod and Scherrer (38), while providing further insight into the mechanisms determining the power-duration relationship.

Exercise across work rates within the severe-intensity domain (42) is characterized by the concomitant progressive increases in oxygen uptake ($\dot{V}_{O_2}$) and blood flow, the depletion of intramuscular phosphocreatine ([PCr]), and the accumulation of inorganic phosphate ([Pi]) and hydrogen ions ([H$^+$]), all of which achieve similar values at the limit of exercise tolerance ($T_{lim}$) (3, 9, 28, 32, 38, 43, 49, 51). Moreover, Vanhatalo et al. (51) demonstrated that [PCr], [Pi], and [H$^+$] at $T_{lim}$ during knee-extension exercise are independent of augmented $O_2$ delivery via inspired hyperoxic gas. Consistent with these muscle physiological responses being independent of $O_2$ delivery, similar skeletal muscle electromyography characteristics (EMG) are expressed between normoxic and hypoxic exercise (15, 41). In contrast, fractional $O_2$ extraction (indicated by deoxygenated-[hemoglobin + myoglobin] (deoxy-[Hb + Mb]) (10, 14, 19, 20, 22)) at $T_{lim}$ appears to be scaled to $O_2$ delivery, such that it is greater with hypoxia (41) and less with hyperoxia (51) than normoxia, respectively. However, it remains to be determined if similar EMG characteristics and fractional $O_2$ extractions are attained at $T_{lim}$ for severe-intensity domain power outputs within a given $O_2$ delivery. Thus, it remains to be determined if reductions in $O_2$ delivery via blood flow occlusion (rather than inspired hypoxic gas) result in similar EMG characteristics and attainment of fractional $O_2$ extraction.
Therefore, the aim of the current study was to assess the influence of blood flow occlusion on the parameters of the power-duration relationship (CP and W’), EMG characteristics, and muscle oxygenation characteristics. According to the prediction of Monod and Scherrer (38) our primary hypotheses were that with blood flow occlusion, 1) CP would not be significantly different from 0 W and 2) W’ would not be significantly different from control. Second, we hypothesized that within each condition 3) deoxy-[Hb + Mb] and 4) EMG characteristics would not be significantly different at T_{lim}. 
Methods

Experimental Procedures

All experimental procedures in the present study were approved by the Institutional Review Board at Kansas State University and conformed to the standards set forth by the Declaration of Helsinki. Prior to providing written informed consent and completion of a health history questionnaire, subjects were informed of the protocol and potential risks of participation. Testing sessions were separated by at least 24 h and subjects were instructed to abstain from vigorous activity during the 24 h prior to testing, in addition to abstaining from caffeine and alcohol consumption during the 2 and 12 h prior to testing, respectively.

A previously described custom-built two-handed handgrip ergometer (4) was utilized for all testing sessions. The ergometer was attached to a pneumatic cylinder by means of a cable-pulley system, which provided a fixed linear displacement of 4 cm per handgrip contraction. Resistance was controlled via pressurization of the pneumatic cylinder and work was accomplished by compressing the air within the pneumatic cylinder. Power output was calculated as $P = Rd f k^{-1}$, where $P$ is power in W, $R$ is resistance in kg, $d$ is displacement in meters (m), $f$ is contraction frequency, and $k$ is the constant 6.12 for the conversion of kg·m·min$^{-1}$ to W. Alterations in power output were accomplished via alterations in resistance, as $d$ and $f$ were held constant. The ergometer was calibrated prior to the study. Subjects were seated in front of the ergometer and grasped the handrail such that both forearms were approximately at heart level. Exercise was performed using a 50% contraction duty cycle (1.5 s contraction: 1.5 s relaxation) at a rate of 20 contractions·min$^{-1}$. An audio recording with the specific timing was used in conjunction with feedback provided by an investigator to ensure correct timing. Prior to data collection, subjects completed three testing sessions for familiarization with the contraction protocol. All testing sessions were continued until $T_{lim}$, determined as the inability to successfully complete three consecutive contraction cycles.
An incremental power output test was first performed for the determination of peak power ($P_{\text{peak}}$). This protocol was initiated at 1.0 W and the power output was increased by 0.5 W·min$^{-1}$ until $T_{\text{lim}}$. The greatest power output for which at least half of the stage was completed was used as $P_{\text{peak}}$. Each subject also completed four constant-power tests for both the control brachial artery blood flow (control) and occluded brachial artery blood flow (occlusion) conditions in a randomized order. The $P_{\text{peak}}$ was utilized to determine power outputs that would elicit $T_{\text{lim}}$ within ~1 – 15 min (43). The control constant-power tests were performed at 80, 90, 110, and 130 %$P_{\text{peak}}$ and the occlusion constant-power tests were performed at ~17 (1 W for all subjects), 35, 80, and 110 %$P_{\text{peak}}$. Pilot work in our laboratory demonstrated these intensities elicited similar $T_{\text{lim}}$ values for occlusion constant-power tests as those recommended for control constant-power tests. The 80 and 110 %$P_{\text{peak}}$ were conducted in both conditions to examine the influence of blood flow, independent of differences in power output. Brachial artery blood flow was occluded with a vascular cuff positioned around the brachial region of each arm, which was rapidly inflated (< 0.3 s) to suprasystolic pressures (≥ 275 mmHg) at the onset of exercise and remained inflated until $T_{\text{lim}}$ (E20 Rapid Cuff Inflator, Hokanson, Bellevue, WA, USA). Blood flow occlusion was verified by the absence of a radial pulse and the cuff pressures were continuously monitored to ensure ≥ 275 mmHg.

**Measurements and data analysis**

The power-duration relationship for both control and occlusion was determined by fitting the power output and $T_{\text{lim}}$ data from the constant-power tests with the two-parameter hyperbolic model:

\[ t = W' / (P - CP) \]

where $t$ is $T_{\text{lim}}$ in s, $W'$ is the finite work capacity in Joules (J), $P$ is the power output in W, and $CP$ is critical power in W.
A frequency-domain multi-distance near-infrared spectroscopy (NIRS) system was used to measure the oxygenation characteristics of the flexor digitorum superficialis of the right forearm during each testing session (Oxiplex TS, ISS, Champaign, IL, USA). Detailed descriptions of the principles and algorithms of the NIRS technology have previously been described (20, 23). Briefly, this device consists of one detector fiber bundle and eight light-emitting diodes (LED) operating at wavelengths of 690 and 830 nm (four LEDs per wavelength). The LED-detector fiber bundle separation distances are 2.0, 2.5, 3.0, and 3.5 cm. This NIRS device measures and incorporates the dynamic reduced scattering coefficients to provide absolute concentrations (μM) for deoxy-[Hb + Mb], oxygenated-[Hb + Mb] (oxy-[Hb+Mb]), total-[Hb + Mb], and %Saturation-[Hb + Mb] (%Sat-[Hb + Mb]). The deoxy-[Hb + Mb] is relatively insensitive to changes in blood-volume (10, 19, 22) and has been used to reliably estimate the fractional oxygen extraction (10, 13, 14, 19, 20, 22, 34). The NIRS probe was calibrated prior to each test according to the manufacturer’s recommendations. The belly of the flexor digitorum superficialis of the right arm was identified using palpation and EMG. The NIRS probe was secured along the belly of the flexor digitorum superficialis and was wrapped with an elastic bandage to prevent movement of the probe. The position of the NIRS probe was marked with indelible ink for reproducible placement throughout the study. The NIRS data were collected at 50 Hz and stored for post-hoc analysis. The NIRS data were analyzed using 1 s time-binned mean values and 9 s time-binned mean values at $T_{lim}$. A kinetics analysis was conducted for the deoxy-[Hb + Mb] data over the initial 60 s of exercise using a mono-exponential model:

$$\text{deoxy-[Hb + Mb]}(t) = \text{deoxy-[Hb + Mb]}(b) + A(1 - e^{-(t-TD)/τ})$$

where $\text{deoxy-[Hb + Mb]}(t)$ is the deoxy-[Hb + Mb] at any point in time, $\text{deoxy-[Hb + Mb]}(b)$ is the baseline deoxy-[Hb + Mb] before the onset of exercise, $A$ is the amplitude of the deoxy-[Hb + Mb]
response, \( TD \) is the time delay before the start of the increase in deoxy-[Hb + Mb], and \( \tau \) is the time constant of the increase in deoxy-[Hb + Mb].

Surface EMG (Trigno EMG, Delsys Inc., Boston, MA, USA) measurements were obtained from the flexor digitorum superficialis of the left forearm during each testing session. The belly of the left flexor digitorum superficialis was identified by palpation and strong electrical activity when the fingers were flexed, but not with ulnar or radial deviation. The position of the EMG sensor was marked with indelible ink for reproducible placement throughout the study. The EMG data were collected at 1000 Hz and stored for post-hoc analysis. The raw EMG data were processed with a band-pass filter (0.05 – 400 Hz) and each electrical burst corresponding to a muscle contraction was detected using a custom-designed computer program. For each muscle contraction, the signal amplitude characteristics were analyzed via root mean square (RMS) to provide an index of muscle activation and motorneuron firing rate. RMS values were normalized to the first minute value of each test. The frequency characteristics were analyzed via median power frequency (MedPF) to provide an index of the muscle action potential conduction velocity.

**Data analysis**

All curve fitting procedures and statistical analyses were performed using a commercially available software package (SigmaPlot and SigmaStat, Systat Software Inc., Point Richmond, CA, USA). Student’s paired t-tests were used to compare the CP and \( W' \) parameters measured for control and occlusion. Occlusion CP was compared to 0 W using a one-sample t-test. One-way ANOVAs with repeated measures were used to compare NIRS or EMG measurements within each condition. Two-way ANOVAs with repeated measures (condition x intensity) were used to compare both the NIRS and EMG measurements for the tests performed at 80 and 110 %\( P_{\text{peak}} \). Tukey’s post-hoc analyses were conducted.
when significant main effects were detected and effect sizes were calculated for both CP and W'.
Differences were considered statistically significant when p < 0.05. 95% confidence intervals (CI)
around CP and W' were determined for each subject in both conditions. All data are presented as mean
± SD unless otherwise noted.
Results

Ten healthy men (age: 24.8 ± 2.6 yrs; height: 180 ± 5 cm; weight: 84.6 ± 10.1 kg) completed the study. The P_peak from the incremental ramp test was 6.1 ± 0.9 W. The durations of the constant-power tests were: 80 %P_peak: 759 ± 243; 90 %P_peak: 471 ± 156; 110 %P_peak: 211 ± 45; 130 %P_peak: 122 ± 32 s for control and 17 %P_peak: 494 ± 118; 35 %P_peak: 301 ± 49; 80 %P peak: 143 ± 24; 110 %P_peak: 102 ± 10 s for occlusion. The time to achieve T_lim was significantly shorter for occlusion compared to control at both 80 %P_peak (143 ± 24 s vs. 759 ± 243 s, p < 0.002) and 110 %P_peak (102 ± 10 s vs. 211 ± 45 s, p < 0.001).

Individual subject hyperbolic model fits are presented in Figure 1. The determination of the control power-duration relationship in one subject was found to be greatly weighted towards a specific constant-power test, as previously described (4, 12, 38, 39, 42, 51). Therefore, this subject’s control power-duration relationship was determined using three constant-power tests (4, 12, 38, 39, 42, 51). The mean hyperbolic model fits (r^2) were 0.98 ± 0.02 for control and 0.99 ± 0.01 for occlusion. Occlusion CP (-0.7 ± 0.4 W; mean 95% CI = -1.3 to 0.0 W) was significantly (p < 0.001, ES = 6.0) lower than control CP (4.1 ± 0.7 W; mean 95% CI = 3.4 to 4.7 W) and significantly (p < 0.001, ES = 1.75) lower than 0 W (Figure 2). Occlusion W’ (808 ± 155 J; mean 95% CI = 533 to 1082 J) was significantly (p < 0.001, ES = 1.4) different from control W’ (558 ± 129 J; mean 95% CI = 158 to 982 J) and all 10 subjects demonstrated an increased occlusion W’ with a mean increase of ~49 % (Figure 2).

The NIRS measurements were not significantly different at T_lim within each blood flow condition across the different intensities, except for %Sat-[Hb + Mb] between 35 and 110% within occlusion (Figures 3 and 4; Table 1). Total-[Hb + Mb] increased significantly above baseline for all control exercise tests and the values at T_lim were not significantly different among these tests. In contrast, total-[Hb + Mb] did not significantly increase above baseline during the occlusion tests (Figure 4), demonstrating complete blood flow occlusion of the limb. For the 80 and 110 %P_peak tests, deoxy-[Hb +
Mb] at $T_{lim}$ was significantly greater for occlusion than control and Oxy-[Hb + Mb], Total-[Hb + Mb0, and %Sat-[Hb + Mb] were significantly lower for occlusion than control (Figure 5; Table 1). The deoxy-[Hb + Mb] kinetics analyses results are presented in Table 2. There were no significant differences in the TD or $\tau$ between control and occlusion, while the $A$ was significantly greater for occlusion than control at both 80 and 110 %$P_{peak}$.

No statistically significant differences for control RMS at $T_{lim}$ were detected, while the MedPF at $T_{lim}$ was significantly less for 110 %$P_{peak}$ compared to both 80 %$P_{peak}$ ($p < 0.001$) and 90 %$P_{peak}$ ($p = 0.005$). Occlusion RMS at $T_{lim}$ was significantly greater for 110 %$P_{peak}$ compared to 17 %$P_{peak}$ ($p < 0.001$). There were no significant differences in occlusion MedPF at $T_{lim}$ (Figure 6). RMS at $T_{lim}$ was significantly lower for occlusion compared to control at 110 %$P_{peak}$ ($p = 0.012$), but there was no significant difference at 80%$P_{peak}$ between occlusion and control ($p = 0.106$). Occlusion MedPF at $T_{lim}$ was significantly lower than control at 80%$P_{peak}$ ($p < 0.001$) and there was no significant difference at 110%$P_{peak}$ between occlusion and control ($p = 0.43$).
Discussion

This study examined the influence of blood flow occlusion on the parameters of the power-duration relationship during handgrip exercise. Handgrip exercise during blood flow occlusion was well-described by the two-parameter hyperbolic model. In contrast to the primary hypotheses, occlusion CP was lower than 0 W and occlusion W’ was greater than control W’. These results support the aerobic nature of CP, as the reduction in O$_2$ delivery with occlusion reduced CP. These results also support that W’ is relatively constant within a given O$_2$ delivery condition, but can vary across O$_2$ delivery conditions. Additionally, this study presents novel findings regarding muscle oxygenation characteristics during control and occluded severe-intensity handgrip exercise. In agreement with our third hypothesis, deoxy-[Hb + Mb] at $T_{lim}$ was similar within each condition. In contrast to our fourth hypothesis, differences in EMG characteristics at $T_{lim}$ were detected within each condition.

The power-duration relationship

A two-parameter hyperbolic model may be used to empirically describe the decrease in $T_{lim}$ with increasing power outputs to yield the parameters CP and W’ (38, 43, 55). The asymptote in this model represents CP, which distinguishes an exercise intensity above which a physiological steady-state is not attained and exercise $T_{lim}$ is limited by W’. As such, CP represents the highest sustainable rate of aerobic ATP production for which W’ will not be continuously utilized (4, 12, 38, 39, 42, 51). The curvature constant in this model represents W’, modeled as a finite amount of work that can be performed above CP that when fully expended results in $T_{lim}$ (21, 38, 43, 55). However, mounting evidence suggests that W’ is not solely a finite amount of work, per se. Rather it appears that similar “limiting” muscle metabolic perturbations in [PCr], [Pi], and [H$^+$] are attained, that in turn constrain the maximal amount of work that can be performed above CP (6, 28, 43, 51). Despite the precise mechanisms of CP and W’ not being fully understood, it is clear that exercise intensities above CP are
predictably limited by W’ and that the limit of exercise tolerance occurs at similar physiological states for these intensities.

Deterministic mechanisms of CP

To date, evidence suggests that CP represents the highest attainable steady-state for aerobic energy production without continuously drawing upon W’ (4, 12, 38, 39, 42, 51). It was with this interpretation of CP in mind that Monod and Scherrer (38) postulated that the maximum amount of work performed under blood flow occlusion would be equal to W’, which would necessitate a CP equal to 0 W. In contrast to this prediction, the current study demonstrated that the calculated occlusion CP was actually reduced to a power output slightly, but significantly less than 0 W. While a negative CP is only theoretical and not physiologically attainable, nonetheless this estimate provides mechanistic insight into CP. An occlusion CP equal to 0 W (i.e., rest) would indicate that indefinite resting occlusion would not hinder the ability of the skeletal muscle to perform contractions. Previous studies have demonstrated hemoglobin and myoglobin deoxygenation and the subsequent depletion of [PCr] during resting occlusion (25, 31). Thus, after sufficient depletion of aerobic energy sources, resting metabolism is sustained by anaerobic energy production and the depletion of [PCr] and accumulation of [Pi] suggests that W’ is utilized during resting occlusion (i.e., 0 W). As CP is the highest sustainable rate of aerobic ATP production without drawing continuously upon W’, it would not be expected that occlusion CP be equal 0 W, as without blood flow there is no sustainable rate of aerobic ATP production. Rather, CP would be expected to be a theoretical value of negative power for which the magnitude is proportional to the resting metabolic rate.

Deterministic mechanisms of W’
W’ was significantly greater with blood flow occlusion in all ten subjects (mean increase ~49%). A greater W’ with occlusion may be due to differences in metabolic economy between occlusion and control exercise (30, 31) altering the degree of metabolic perturbation for a given amount of mechanical work. Moreover, as $T_{\text{lim}}$ during occlusion appears to be the result of the accumulation of inhibitory by-products of glycolytic ATP turnover (31), it may be that a greater degree of accumulation is tolerated during occlusion exercise and thus, more work above CP may be performed. Furthermore, if the 250 J increase in W’ for occlusion arose solely from oxidative energy production, it would require a greater $O_2$ extraction of 12 ml (assuming 0.000239 kcal·J$^{-1}$ and 5 kcal·l$^{-1}$ $O_2$). The greater deoxy-[Hb + Mb] for occlusion than for control suggests that a small portion of the increase in W’ may be due to an increased $O_2$ extraction. However, the greater deoxy-[Hb + Mb] for occlusion (~64 μM) than for control (~50 μM) would amount only to 0.05 ml $O_2$ (assuming 150 g flexor digitorum superficialis and 1060 g·l$^{-1}$ muscle density), which represents 0.4 % of the 12 ml $O_2$ needed for the increase in W’ to be the result of $O_2$ extraction. Moreover, no relationship between the increase in deoxy-[Hb + Mb] and W’ was detected. Thus, it does not appear that the increased W’ during occlusion is the result of the greater fractional $O_2$ extraction.”

The results of the current study lend credence to W’ not being determined by a finite amount of work per se, but rather by other mechanisms such as the rate of attainment of “limiting” muscle metabolic perturbations (7, 21, 28, 43, 51), the magnitude of the severe domain (5, 51), and/or the $V_{O_2}$ slow component (40). Modeling the current data reveals that while W’ is utilized in its entirety for exercise intensities above CP, the proportion of W’ that contributes directly to external work is not constant across this range of power outputs (Figure 7). For example, at rest (i.e., 0 W) under occlusion, W’ will be used in its entirety to support factors distinct from external work (i.e., resting cellular processes, ion handling, etc.). This is demonstrated by resting blood flow occlusion leading to a
desaturation in myoglobin (46), increased adenosine diphosphate ([ADP]), and a decreased [PCr] (2, 25). With increasing power outputs, a greater proportion of W’ would be utilized for external work, as the proportion of energy turnover via external work will increase (Figure 7). Thus, at sufficiently high power outputs (i.e., right side of Figure 7 bottom) the majority of W’ is associated with external work. However, it appears that some of the energy derived from the utilization of W’ still contributes to the factors that are distinct from external work, including the internal work of handgrip contraction. This model may explain why W’ (determined as the amount of external work performed above CP) is constant when determined under normal blood flow conditions, as power outputs utilized to determine the normal power-duration relationship are on the upper-right portion of the curve in Figure 7 bottom. This is consistent with previous suggestions that W’ is determined by an integration of multiple mechanisms, rather than a single mechanism alone (7, 17).

**Muscle oxygenation characteristics**

In the current study, fractional O₂ extraction was significantly greater for occlusion than for control. This is consistent with previous reports of alterations in the fractional O₂ extraction with varying inspired O₂ concentrations (41, 46, 51). These alterations in fractional O₂ extraction may be the consequence of the Bohr Effect. In the current study, an elevated [H⁺] with occlusion (31) may have facilitated oxyhemoglobin dissociation, resulting in the greater fractional O₂ extraction (50).

Fick’s law of diffusion states that the flux of O₂ (\(\dot{V}_{O_2}\)) is dependent on the diffusivity of oxygen (\(\dot{D}_{O_2}\)) and the P\(_{O_2}\) gradient between the microvasculature and the mitochondria [\(\dot{V}_{O_2} = \dot{D}_{O_2} \times (P_{O_{2mv}} - P_{O_{2mit}})\)]. Exercise hyperemia increases microvascular hematocrit, and therefore enhances \(\dot{D}_{O_2}\) (16, 24, 29, 33). The similar peak plateaus in microvascular hematocrit (i.e., total-[Hb + Mb]) in the current study for control exercise suggest that the peak microvascular hematocrit, and therefore \(\dot{D}_{O_2}\), is
constrained for a given condition. The peak O\textsubscript{2} diffusion gradient (P\textsubscript{O\textsubscript{2}}\textsubscript{mv} – P\textsubscript{O\textsubscript{2}}\textsubscript{mit}) during severe exercise would also be constrained, as intramuscular P\textsubscript{O\textsubscript{2}} (P\textsubscript{O\textsubscript{2}}\textsubscript{mit}) achieves similar low values during exercise (37, 44-46) (assuming similar P\textsubscript{O\textsubscript{2}}\textsubscript{mv} at T\textsubscript{lim} for a given condition). These constraints directly impact aerobic energy production, thus dictating \( \dot{V}_{O_{2\text{max}}} \) (44, 53, 54), and presumably CP (4, 12, 39, 51). CP in the current study was greatly attenuated during occlusion, due presumably, in part, to the prevented increase in microvascular hematocrit (i.e., no increase total-[Hb + Mb] above baseline) and the expected exacerbated fall in P\textsubscript{O\textsubscript{2}}\textsubscript{mv}. As such, W’ would be utilized earlier and at a faster rate in the occlusion exercise bouts compared to control, thus resulting in the earlier attainment of T\textsubscript{lim}. Moreover, the similar nadirs above zero in oxy-[Hb + Mb] at T\textsubscript{lim} for occlusion exercise suggest that complete deoxygenation of Hb and/or Mb did not occur, consistent with previous findings that Hb and Mb do not fully desaturate during blood flow occlusion exercise (11, 31, 47, 48). These similar nadir values of deoxygenation may result from the continual fall in \( P_{O2}\text{mv} \) (decrease in oxy-[Hb + Mb]) as oxygen is utilized and not replenished during occlusion exercise, until the capillary-mitochondria P\textsubscript{O\textsubscript{2}} gradient achieves equilibrium with the inherent resistance to O\textsubscript{2} diffusion (1/\( D_{O2} \)). At this point, further O\textsubscript{2} flux into the mitochondria would be prevented (i.e., oxy-[Hb + Mb] nadir). Additionally, the accumulation of metabolic by-products (i.e., \([H^+]\)) may inhibit oxidative phosphorylation (8) despite the presence of oxygen remaining in the microcirculation (i.e., oxy-[Hb + Mb] above 0 \( \mu \text{M} \)). Therefore severe-intensity exercise tolerance appears to be dependent upon perfusive and diffusive \( O_2 \) supply dictating CP, along with the magnitude of W’ and its rate of utilization (i.e., the power output).

During occlusion exercise, the Fick principle (\( \dot{V}_{O2} = Q \times (a-v)O_2\text{diff} \)) dictates that \( \dot{V}_{O2} \) is proportional to \( O_2 \) extraction. Interestingly, the time constant (\( \tau \)) for the change in the deoxy-[Hb + Mb] was not significantly different between conditions at the same power output, while the amplitude was
greater for occlusion. Consistent with this, Vanhatalo et al. (51) demonstrated an unchanged τ for deoxy-[Hb + Mb] between hyperoxic and normoxic knee-extension exercise. These results suggest that O₂ delivery, per se, does not determine the τ for deoxy-[Hb + Mb]. Rather, it appears that at the onset of exercise sufficient levels of O₂ are present within the muscle and surrounding tissue so as to not limit O₂ flux despite O₂ delivery interventions. It is not until later (~ >30 s) into the exercise bout that the O₂ delivery interventions begin to exert influence on fractional O₂ extraction.

Motor unit recruitment and firing characteristics

In the current study, RMS and MedPF at Tlim were not always similar within each condition. Moreover, significant differences were detected between control and occlusion RMS at 80 %Ppeak and MedPF at 110 %Ppeak. These findings differ from those of prior studies demonstrating similar EMG characteristics between normoxia and hypoxia (41) (15). The current results may differ from previous findings due to greater magnitude of O₂ delivery reduction with occlusion compared to hypoxia. Together these results suggest that EMG characteristics appear not to be influenced by reductions in O₂ delivery up to a certain point, but further reductions in O₂ delivery past this point result in EMG characteristics differences.

Implications of current findings

The findings of the current study further demonstrate the integration of perfusive and diffusive O₂ delivery in determining aerobic energy production, and therefore CP. It is this established CP that dictates the intensities at which W’ will be continually utilized until fatigue ensues. Specifically, the current findings indicate that reductions in blood flow (i.e., O₂ delivery) lower CP which results in the utilization of W’ and fatigue at lower intensities. Cumulatively, current evidence
suggests that alteration in O₂ delivery via changes in blood flow or inspired O₂ concentrations directly affect CP and W’ utilization (4, 12, 39, 51).

**Limitations**

Several experimental limitations must be considered when interpreting the current data. It is not known from the current data if similar metabolic perturbations are occurring within the muscle during occlusion and control. Therefore, it remains to be determined if the same limiting muscle metabolic perturbations are being achieved at T_{lim} during blood flow occlusion exercise as during control. With this, the current study and many previous studies have utilized small muscle mass exercise (e.g., handgrip and knee-extension). It remains to be determined if large muscle mass exercise (i.e., whole-body exercise such as cycling and running) elicits similar intramuscular metabolic responses for power outputs within the severe-intensity domain. Furthermore, the current study is not able to determine which other non-mechanical-work energy consuming processes may be utilizing W’. Previous publications have demonstrated that a substantial amount of energy is utilized for ion pumping during muscular contraction (1). However, it is not known if these previous findings are applicable in the extreme case of blood flow occlusion exercise. As such, it currently is not known how the relationship between W’ and the severe-intensity domain is altered with blood flow occlusion. As [PCr], [Pi], and [H⁺] were not measured in the current study, it cannot be certain that the consistent muscle oxygenation coincided with consistent concentration of these intramuscular metabolites. Prior evidence suggests that consistent values for these metabolites are to be expected despite alterations in O₂ delivery (28, 49, 51). However, it remains to be determined if these values are altered with blood flow occlusion. The noise inherent in EMG measurements limits the confidence in conclusively interpreting the data. As a result, the EMG data are not presented to precisely state the EMG characteristics of the muscle, but rather to
suggest that the muscle may not be achieving similar EMG characteristics at $T_{\text{lim}}$ within and between O$_2$ delivery conditions. Future studies are needed to more completely evaluate the EMG responses for each condition.

**Conclusions**

The current study demonstrated a greater fractional O$_2$ extraction during occlusion exercise compared to control. Moreover, muscle oxygenation characteristics attained similar values within a given O$_2$ delivery condition. Additionally, EMG characteristics appear to be independent of O$_2$ delivery, but rather to be determined by the performed power output. Cumulatively, current evidence suggests that intramuscular [PCr], [Pi], [H$^+$] at $T_{\text{lim}}$ are similar and independent of alterations in O$_2$ delivery, but that fractional O$_2$ extraction is directly influenced by alterations in O$_2$ delivery. Moreover, the reduction of O$_2$ delivery with blood flow occlusion exercise decreased the estimated CP below 0 W and led to an increased W’ compared to control. It appears that the resting metabolic rate and/or the internal work of handgrip exercise may result in the estimated apparent CP being below 0 W during occlusion. The findings of the current study support the aerobic nature of CP. Additionally, the findings demonstrate that the amount of work that can be performed above CP is constant for a given condition, but can vary across conditions. Moreover, this amount of work that can be performed above CP does not appear to be the determining mechanism of W’, but rather a consequence of the depletion of intramuscular energy stores and/or the accumulation of fatigue inducing metabolites which limit exercise tolerance and determine W’.
Table 3.1 End-exercise NIRS values for control and occlusion.

<table>
<thead>
<tr>
<th></th>
<th>Deoxy-[Hb + Mb] (μM)</th>
<th>Oxy-[Hb + Mb] (μM)</th>
<th>Total-[Hb + Mb] (μM)</th>
<th>Sat-[Hb + Mb] (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80 %(P_{\text{peak}})</td>
<td>47.0 ± 14.7</td>
<td>64.7 ± 20.2</td>
<td>111.70 ± 13.2</td>
<td>57.4 ± 14.5</td>
</tr>
<tr>
<td>90 %(P_{\text{peak}})</td>
<td>50.0 ± 12.1</td>
<td>57.2 ± 9.5</td>
<td>107.2 ± 12.2</td>
<td>53.7 ± 8.6</td>
</tr>
<tr>
<td>110 %(P_{\text{peak}})</td>
<td>50.6 ± 15.7</td>
<td>59.5 ± 10.7</td>
<td>110.0 ± 16.1</td>
<td>54.7 ± 10.5</td>
</tr>
<tr>
<td>130 %(P_{\text{peak}})</td>
<td>51.3 ± 15.1</td>
<td>31.2 ± 18.4</td>
<td>112.4 ± 19.5</td>
<td>54.5 ± 11.7</td>
</tr>
<tr>
<td><strong>Occlusion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17 %(P_{\text{peak}})</td>
<td>63.9 ± 14.6</td>
<td>21.0 ± 17.4</td>
<td>84.2 ± 13.7</td>
<td>24.0 ± 18.2</td>
</tr>
<tr>
<td>35 %(P_{\text{peak}})</td>
<td>70.0 ± 21.9</td>
<td>16.8 ± 14.0</td>
<td>86.8 ± 11.9</td>
<td>20.5 ± 17.7(^{c})</td>
</tr>
<tr>
<td>80 %(P_{\text{peak}})</td>
<td>62.8 ± 15.5(^{†})</td>
<td>26.7 ± 11.8(^{†})</td>
<td>89.5 ± 12.6(^{†})</td>
<td>30.1 ± 13.3(^{†})</td>
</tr>
<tr>
<td>110 %(P_{\text{peak}})</td>
<td>59.2 ± 17.7(^{†})</td>
<td>28.4 ± 13.2(^{†})</td>
<td>87.6 ± 15.2(^{†})</td>
<td>33.0 ± 16.2(^{†})</td>
</tr>
</tbody>
</table>

Deoxy-[Hb + Mb], deoxygenated hemoglobin + myoglobin; Oxy-[Hb + Mb], oxygenated hemoglobin + myoglobin; Total-[Hb + Mb], total hemoglobin + myoglobin; Sat-[Hb + Mb], percent saturation of hemoglobin + myoglobin; \(P_{\text{peak}}\), peak power from the incremental maximal exercise test. \(^{†}\) significantly (p < 0.05) different from control at the same \(P_{\text{peak}}\). \(^{c}\) significantly (p < 0.05) different from 110 %\(P_{\text{peak}}\) within condition.
Table 3.2 Exercise onset deoxy-[Hb + Mb] kinetics parameters for control and occlusion

<table>
<thead>
<tr>
<th></th>
<th>y0 (μM)</th>
<th>A (μM)</th>
<th>τ (s)</th>
<th>TD (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80 %P_{\text{peak}}</td>
<td>26.7 ± 4.8</td>
<td>17.8 ± 8.4</td>
<td>10.2 ± 3.4</td>
<td>8.8 ± 3.0(^A)</td>
</tr>
<tr>
<td>90 %P_{\text{peak}}</td>
<td>26.7 ± 5.3</td>
<td>21.8 ± 11.5</td>
<td>11.6 ± 12.2</td>
<td>6.9 ± 1.5</td>
</tr>
<tr>
<td>110 %P_{\text{peak}}</td>
<td>28.1 ± 6.7</td>
<td>22.1 ± 11.2</td>
<td>7.8 ± 2.6</td>
<td>6.7 ± 1.8</td>
</tr>
<tr>
<td>130 %P_{\text{peak}}</td>
<td>27.0 ± 5.7</td>
<td>24.0 ± 11.6</td>
<td>12.0 ± 11.6</td>
<td>4.5 ± 2.4</td>
</tr>
<tr>
<td><strong>Oclusion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17 %P_{\text{peak}}</td>
<td>26.1 ± 5.4</td>
<td>38.1 ± 15.7</td>
<td>32.2 ± 14.3</td>
<td>11.2 ± 3.1</td>
</tr>
<tr>
<td>35 %P_{\text{peak}}</td>
<td>28.7 ± 7.0(^C)</td>
<td>38.0 ± 17.4</td>
<td>17.4 ± 7.1(^B)</td>
<td>10.4 ± 2.7(^C)</td>
</tr>
<tr>
<td>80 %P_{\text{peak}}</td>
<td>27.6 ± 5.5</td>
<td>33.4 ± 10.1(^\dagger)</td>
<td>8.7 ± 2.6(^B)</td>
<td>8.4 ± 2.0(^{BC})</td>
</tr>
<tr>
<td>110 %P_{\text{peak}}</td>
<td>23.0 ± 4.6</td>
<td>34.0 ± 16.0(^\dagger)</td>
<td>12.1 ± 9.9(^B)</td>
<td>4.9 ± 3.6(^B)</td>
</tr>
</tbody>
</table>

Data were analyzed over the first 60 s of exercise with a mono-exponential model. Deoxy-[Hb + Mb], deoxygenated hemoglobin + myoglobin; y0, baseline concentration; A, amplitude of response; τ, time constant of response; TD, time delay from exercise onset to the increase in response. \(^\dagger\) significantly (p < 0.05) different from control. \(^A\) significantly (p < 0.05) different from 130 %P_{\text{peak}} within condition. \(^B\) significantly different from 17 %P_{\text{peak}} within condition. \(^C\) significantly (p < 0.05) different from 110 %P_{\text{peak}} within condition.
Figure 3.1 Individual subject constant-power and hyperbolic curve fit data.
Subjects completed four constant-power tests for both control and occlusion at power outputs selected to elicit exhaustion in ~1 – 15 min. Each subject’s constant-power data were fit with a two-parameter hyperbolic model to provide parameter estimated for critical power (CP) and the curvature constant (W’).
Critical power (CP) and the curvature constant (W') were determined for both control blood flow (control) and brachial artery blood flow occlusion (occlusion). The grey lines indicate individual subject responses. † significantly different from control (p < 0.001). ‡ significantly different from 0 Watts (p < 0.0001).
Figure 3.3 Mean NIRS muscle oxygenation data for control exercise.

Deoxygenated-[hemoglobin + myoglobin] (deoxy-[Hb + Mb]), oxygenated (oxy-[Hb + Mb]), total-[Hb + Mb], and percent saturation (%Sat-[Hb + Mb]) data during 80, 90, 110, and 130 %peak power (%P_{peak}). No significant differences were detected between intensities at the limit of exercise tolerance (T_{lim}). Graph insert: deoxy-[Hb + Mb] during the initial 60 s of exercise onset.
Figure 3.4 Mean NIRS muscle oxygenation data for occlusion exercise.

Deoxygenated-[hemoglobin + myoglobin] (deoxy-[Hb + Mb]), oxygenated (oxy-[Hb + Mb]), total-[Hb + Mb], and percent saturation (%Sat-[Hb + Mb]) data during 17, 35, 80, and 110 %peak power (%P_peak). † significantly (p < 0.05) different from 110% P_peak at the limit of exercise tolerance (T_lim). Total-[Hb + Mb] did not significantly increase above baseline for occlusion. Graph insert: deoxy-[Hb + Mb] during the initial 60 s of exercise onset.
Figure 3.5 Mean NIRS muscle oxygenation data for control and occlusion at 110 %P\textsubscript{peak}.

Deoxygenated-[hemoglobin + myoglobin] (deoxy-[Hb + Mb]), oxygenated (oxy-[Hb + Mb]), total-[Hb + Mb], and percent saturation (%Sat-[Hb + Mb]) at 110 % peak power (%P\textsubscript{peak}). † significantly (p < 0.05) different from control. Total-[Hb + Mb] did not significantly increase above baseline for occlusion. Graph insert: deoxy-[Hb + Mb] during the initial 60 s of exercise onset.
Figure 3.6 Mean EMG data for control and occlusion.

Root mean square (RMS) and median power frequency (MedPF) data at all intensities for control and occlusion. † significantly different from 17 % peak power ($P_{peak}$). ‡ significantly different from 80 and 90 %$P_{peak}$ within control.
Figure 3.7 Schematic diagram demonstrating the contribution of W’ to mechanical- and non-mechanical-work energy consumption processes.

Top: Critical power (CP; the horizontal asymptote) and curvature constant (W’) for blood flow occlusion handgrip exercise. CP was significantly below 0 Watts (W). The area defined by the power output and the duration of exercise between CP and 0 W represents the amount of W’ associated with factors distinct from external work (i.e., ion handling, resting metabolic rate, internal work, etc.) and the area between 0 W and power output is assumed to represent the amount of W’ associated with external work. Below: The mean amount of W’ associated with external work and factors distinct from external work (i.e., ion handling, resting metabolic rate, internal work, etc.) at the four occlusion exercise intensities which accounted for the amount of W’ positioned between CP and 0 W. This demonstrates the nature of W’ and that varying proportions of W’ are utilized for different processes depending on the intensity of the exercise.
References


Chapter 4 - Influence of blood flow occlusion on the development of peripheral and central fatigue during small muscle mass handgrip exercise
Summary

The influence of the muscle metabolic milieu on peripheral and central fatigue is currently unclear. Moreover, the relationship between peripheral and central fatigue and the curvature constant (W') have not been investigated. Six men (age: 25 ± 4 years, body mass: 82 ± 10 kg, height: 179 ± 4 cm) completed four constant power handgrip tests to exhaustion under conditions of control exercise (Con), blood flow occlusion exercise (Occ), Con with 5 min post-exercise blood flow occlusion (Con + Occ), and Occ with 5 min post-exercise blood flow occlusion (Occ + Occ). Neuromuscular fatigue measurements and W' were obtained for each subject. Each trial resulted in significant peripheral and central fatigue. Significantly greater peripheral (-79.7 ± 5.1 % vs. -22.7 ± 6.0 %) and central (-42.6 ± 3.9 % vs. -4.9 ± 2.0 %) fatigue occurred for Occ than for Con. In addition, significantly greater peripheral (-83.0 ± 4.2 % vs. -69.0 ± 6.2 %) and central (-65.5 ± 14.6 % vs. -18.6 ± 4.1 %) fatigue occurred for Occ + Occ than for Con + Occ. W' was significantly related to the magnitude of peripheral (r = 0.85) and central (r = 0.60) fatigue. The current findings demonstrate that blood flow occlusion exacerbated the development of both peripheral and central fatigue and that post-exercise blood flow occlusion prevented the recovery of both peripheral and central fatigue. Moreover, the current findings suggest that W' may be determined by the magnitude of fatigue permitted to develop during exercise.
Introduction

The tolerance of exercise within the severe-intensity domain is well described as the hyperbolic power-duration relationship. The asymptote of this relationship is critical power (CP) and represents the highest attainable steady-state for aerobic energy production without continually drawing upon the second parameter of this relationship, the curvature constant (W’) (14, 21, 44, 45, 47, 58). The precise deterministic mechanisms of W’ have remained elusive, yet it appears that W’ represents a finite anaerobic capacity that when completely utilized, results in similar amounts of work performed above CP and similar end-exercise intramuscular perturbations (i.e., phosphocreatine [PCr], inorganic phosphate [Pi], and hydrogen ion [H⁺]) (35, 44, 45, 48, 58). The consistency of these variables suggests that the mechanisms determining W’ must be constant within a given exercise condition. Moreover, the hyperbolic nature of the power-duration relationship implies that exercise tolerance for any power output within the severe-intensity domain is determined by the same mechanisms. Furthermore, the robust hyperbolic nature of the power-duration relationship across exercise modalities (13-15, 17, 33, 35, 45, 48, 58) and species (19, 40), where the determinants of exercise tolerance likely differ (i.e., central cardiovascular limitations, convective O₂ transport limitations, diffusive O₂ transport limitations, etc.), suggests a mechanism of exercise tolerance regulation that is common to severe-intensity exercise. Importantly, Burnley et al. (16) demonstrated that knee-extension critical torque (the isometric exercise equivalent to CP) represents a “critical threshold” for neuromuscular fatigue development, suggesting that exercise tolerance within the severe-intensity domain may be determined by the magnitude of fatigue development or degree of system impairment tolerated.

Accumulating evidence suggests that “high-intensity” (more precisely, severe-intensity (16)) exercise tolerance is limited by the attainment of a specific level of peripheral muscle fatigue (5, 6, 24, 27, 49, 51, 53). Amann et al. (10) elegantly merged the concepts of a “critical threshold” of muscle fatigue, a “sensory tolerance limit” of group III/IV muscle afferent feedback, and central motor drive
into a paradigm describing the mechanism determining exercise tolerance. This paradigm highlights the important function of the feedback from group III/IV muscle afferent fibers to the central nervous system regarding the physiological state of the working skeletal muscles (1, 36, 37) in determining the “critical threshold” of fatigue (8, 28) and the point where central motor drive becomes limited or limiting (57). Recently, Pethick et al. (46) demonstrated that beyond a decrease in torque-generating capacity, fatigue also limits the ability of the neuromuscular system to adapt to external perturbation. It has been postulated that these mechanisms serve to limit the magnitude of fatigue developed during exercise, presumably as a component of homeostasis (7, 10, 51).

The findings of Burnley et al. (16) in combination with the fatigue paradigm of Amann et al. (10), suggest that CP may represent the exercise intensity above which exercise tolerance is limited by the attainment of the “sensory tolerance limit”. Therefore, the mechanisms determining W’ may be related to the magnitude of fatigue developed during severe-intensity exercise. A constant “sensory tolerance limit” would constrain the amount of work that could be performed and the degree of intramuscular metabolic perturbation prior to fatigue within the severe-intensity domain. This constraint may explain the consistency in the amount of work performed and the intramuscular metabolic perturbations associated with the complete utilization of W’ (35, 44, 45, 48, 58). Previous research suggests that peripheral fatigue (and therefore the “sensory tolerance limit”) is constant for whole-body exercise (i.e., cycling) across normoxic, hypoxic, and hyperoxic conditions (6, 49). However, the results are equivocal for smaller muscle mass exercise, as the sensory tolerance limit has been demonstrated to be similar (42) and different (18, 52) with varying O2 delivery conditions. Thus, the “sensory tolerance limit” may be regulated differently between large and small muscle mass exercise and the magnitude of fatigue permitted to develop by magnitude of the “sensory tolerance limit” during severe-intensity exercise may be a determining mechanism of W’.
To date, we are unaware of a study that has assessed the magnitude of fatigue development and the “sensory tolerance limit” using small muscle mass (handgrip) exercise with reductions in O₂ delivery (via blood flow occlusion) during and post-exercise in order to determine the influence of the muscle metabolic milieu on peripheral and central fatigue. Moreover, we are aware of no study that has examined the relationship between the magnitude of fatigue developed during exercise and W’. Therefore, the current study utilized handgrip exercise with periods of blood flow occlusion during and post-exercise to determine the influence of O₂ delivery on the development of peripheral and central fatigue. Furthermore, the current study assessed the relationship between the magnitude of fatigue development and the magnitude of W’. We tested the hypotheses that 1) peripheral and central fatigue development would be significantly exacerbated during exercise with blood flow occlusion compared to control exercise, 2) there would be no significant recovery of peripheral and central fatigue during post-exercise blood flow occlusion, and 3) a greater magnitude of peripheral fatigue developed during exercise would be associated with a greater magnitude of W’.
Methods

Ethical approval

All experimental procedures were approved by the Institutional Review Board of Kansas State University and conformed to the standards set by the Declaration of Helsinki. Written informed consent was attained after subjects were informed of the overall protocol and the potential risks of participation. Subjects were free of overt cardiovascular or metabolic disease, determined via medical health history evaluation.

Experimental design

After thorough familiarization with the handgrip contraction and fatigue assessment protocol, subjects completed a total of five testing sessions. Testing sessions were separated by at least 24 h and the subjects were instructed to abstain from vigorous activity during the 24 h prior to testing. Additionally, subjects were instructed to abstain from caffeine and alcohol consumption during the 2 and 12 h, respectively, prior to testing. All testing was conducted using a custom-built two-handed handgrip ergometer (14), which was calibrated prior to the study. The ergometer was attached to a pneumatic cylinder by means of a cable-pulley system, which provided a fixed linear displacement of 4 cm per handgrip contraction. Resistance was controlled via pressurization of the pneumatic cylinder and work was accomplished by compressing the air within the pneumatic cylinder. Power output was calculated as $P = Rd f \cdot k^{-1}$, where $P$ is power in W, $R$ is resistance in kg, $d$ is displacement in meters (m), $f$ is contraction frequency, and $k$ is the constant 6.12 for the conversion of kg-m-min$^{-1}$ to W. Alterations in power output were accomplished via alterations in resistance (air pressure), as $d$ and $f$ were held constant. Subjects were seated in front of the ergometer and grasped the handrail such that both forearms were approximately at heart level. Exercise was performed using a 50% contraction duty cycle (1.5 s contraction: 1.5 s relaxation) at a rate of 20 contractions-min$^{-1}$. An audio recording with the
specific timing was used in conjunction with feedback provided by an investigator to ensure correct timing. All testing sessions were continued until the limit of tolerance (T<sub>lim</sub>), determined as the inability to successfully complete three consecutive contraction cycles.

Subjects completed an incremental power output test (1.0 W + 0.5 W·min<sup>−1</sup>) to determine peak power (P<sub>peak</sub>) during the first testing session. P<sub>peak</sub> was determined as the greatest power output for which at least half of the stage was completed. Subjects subsequently completed four constant-power testing sessions at 85 %P<sub>peak</sub>. The protocols were randomly ordered conditions of control exercise (Con), blood flow occlusion exercise (Occ), control exercise with 5 minutes post-exercise blood flow occlusion (Con + Occ), and blood flow occlusion exercise with 5 minutes post-exercise blood flow occlusion (Occ + Occ). Brachial artery blood flow was occluded with a vascular cuff positioned around the brachial region of each arm, which was rapidly inflated (< 0.3 s) to suprasystolic pressures (≥ 275 mmHg) at the onset of exercise and remained inflated until the appropriate time within the specific protocol (E20 Rapid Cuff Inflator, Hokanson, Bellevue, WA, USA). Blood flow occlusion was verified by the absence of a radial pulse and the cuff pressures were continuously monitored to ensure ≥ 275 mmHg. Neuromuscular function was assessed prior to and following each protocol (Figure 4.1). In a recent study (13), the parameters of the power-duration relationship were determined for each of the current subjects for control and blood flow occlusion conditions (Con CP, Con W’, Occ CP, Occ W’), affording the opportunity to examine the relationships between the parameters of neuromuscular fatigue and the power-duration relationship. Importantly, P<sub>peak</sub> (5.8 ± 0.9 W vs. 6.1 ± 1.1 W, p = 0.1) and T<sub>lim</sub> at similar power outputs (5.2 ± 0.9 W vs. 5.3 ± 0.9 W, p = 0.2) were not statistically different (459 ± 154 s vs. 470 ± 140 s, p = 0.8), suggesting that the physiological determinants of exercise tolerance had not changed for the subjects. In addition, all subjects reported no changes in whole-body and handgrip muscle training status.
Near-infrared spectroscopy

Oxygenation characteristics were measured during the pre-exercise and exercise portions of each protocol using a frequency-domain multi-distance NIRS system (Oxiplex TS, ISS, Champaign, IL, USA). Detailed descriptions of the principles and algorithms of the NIRS technology have previously been described (26, 31). Briefly, this NIRS device consists of one detector fiber bundle and eight light-emitting diodes (LED) operating as wavelengths of 690 and 830 nm (four LEDs per wavelength). The LED-detector fiber bundle separation distances are 2.0, 2.5, 3.0, and 3.5 cm. This NIRS device measures and incorporates the dynamic reduced scattering coefficients to provide absolute concentrations (μM) for deoxygenated-[hemoglobin + myoglobin] (deoxy-[Hb + Mb]), oxygenated-[Hb + Mb] (oxy-[Hb + Mb]), total-[Hb + Mb], and %Saturation-[Hb + Mb] (%Sat-[Hb + Mb]). The deoxy-[Hb + Mb] is relatively insensitive to changes in blood-volume (20, 25, 30) and has been used to reliably estimate the fractional oxygen extraction (20, 22, 23, 25, 26, 30, 41). The NIRS device was calibrated prior to each test according to the manufacturer’s recommendations. The flexor digitorum superficialis of the left arm was identified using palpation and EMG. The NIRS probe was secured along the belly of the muscle with a Velcro strap and an elastic bandage. The position of the probe was marked with indelible ink to assess movement of the probe during the testing session and for reproducible placement of the probe throughout the study. NIRS data were collected at 50 Hz and analyzed using 9 s time-binned mean values.

Electromyography

Surface EMG measurements were obtained during the pre-exercise and exercise portions of each protocol using a commercially available system (Trigno EMG, Delsys Inc., Boston, MA, USA). The
EMG sensor consists of four silver electrodes (5 x 1mm) arranged in a 2 x 2 orientation used to make single differential EMG measurements. The flexor digitorum superficialis of the right arm was identified by palpation and strong EMG activity when the fingers were flexed, but not with ulnar or radial deviation. The sensor was secured along the belly of the muscle using adhesive surgical tape and the position marked with indelible ink. The EMG data were collected at a sampling rate of 1000 Hz and band-pass filtered (0.05 – 400 Hz) using fifth-order Butterworth filter. The EMG signal corresponding to each muscle contraction was detected using code ‘developed in house’ (MATLAB R2011a, The Mathworks, Natick, MA, USA). The amplitude characteristics were analyzed via integrated electromyography (iEMG) to provide an index of muscle activation and motoneuron firing rate. The frequency characteristics were analyzed via median power frequency (MedPF) to provide an index of the muscle action potential conduction velocity. The EMG data were analyzed using 9 s time-binned mean values.

Neuromuscular function

Neuromuscular function testing was conducted with the subjects standing at the dynamometer, such that the shoulders were in-line with the dynamometer and the right arm was resting on a platform at shoulder level with the elbow fully extended. The handgrip dynamometer was attached to a calibrated force transducer (LBG1, BLH Electronics, Waltham, MA, USA) that was fixed to the platform to prevent movement. Force was sampled at 1000 Hz and displayed on a computer screen (LabVIEW, National Instruments, Austin, TX, USA). Adhesive stimulation electrodes (4 x 6 cm) were attached to the antebrachial region of the right arm for electrical stimulation of the flexor digitorum superficialis. The anode was positioned proximal to the olecranon process on the posterior brachial region of the arm and the cathode was positioned over the median nerve on the anterior antebrachial region of the arm.
During the familiarization session, the cathode location that provided the greatest force development with electrical stimulation was determined. The positions of the electrodes were marked with indelible ink for reproducible placement throughout the study. The flexor digitorum superficialis was stimulated using a high-voltage constant-current electrical stimulator (DS7AH, Digitimer, Welwyn Garden City, UK). Paired stimuli (doublets) were delivered at 400 V with 100 μs square-wave pulse durations and a 10 ms pulse interval. Stimulation intensity was initiated at 50 mA and was increased in 10 mA increments until the measured force and compound muscle action potential (M-wave) no longer increased. The stimulator current was then increased by a further 19 ± 4 % to ensure the stimuli were supramaximal (range 140 – 230 mA). Subjects subsequently performed a series of six, 3 s maximal voluntary contractions (MVCs), separated by 30 s (~2.75 min total duration). Doublet muscle stimulations were delivered 5 s prior to each MVC, 1.5 s into the MVC, and 5 s after each MVC to obtain measurements of unpotentiated, superimposed, and potentiated twitch forces, respectively.

Neuromuscular assessment was completed prior to exercise and following the end of the protocol for the testing session (Figure 1). In all cases, neuromuscular assessment was initiated < 45 s after the cessation of the protocol. MVC was measured as the greatest force attained prior to the superimposed muscle doublet stimulation. Superimposed twitch force was measured as the increment in force following the delivery of doublet stimulation during the MVC. Voluntary activation (VA) was calculated using twitch interpolation (11, 12, 56) corrected for when the superimposed doublet stimulation did occur at MVC:

$$\%VA = \left[1 - \left(\frac{\text{force prior to superimposed twitch}}{\text{MVC}}\right) \cdot \left(\frac{\text{superimposed twitch force}}{\text{potentiated twitch force}}\right)\right] \cdot 100.$$ 

Potentiated twitch force ($Q_{tw}$) was measured as the greatest force produced with double stimulation 5 s after the MVC. The last four MVCs of each six MVC series were utilized for data analysis, as the degree of potentiation was lessened after the first two MVCs (3, 50).
Statistical analysis

All statistical analyses were performed using a commercially available software package (SigmaStat, Systat Software Inc., Point Richmond, CA, USA). Two-way ANOVAs with repeated measures (trial x time) were used to compare main effects for all of the NIRS variables at baseline and end-exercise. One-way ANOVAs with a repeated measure were used to compare main effects for $T_{lim}$ and then EMG variables at end-exercise. Tukey’s post-hoc analyses were conducted when main effects were detected. Student’s paired t-tests were used to compare pre- and post-exercise $Q_{tw}$, MVC, %VA within each exercise test and the %change in $Q_{tw}$, MVC, %VA for Con vs. Occ and Con + Occ vs. Occ + Occ. Linear regression analyses were used to describe the relationship between $W'$ and MVC, $Q_{tw}$, and %VA. The $\alpha$-level was set at 0.05 a priori. All data are presented as mean ± SD, unless otherwise noted.
Results

Six recreationally active men (age: 25 ± 4 years, body mass: 82 ± 10 kg, height: 179 ± 4 cm) volunteered to participate in the study. The $P_{\text{peak}}$ from the incremental power test was 6.1 ± 1.1 W and 85% $P_{\text{peak}}$ was 5.2 ± 0.9 W. The $T_{\text{lim}}$ for the trials were: Con: 472 ± 150 s, Con + Occ: 446 ± 165 s, Occ: 131 ± 12 s, Occ + Occ: 134 ± 25 s. $T_{\text{lim}}$ was significantly ($p < 0.001$) shorter for exercise during blood flow occlusion than for exercise during control blood flow. Occ CP (-0.7 ± 0.5 W) was significantly lower than Con CP (3.9 ± 0.8 W), while Occ W’ (810 ± 205 J) was significantly greater than Con W’ (550 ± 127 J).

NIRS

For all muscle oxygenation measurements at end-exercise, both Occ and Occ + Occ values were significantly different from both Con and Con + Occ, while there were no significant differences within each exercise condition (Figure 4.2). Baseline muscle oxygenation values were not significantly different between trials. Deoxy-[Hb + Mb] at end-exercise was significantly greater than baseline for all trials. End-exercise total-[Hb + Mb] was significantly greater than baseline for Con and Con + Occ, while there was no significant difference between end-exercise and baseline for Occ and Occ + Occ. Oxy-[Hb + Mb] was significantly lower at end-exercise compared to baseline for Occ and Occ + Occ, but no significance differences were detected for Con or Con + Occ. %Sat-[Hb + Mb] was significantly lower at end-exercise compared to baseline for all trials (Figure 4.2).

EMG

EMG measurements were not significantly different between trials for the first 9 s of exercise. There were no significant differences detected for EMG measurements at end-exercise within each
exercise condition (control or occlusion). MedPF was significantly lower at end-exercise for occlusion exercise than control exercise, while no significant difference was detected for iEMG (Figure 4.3).

**Neuromuscular function and $W'$**

For all exercise trials, post-exercise neuromuscular fatigue measurements were significantly lower than pre-exercise values. The reductions in $Q_{lw}$, MVC, and %VA were significantly greater for Occ than for Con (Figure 4.4) and for Occ + Occ than for Con + Occ (Figure 4.5). $W'$ was significantly related to the pre- to post-exercise reduction in MVC ($r = 0.87$, $p < 0.001$), $Q_{lw}$ ($r = 0.85$, $p < 0.001$), and %VA ($r = 0.60$, $p = 0.04$) (Figure 4.6).
Discussion

The purpose of the current study was to determine the influence of reductions in O$_2$ delivery (via blood flow occlusion) on the development of peripheral and central fatigue during handgrip exercise. It was demonstrated that blood flow occlusion during exercise exacerbated the development of both peripheral and central fatigue. Moreover, continued blood flow occlusion after the cessation of exercise prevented the recovery of (or worsened the magnitude of) peripheral and central fatigue. These results suggest that the “sensory tolerance limit” for handgrip exercise is not constant, as different magnitudes of fatigue were measured across O$_2$ delivery conditions. The current study is the first to identify a significant relationship between the magnitude of fatigue developed during exercise and the magnitude of W’. This relationship suggests that the magnitude of fatigue permitted to develop during severe-intensity exercise may be a determining mechanism of W’.

Influence of O$_2$ delivery on fatigue

It has been postulated that the voluntary termination of severe-intensity exercise is the result of attaining a “sensory tolerance limit” (28). Accumulating evidence suggests that the ensemble group III/IV afferent input from the active locomotor muscles plays a vital role in determining this “sensory tolerance limit” (2, 4, 6, 8, 9, 37, 51) and the subsequent reduction in central motor drive (57). This reduction in central motor drive is hypothesized to be a protective mechanism that constrains the magnitude of fatigue development within the muscle by limiting intramuscular perturbations (6). The consistency of peripheral fatigue development (and therefore the “sensory tolerance limit”) during exercise is not without some degree of ambiguity. It appears that the “sensory tolerance limit” for large muscle mass activity (e.g., cycling) is constant and does not vary with alterations in O$_2$ delivery (6, 49). In contrast, a constant “sensory tolerance limit” is not consistently found for small muscle mass activity (e.g., knee-extension and handgrip exercise). Christian et al. (18) demonstrated a greater magnitude of
peripheral fatigue development during knee-extension exercise in hypoxia than normoxia. Russ and Kent-Braun (52) demonstrated that ischemic handgrip exercise resulted in greater peripheral fatigue development than control handgrip exercise. However, Millet et al. (42) demonstrated similar levels of peripheral fatigue with knee-extension exercise during normoxic and hypoxic exercise with and without ischemia. The current study demonstrated that reductions in O$_2$ delivery (vial blood flow occlusion) exacerbated the magnitude of fatigue development through both peripheral and central origins for small muscle mass handgrip exercise. Moreover, the current study demonstrated a greater magnitude of peripheral fatigue was incurred during occlusion exercise, despite lower iEMG values. The iEMG signal has previously been used as a surrogate measure of central motor drive (10). In the paradigm of Amann et al. (10) the “sensory tolerance limit” is attained via increases in afferent feedback from the active muscle and central motor drive. This suggests that occlusion exercise augmented the influence of afferent feedback relative to central motor drive, such that the greater “sensory tolerance limit” for occlusion exercise was attained despite central motor drive being relatively low. Thus, for “small” muscle mass exercise it appears that the “sensory tolerance limit” may be sensitive to alterations in O$_2$ delivery or that the magnitude of fatigue permitted to develop during exercise is regulated differently between large and small muscle mass exercise.

It was demonstrated in the current study that recovery of peripheral and central fatigue is prevented (and may be worsened) if blood flow occlusion is maintained post-exercise. It is well documented that the accumulation of intramuscular metabolites during exercise increases the firing frequency of group III/IV afferents (1, 36), which, in turn, have been implicated as determinants of the magnitude of fatigue developed during exercise (2, 37). Recently, Kennedy et al. (37) demonstrated that an ischemic period after a fatiguing knee-extension protocol decreased VA, presumably due to activity of group III/IV muscle afferents. Consistent with this, it was demonstrated in the current study that
post-exercise blood flow occlusion resulted in the persistence (or further development) of not only central fatigue, but also peripheral fatigue.

Moreover, blood flow occluded exercise resulted in significantly greater levels of peripheral and central fatigue. Interestingly, peripheral fatigue appears to be more sensitive to the reduction in $O_2$ delivery than central fatigue. Central fatigue has been demonstrated to be influenced by cerebral $O_2$ delivery, as it was demonstrated that central fatigue is exacerbated during exercise with blood flow occlusion when cerebral $O_2$ delivery is reduced via hypoxia (42, 43). Thus, central fatigue may have been less sensitive to the effects of occlusion exercise, as cerebral oxygenation was likely not challenged during the current study. Cumulatively, these findings support the notion that the concentration of intramuscular metabolites contributes to the magnitude of fatigue developed within the muscle, by affecting the firing frequency of group III/IV muscle afferents.

Despite an apparent difference in fatigue regulation between large and small muscle mass exercise, cycling, knee-extension, and handgrip exercise have all been demonstrated to hold true to the hyperbolic power-duration relationship, even with alterations in $O_2$ delivery (13-15, 45, 48, 58). This implies that the determinants of exercise tolerance are regulated within each muscle mass and $O_2$ delivery condition, and that the mechanisms of regulation may vary across muscle mass and $O_2$ delivery conditions. However, some commonality in exercise tolerance regulation must nonetheless exist, as there appears to be no deviation from the hyperbolic power-duration relationship.

*Relationship between fatigue and $W'$*

The findings of the current study demonstrate that the magnitude of fatigue accrued during handgrip exercise is significantly related to the magnitude of $W'$. $W'$ has repeatedly been associated with a finite amount of work that can be performed above CP for a given exercise condition (44, 45, 48).
The relationship between W’ and fatigue suggests that the mechanisms determining when fatigue occurs (via a reduction in central motor drive) constrain the amount of work that can be performed above CP. Thus, the greater amount of fatigue that is allowed to develop, the greater the amount work that can be performed. For example, Broxterman et al. (13) demonstrated a significantly greater W’ for exercise with blood flow occlusion than for control exercise. The findings of the current study suggest that the greater W’ with blood flow occlusion exercise may likely be due to the greater magnitude of fatigue permitted to develop. It has also been demonstrated that W’ is associated with the attainment of consistent intramuscular metabolite concentrations at end-exercise (48, 58). The magnitude of fatigue permitted to develop during exercise would constrain the amount of intramuscular metabolic perturbation. This may explain the consistent levels measured within given exercise conditions. However, it does not appear that intramuscular metabolic perturbations at end-exercise vary with O₂ delivery conditions (32, 58). Thus, it appears that different magnitudes of fatigue and amounts of work can be performed for given intramuscular metabolic perturbations. This may arise from differences in efficiency and energy yield as a result of O₂ delivery to the muscle (38, 39, 55, 58). Consistent with this, W’ (determined as the amount of work performed above CP) was decreased in hyperoxia, while no change in the end-exercise intramuscular metabolic perturbations was measured (58). Importantly, the attainment of these consistent end-exercise intramuscular metabolite concentrations may not be a direct determining mechanism of W’, as these concentrations may be attained and maintained for several minutes before the limit of exercise tolerance (see Figure 2 in ref. (58)). Moreover, it appears that specific exercise training protocols alter peripheral and central fatigue characteristics (59), which may potentially explain alterations in W’ with exercise training (34, 54). However, as CP and W’ were not measured in the study by Zgahal et al. (59) it cannot be known if the reported changes in peripheral and central fatigue were related to alterations in the magnitude of W’. The findings of the current study
suggest that the amount of work available or the degree of intramuscular perturbation may not mechanistically determine W’. Rather, the amount of fatigue permitted to develop during exercise may determine W’ and therefore exercise tolerance above CP.

Limitations

It has previously been demonstrated that compression block influences afferent activity (29). Thus, the vascular cuffing used in the current study potentially could have altered afferent feedback due to nerve compression. However, compression block is typically performed by occluding blood flow for ~20 min. In the current study, blood flow occlusion was not initiated until the onset of exercise and the total occlusion duration never exceeded 20 min. There were no measurements of intramuscular metabolite concentrations or afferent firing in the current study. Therefore, inferences were made from previous studies demonstrating no effect of inspired O₂ concentration on end-exercise intramuscular metabolite concentrations (32, 58), and that group III/IV afferent firing increases with metabolite accumulation (1, 36). Lastly, no comparisons were made between fatigue measurements from the post-exercise blood flow occlusion data and fatigue measurements obtained immediately post-exercise. This was purposeful in order to prevent attributing the difference in fatigue between these conditions to occlusion, as it is not known what the fatigue measurements would be 5 minutes after the cessation of exercise.

Conclusion

This study provides further evidence that the magnitude of fatigue development is not constant for small muscle mass exercise. Moreover, the current study demonstrated that post-exercise blood flow occlusion prevented the recovery of both peripheral and central fatigue, presumably due to the persisting
(or worsening) intramuscular metabolic milieu. In combination, it appears that fatigue is regulated differently between large and small muscle mass exercise and that the stimulation of group III/IV muscle afferents via intramuscular metabolites contributes to the development of fatigue. The current study is the first to provide evidence of a relationship between the magnitude of fatigue development during exercise and the magnitude of $W'$. This evidence suggests that $W'$ may be determined by the magnitude of fatigue accrued during exercise, which may constrain the amount of work that can be performed and the intramuscular metabolic perturbations for severe-intensity exercise.
Figure 4.1 Experimental design.
Control (Con) and occluded (Occ) brachial artery blood flow. The arrows signify when neuromuscular function testing was conducted.
Figure 4.2 Mean NIRS muscle oxygenation data during each exercise trial.

Deoxygenated-[hemoglobin + myoglobin] (deoxy-[Hb + Mb]), total-[Hb + Mb], oxygenated (oxy-[Hb + Mb]), and percent saturation (%Sat-[Hb + Mb]) data during each exercise trial. No significant differences were detected within control or occlusion exercise data. † Occ and Occ + Occ end-exercise data significantly different from Con and Con + Occ at end-exercise. ‡ end-exercise significantly different from baseline within exercise condition.
Figure 4.3 Mean EMG data for each exercise trial.
Integrated EMG (iEMG) and median power frequency (MedPF) data for each exercise trial. † Con and Con + Occ significantly different from Occ at end-exercise. ‡ end-exercise significantly different from initial 9 s value within exercise condition. * Occ and Occ + Occ significantly different from Con and Con + Occ at end-exercise.
Figure 4.4 Neuromuscular function for Control and Occlusion exercise trials.

Maximal voluntary contraction (MVC), potentiated twitch force ($Q_{tw}$), and voluntary activation (%VA) determined pre- and post-exercise for control (Con) and occlusion (Occ) blood flow conditions. The percent change from pre- to post-exercise is presented above the respective exercise trial bar graph. † significantly different from pre-exercise. ‡ significantly different from Con percent change.
Figure 4.5 Neuromuscular function for Control + Occlusion and Occlusion + Occlusion exercise trials.

Maximal voluntary contraction (MVC), potentiated twitch force (Qtw), and voluntary activation (%VA) determined pre- and post-exercise during control blood flow exercise with post-exercise blood flow occlusion (Con + Occ) and blood flow occlusion exercise with post-exercise blood flow occlusion (Occ + Occ). The percent change from pre- to post-exercise is presented above the respective exercise trial bar graph. † significantly different from pre-exercise. ‡ significantly different from Con + Occ percent change.
Figure 4.6 Relationship between $W'$ and the change in neuromuscular function variables.

Maximal voluntary contraction (MVC), potentiated twitch force ($Q_{tw}$), and voluntary activation (%VA) determined from neuromuscular function testing. The solid symbols represent Con data and the open symbols represent Occ data, while distinct symbol shapes represent individual individual subjects.
References


Chapter 5 - Conclusions

The purpose of this dissertation was to test the overarching hypothesis that muscle contraction characteristics (i.e., intensity of contraction, muscle contraction-relaxation duty cycle, etc.) alter oxygen delivery and oxygen utilization, which directly influence the power-duration relationship and fatigue development, and therefore, exercise tolerance. In support of this hypothesis, alterations in oxygen delivery and oxygen utilization via muscle contraction characteristics and blood flow occlusion directly influenced CP. These results further support that CP is aerobic in nature. W’ was not affected with alterations in muscle contraction-relaxation duty cycle, but was increased during blood flow occlusion exercise compared to control blood flow exercise. The magnitude of fatigue development was also greater during blood flow occlusion exercise compared to control blood flow exercise.

Importantly, a significant relationship was observed between the magnitude of fatigue developed and the magnitude of W’. These results suggest that W’ is not influenced directly by manipulations in oxygen delivery and oxygen utilization, per se. Rather, manipulations in oxygen delivery and oxygen utilization influence the magnitude of fatigue accrued during exercise, which dictates the magnitude of W’ measured as the amount of work performed above CP, the amount of energy store depletion, or the degree of intramuscular metabolic perturbation. Therefore, CP represents the threshold above which exercise tolerance becomes predictably limited. This exercise tolerance appears to be determined by the magnitude of fatigue permitted to develop, via the attainment of the “sensory tolerance limit” and the consequential limiting of central motor drive. The findings presented highlight important physiological mechanisms that determine exercise tolerance and demonstrate that characteristics of muscle contraction affect exercise tolerance by influencing oxygen delivery and oxygen utilization. Furthermore, these findings demonstrate that enhancing oxygen delivery and oxygen utilization should be a primary focus.
of interventions designed to improve exercise tolerance, particularly for improving activity tolerance in diseased patients, such as chronic heart failure.
Appendix A - Curriculum Vitae

CURRICULUM VITAE
Ryan Michael Broxterman, M.S.

Date of Birth: September 8, 1986
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Address: Department of Kinesiology
1A Natatorium
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Education:

2011 M.S. in Kinesiology, Kansas State University, Manhattan, KS, 2011
Thesis: “A Single Test for the Determination of the Velocity: Time-to-
Exhaustion Relationship”
Advisor: Thomas J. Barstow, Ph.D.
Committee: David C. Poole, Ph.D.; Craig A. Harms, Ph.D.

2009 B.A. (Summa cum laude) in Physical Education emphasis Exercise
Physiology, Washburn University, Topeka, KS

Academic Appointments:

2013 – Present Adjunct Instructor, Department of Kinesiology, Kansas State University,
Manhattan, KS

2011 – Present Graduate Research Assistant, Department of Kinesiology, Kansas State
University, Manhattan, KS

2012 – 2013 Adjunct Instructor, Department of Kinesiology, Washburn University,
Topeka, KS
2010 – 2011  Adjunct Instructor, Department of Biological Science, Manhattan Area Technical College, Manhattan, KS

2010 - 2011  Instructor of Multicultural Academic Program Success (MAPS), Department of Kinesiology, Kansas State University, Manhattan, KS

2009 – 2011  Graduate Teaching Assistant, Department of Kinesiology, Kansas State University, Manhattan, KS

**Teaching Experience:**

2015 – Present  Kansas State University, Department of Kinesiology, KIN 609 “Environmental Physiology.” Adjunct Instructor.

2013 – Present  Kansas State University, Department of Kinesiology, KIN 815 “Research Methods.” Adjunct Instructor.

2013 – Present  Kansas State University, Department of Kinesiology, KIN 603 “Advanced Cardiovascular Physiology.” Adjunct Instructor.

2012 – 2013  Washburn University, KS, Department of Kinesiology, KN 320 “Motor Learning.” Adjunct Instructor.


2010 – 2012  Kansas State University, KS, Department of Kinesiology. “Exercise Physiology.” Laboratory.

2009 – 2012  Kansas State University, KS, Department of Kinesiology. “Biomechanics.” Laboratory.


2009 – 2010 Kansas State University, KS, Department of Kinesiology. “Public Health.” Laboratory.

Invited Lecturer:

1. “Anatomy and Biomechanics of the Shoulder Girdle.” Department of Kinesiology Biomechanics Lecture, Kansas State University, 2011.


Honors and Awards:

2015 GRA of the Year, Chapter of Golden Key International Honour Society, Kansas State University

2015 Graduate Award for Outstanding Academics, Alumni Association, Kansas State University

2015 Doctoral Scholar Award, American Kinesiology Association

2014 Finalist, GRA of the Year, Chapter of Golden Key International Honour Society, Kansas State University

2014 Distinguished Doctoral Student, Department of Kinesiology, $300, Kansas State University

2014 College of Veterinary Medicine Dr. Albert L. Burroughs Memorial Award, $1,000, Kansas State University

2014 Graduate Student Travel Award, $500, Kansas State University

2013 College of Veterinary Medicine Frank Blecha Award, $800, Kansas State University

2013 Graduate Student Travel Award, $450, Kansas State University
2012 Outstanding Graduate Student, Department of Kinesiology, Kansas State University

2012 College of Veterinary Medicine Frank Blecha Award, $1000, Kansas State University

2012 Graduate Student Travel Award, $75, Kansas State University

2011 Graduate Student Travel Award, $75, Kansas State University

2010 Graduate Student Travel Award, $75, Kansas State University

2009 B.A. Major of the Year, Department of Health, Physical Education, & Exercise Science, $1000, Washburn University

2009 Transformational Experience Travel Award, $1000, Washburn University

2008 Helen Hocker Scholarship for outstanding Physical Education student, $1000, Washburn University

**Laboratory Experience:**

2009 – Present Human Exercise Physiology Laboratory. Lab Directors: Thomas J. Barstow, Ph.D. & Craig A. Harms, Ph.D.

**Research Grant Awards, Awarded:**


**Research Grant Awards, Submitted:**


**Professional Memberships:**

2009 – present American College of Sports Medicine

2010 – present American Physiological Society

2013 – present American College of Sports Medicine Central States

Committees (Departmental): Department Head Search Committee, Dr. Craig A. Harms, 2013.

Invited Presentations:


Scientific Meeting Presentations:


Publications:

Research Papers, Peer Reviewed


**Published Letters**


**Abstracts**


