CHARACTERIZATION OF FATIGABILITY AND CARDIORESPIRATORY FUNCTION IN PEOPLE WITH CHRONIC MOTOR-INCOMPLETE SPINAL CORD INJURY

by

Jared M. Gollie

A Dissertation
Submitted to the
Graduate Faculty
of
George Mason University
in Partial Fulfillment of
The Requirements for the Degree
of
Doctor of Philosophy
Rehabilitation Science

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George Mason University
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by

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DEDICATION

This is dedicated to my late grandparents; Arthur & Marilyn Roncolato and George & Alberta Gollie. Thank you for all you have done for me and continue to do for me!

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I would first like to thank the Lord Jesus Christ, for it is because of my faith that I am able to do the things I do in life. I want to thank my wife for her unconditional support and love throughout this process and for being the driving force in my life. I would also like to thank my parents, Michael and Donna Gollie, for setting such a great example and raising me to understand the importance of hard work and being a good person. I want to thank my brothers, Daryn and Kurtis, and all my family and friends who have supported me throughout my life. And to my nieces and nephews, thank you for being my inspiration.

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LIST OF ABBREVIATIONS AND SYMBOLS

Spinal cord injury ..... SCI
Pulmonary oxygen uptake kinetics ..... VO_2 on-kinetics
Motor-incomplete spinal cord injury ..... miSCI
American Spinal Injury Association Impairment Scale ..... AIS
Constant work-rate ..... CWR
Heart rate ..... HR
Electrocardiography ..... ECG
Baseline Pulmonary VO_2 ..... BL
Time constant ..... *t*p
Time delay ..... TDp
Amplitude ..... ΔVO_2
Near-infrared spectroscopy ..... NIRS
Deoxygenated myoglobin/hemoglobin concentration ..... [HHb]
Oxygenated myoglobin/hemoglobin concentration ..... $[O_2Hb]$
Total myoglobin/hemoglobin concentration ..... [tHb]
Difference in oxygenated-deoxygenated myoglobin/hemoglobin concentrations ... [Hbdiff]
Tissue saturation index ..... TSI
Deoxygenated myoglobin/hemoglobin halftime ..... [HHb] ½ time
Deoxygenated myoglobin/hemoglobin capacity ..... $[HHb]_{total}$
Body mass index ..... BMI
Functional electrical stimulation ..... FES
Miles per hour ..... mph
Seconds ..... sec
Arbitrary units ..... a.u.

ABSTRACT

CHARACTERIZATION OF FATIGABILITY AND CARDIORESPIRATORY FUNCTION IN PEOPLE WITH CHRONIC MOTOR-INCOMPLETE SPINAL CORD INJURY

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George Mason University, 2016

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Purpose: Fatigue presents a major challenge for those living with spinal cord injury (SCI). Additionally, prolonged pulmonary oxygen uptake kinetics (VO_2 on-kinetics) and reduced skeletal muscle oxidative capacity are experienced after SCI. These alterations may contribute to increased fatigability during walking if present in those with chronic motor-incomplete SCI (miSCI). The purpose of this study was to characterize fatigability, VO_2 on-kinetics, and muscle oxygenation in individuals with chronic miSCI compared to an able-bodied reference group. **Methods:** Eight chronic miSCI participants and eight able-bodied participants completed a two constant work-rate walking bouts at a self-selected walking speed. Fatigability was calculated as the ratio of perceived fatigability and performance fatigability. VO_2 on-kinetics was determined using a mono-exponential model in which a time constant (τp) and amplitude (ΔVO_2) was calculated during phase 2 of the biphasic kinetic response during bout 1 of walking.

Concentration changes in resting deoxygenated myoglobin/hemoglobin capacity ($[HHb]_{total}$) and halftime ([HHb] ½ time) were determined in the left lateral gastrocnemius during arterial occlusion using near-infrared spectroscopy (NIRS). **Results:** miSCI group experienced greater fatigability, perceived fatigability, and performance fatigability compared to the reference group (6.62 ± 4.86 vs 1.87 ± 0.98, p=0.017; 5.75 ± 0.71 vs 3.38 ± 1.77, p=0.006; and 1153.38 ± 529.47 vs 1800 ± 0.00 seconds, p=0.011, respectively). VO2 on-kinetic profiles of the miSCI were prolonged compared to the reference (41.2 ± 7.67 vs 23.3 ± 6.48; p<0.0001). Significant correlation was found between fatigability and (*t*p r = 0.56; p = 0.012). During resting arterial occlusion the miSCI group experienced slower [HHb] ½ time compared to the reference (185.9 ± 28.7 vs 157.9 ± 18.9 sec., p=0.047). **Conclusion:** These individuals living with chronic miSCI appeared to more fatigable as a result of higher levels of performance and perceived fatigability. The results suggest that poor cardiorespiratory function may be a mediator of fatigability and demonstrate that cardiorespiratory function measures can be used as physiological markers of fatigability in this population. Furthermore, reduced skeletal muscle oxidative capacity is implicated as a contributing mechanism to the observed slowed VO_2 on-kinetics.

CHAPTER ONE

Fatigue presents a major challenge for those living with spinal cord injury (SCI).[1–13] Fatigue is a symptom, defined as a subjective lack of physical and/or mental energy that is perceived by the individual to interfere with usual or desired activities. Fatigability on the other hand is a determinant characteristic of fatigue comprised of two domains, perceived fatigability and performance fatigability.[14] Perceived fatigability is an increase in feelings of exhaustion, tiredness, or lack of energy [15,16,17,14] and performance fatigability represents decrements in physical performance of a task with respect to time, intensity or frequency of activity.[16,17,14] Measurements of perceived fatigability are obtained using subjective self-report questionnaires whereas performance fatigability can be measured objectively by field or laboratory tests.[14]

Fatigability in healthy non-diseased populations is most commonly viewed as a peripherally mediated phenomenon (i.e. within the active skeletal muscle).[18–23] Several potential mechanistic sites have been proposed in support of this hypothesis including sarcolemma excitability, excitation-contraction coupling, contractile mechanism, metabolic energy supply and metabolite and ion accumulation.[19–22] Similarly, it has been suggested that in paralyzed muscle of individuals with SCI fatigue is the result of impaired skeletal muscle contractile function and altered metabolic properties.[1,11,23–30]

Despite these findings it has yet to be determined if reductions in skeletal muscle oxidative capacity following SCI contributes to fatigability experienced during walking.

In addition, pulmonary oxygen uptake kinetics has been proposed as a potential biomarker of fatigue and exercise intolerance.[31] Pulmonary oxygen uptake kinetics at the rest-to-work transition (VO_2 on-kinetics) is suggested to reflect the integration of the pulmonary, circulatory, and skeletal muscle bioenergetic systems to meet the energetic demands at the initiation of activity.[32] The use of pulmonary VO_2 on-kinetics as a biomarker for fatigue is based on empirical evidence linking prolonged VO_2 on-kinetics with greater metabolic disturbances and thus increases in metabolite and ion accumulation.[21,31] Given previous reports of slowed pulmonary VO_2 on-kinetics in SCI during arm ergometry and leg cycling exercise with electric stimulation, VO_2 on-kinetics may provide critical insights into fatigability during walking in this population.

The combination of slowed VO_2 on-kinetics and decreased skeletal muscle oxidative capacity may contribute to increased fatigability during walking if present in those with chronic motor-incomplete SCI (miSCI) (figure 1). Therefore, the purpose of this study was to characterize fatigability, VO_2 on-kinetics, and muscle oxygenation in individuals with chronic miSCI compared to an able-bodied reference group. It was hypothesized that individuals with chronic miSCI would present with greater levels of fatigability and prolonged VO_2 on-kinetics and resting muscle deoxygenation compared to an able-bodied reference group.

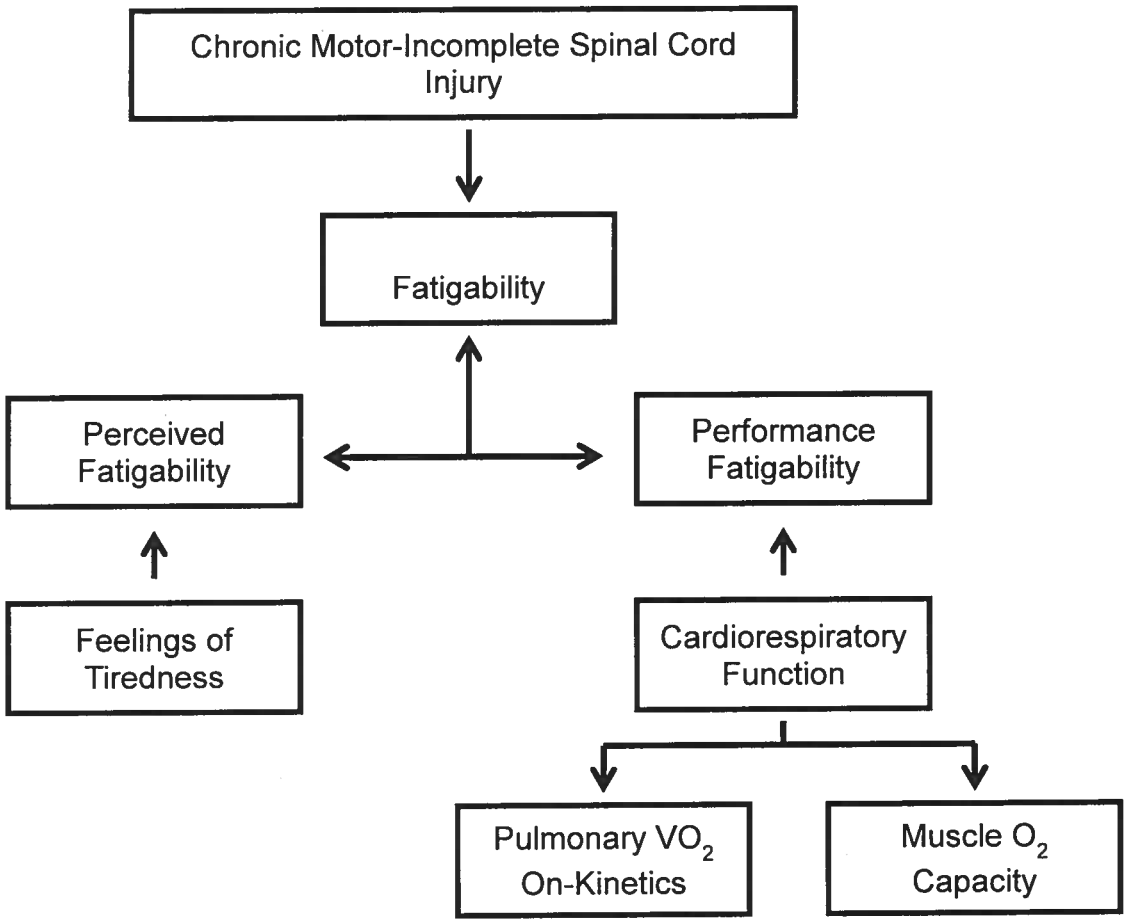

Figure 1 Conceptual framework modified from Enoka & Duchateau (2016)[14] describing the relationship between perceived and performance fatigability and its influence on fatigability in individuals with chronic motor-incomplete spinal cord injury.

CHAPTER TWO

Methods

Ethical Approval

The protocol and procedures were approved by the Institutional Review Board of George Mason University (#618911-6). Verbal and written explanations of the experimental protocol and risks related to testing procedures were presented prior to data collection. Informed consent was obtained from all participants prior to voluntary participation in this study.

Study Design

The study used a cross-sectional design comparing two groups; one group with chronic miSCI and a non-injured reference group. Participants were recruited from the greater Washington D.C. metropolitan area and enrolled on a convenient basis. Reference data were obtained from eight untrained non-injured but otherwise healthy individuals.

Participants

Participants of the chronic miSCI group included individuals with chronic (≥ 1 year post injury) incomplete SCI C & D according to the American Spinal Injury Association Impairment Scale (AIS).[33] Participants were considered for study inclusion if they were 18 years of age or older, at least 12-months post-injury, possessed the ability to stand with minimal assistance from one other person and initiate and complete at least one step independently with or without assistive walking aids, and demonstrate the ability to walk safely on a treadmill. Exclusion criteria included individuals with complete spinal cord injury (AIS A) and incomplete spinal cord injury AIS B, any significant orthopedic complications, spasms or contractures preventing safe ambulation on the treadmill, any history of ischemic heart disease, known cardiovascular, pulmonary, or metabolic diseases, HIV infection or use of antiretroviral therapy, or severe psychiatric disease. Participants were asked to refrain from engaging in any structured locomotor training activities at least 48 hours prior to the initial exercise testing session and during their time enrolled in the study. Inclusion criteria for the reference group included eight neurologically intact and otherwise healthy individuals.

Experimental Procedures

Following the completion of the informed consent and enrollment in the study, a health history and physical activity recall questionnaire was completed. Participants then underwent standard assessments for height and weight. Participants completed a thigh arterial occlusion assessment to determine the maximal capacity of muscle oxygen utilization of the left lateral gastrocnemius prior to exercise testing. After the thigh arterial occlusion assessment, standard measurements of pulmonary gas exchange and left lateral gastrocnemius oxygen utilization were obtained during two separate bouts of constant work-rate treadmill walking performed at a self-selected speed. Resting blood pressure and resting heart rate were obtained in the seated position prior to initiation of the constant work-rate treadmill testing.

Constant Work-Rate (CWR) Treadmill Test

The CWR treadmill protocol included two bouts of walking at a self-selected walking speed; one for 6 minutes (bout 1) and the second for 30 minutes or until volitional exhaustion (bout 2), whichever came first. Prior to the start of the CWR treadmill test, a familiarization period was completed which included walking on the treadmill at a variety of speeds for several gait cycles to ensure all participants could safely perform the test and to determine each participant's self-selected walking speed. Each participant was instructed to select a speed which best approximated their preferred walking speed

while walking on a treadmill or a speed which felt most comfortable. The self-selected speed chosen at baseline was the same speed used during the post-testing session. All participants were allowed to use the handrails for balance during the CWR treadmill test but were asked not to unload the lower extremity during the test. All walking bouts were performed in complete weight-bearing and under voluntary control without the use of adjuvant therapies (i.e. body-weight support, neuromuscular electrical stimulation, robotics, manual assistance).

Walking bout 1 of the CWR treadmill test started with a 3-minute period of static standing during which baselines values of pulmonary VO_2 were obtained. Immediately following 3-minutes of static standing 6-minutes of constant work-rate treadmill walking was performed at the participant's self-selected walking speed to assess pulmonary VO_2 kinetic parameters. At the completion of walking bout 1 each participant rested for 6-minutes and pulmonary gas exchange was measured. 4-minutes of the 6-minute resting period were completed with the participant in the seated position while the last 2-minutes were completed in the standing position just prior to the onset of walking bout 2. Walking bout 2 consisted of each participant walking until volitional exhaustion or 30-minutes, whichever came first. A cut-off of 30-minutes was selected based on previous observations and the assumption none of the participants in the miSCI group would be able to walk on the treadmill of 30-minutes in duration. Volitional exhaustion was determined by the participant as the point at which they could no longer sustain the self-selected walking speed or when the test reached a maximum of 30-minutes in duration.

After walking bout 2, participants transitioned to recovery stage of the protocol in a seated position until pulmonary gas exchange and heart rate values returned to baseline values. Blood pressure was also monitored during this time. All treadmill walking tests were performed on a standard motorized treadmill (Trackmaster TMX22).

Fatigability

Fatigability was determined as the ratio of perceived fatigability divided by performance fatigability (Eq. 1).[16]

Fatigability = perceived fatigability / performance fatigability (seconds)*1000 Eq.1

Therefore, the outcome of fatigability is a composite score of the subjective feeling of tiredness or feeling energetic and how long the participant was able to walk at their self-selected walking speed.[16] For example, if a participant had a perceived fatigability score of 5 following bout 2 of walking and walked for 480 seconds, that participant would have a fatigue score of 10.6. Thus, if the same participant had a perceived fatigability score of 5 following training but walked 600 seconds, that participant would then have a fatigability score of 8.3. Individuals with higher scores are reported to have greater fatigability[16]

Perceived Fatigue and Fatigability Severity Scales

The perceived fatigue and fatigability severity of each participant was assessed by asking them to rate their level of tiredness before and at the completion of walking bout 2 of the CWR treadmill test. Perceived fatigability severity scale is a 7 item scale completed after walking bout 2 (table 1). Immediately following the completion of walking bout 2, the participant was asked if they felt either tired or energetic compared to before the walking bout. If the participant reported feeling tired, they were then asked if they felt a little more tired, somewhat more tired, or extremely tired and their score was recorded (the same procedure was followed if they reported feeling energetic).[16]

Table 1 Perceived fatigue and fatigability scale.[16]

Fatigue Scale Items (Before Walking Test)	Score	Fatigability Scale Items (After Walking Test)
Extremely tired	7	Extremely more tired
Somewhat tired	6	Somewhat more tired
A little tired	5	A little more tired
Neither tired nor energetic	4	Neither more tired nor energetic
A little energetic	3	A little more energetic
Somewhat energetic	2	Somewhat more energetic
Extremely energetic	1	Extremely more energetic

*Reprinted with permission.

Performance Fatigability

Performance fatigability was calculated during bout 2 of the CWR treadmill test. Participants in the miSCI group were asked to walk as long as possible to at their self-selected walking speed. The test was terminated at 30-minutes if the participant was able to walk for this duration. A cut-off of 30-minutes was chosen based on the assumption that miSCI participants would be unable to walk for that time period. Following the termination of bout 2 of the CWR treadmill test, performance fatigability was then calculated as the time walked in seconds.

Pulmonary Gas Exchange

Pulmonary VO_2 was measured continuously using breath-by-breath open circuit spirometry (Medgraphics, CardiO2 Ultima, Medical Graphics Corp, St. Paul, MN) and heart rate (HR) was measured at rest and during constant work-rate treadmill walking by 12-lead electrocardiography (ECG) (Mortora Instrument Inc., Milwaukee, WI, USA). Prior to the placement of electrodes the participants skin was prepared by shaving, cleaning, and lightly abrading the location of interest. Before measurements of pulmonary VO_2 were obtained standardized calibration techniques were applied according to the Ultima^{tm} Series Operator Manual (www.mgcdiagnostics.com). Procedures included entering the appropriate temperature, barometric pressure and humidity. This was followed by the flow sensor calibration in which a syringe consisting

of 175 ml was used to test the rate and volume of inspiratory and expiratory flow. After the completion of the flow sensor calibration a gas calibration was performed to ensure appropriate concentrations of oxygen and carbon dioxide gases.

The principal outcome measures for the CWR treadmill protocol were VO_2 on-kinetics parameters calculated during phase II of a biphasic kinetic response in pulmonary VO_2. Pulmonary VO_2 data were analyzed using a curvilinear least squares fitting procedure (OriginLab, 2016) with a mono-exponential model (Eq. 2) as described in Eq 2.[34,35]

$$\Delta\dot{V}O_2(\tau) = \Delta\dot{V}O_2(1 - e^{-\tau - TDp/\tau p}) \qquad \text{Eq. 2}$$

Briefly, the tri-phasic VO_2 on-kinetic response (Figure 2) is determined by the time constant (τp), time delay (TDp), and amplitude (ΔVO_2) characteristics of the rise in VO_2 to a steady state or asymptote. A mean response time can be estimated algebraically from the time taken to reach 63% of the ΔVO_2 and τp can be estimated by subtracting the time delay (phase 1) from the mean response time.[34]

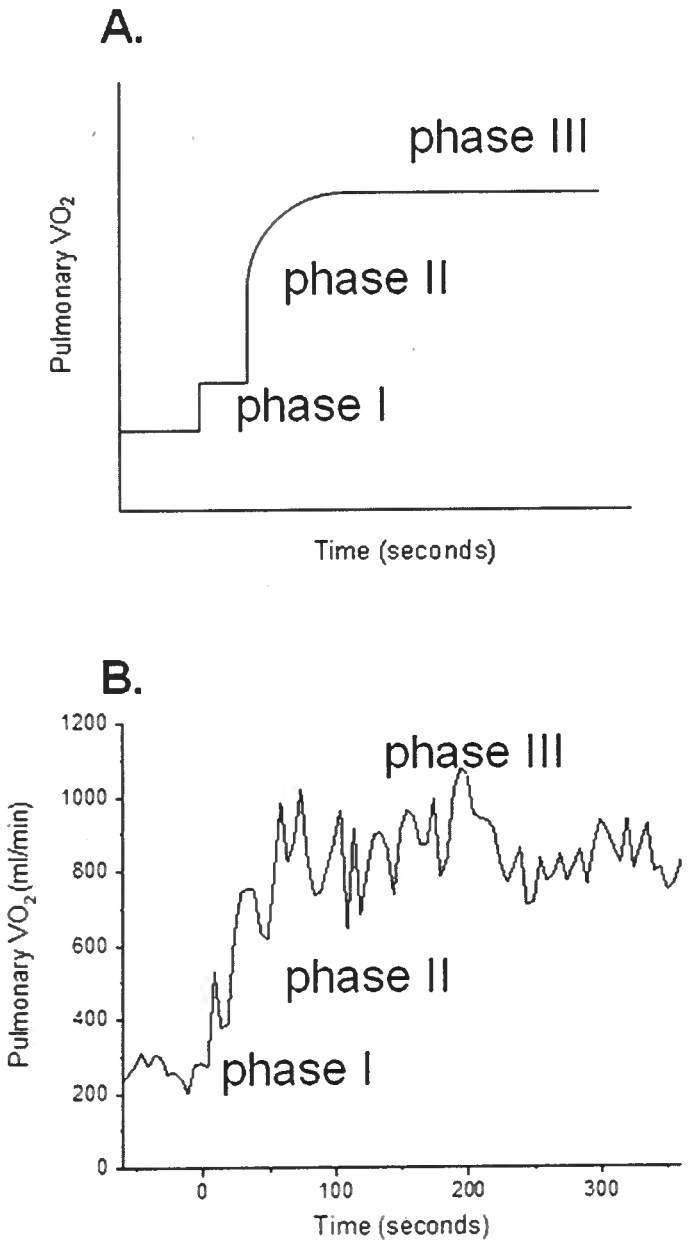

Figure 2 Graph (A) depicts a schematic of the phases of pulmonary VO_2 response at the rest-to-activity transition. Phase I refers to the cardiodynamic phase, phase II refers to the primary phase, and phase III refers to steady-state. Graph (B) depicts the pulmonary VO_2 response and the various phases during CWR treadmill walking at 3.0 mph of a representative participant of the reference group.

Phase I of the response has been identified as the "cardiodynamic response" and reflects an initial, bolus increase in venous return due to initiation of the muscle pump in addition to muscle oxygen utilization.[35–37] Therefore, *t*p was used as the primary measure of VO_2 on-kinetics. Data were cleaned to attempt to exclude errant breaths (coughing, swallowing, sighing, etc), by calculating 99% confidence bands and omitting only breaths outside these bands.[38,39] The individual pulmonary VO_2 breath-to-breath responses for Walking Bout 1 were then time aligned so that the start of the bout was identified as time point zero, interpolated on a second-by-second basis, and time-averaged in 5-second bins to reduce the "noise" and increase the confidence of the parameter estimation.[35] Figure 3 depicts the VO_2 on-kinetic profiles of a representative participant from the miSCI and reference group.

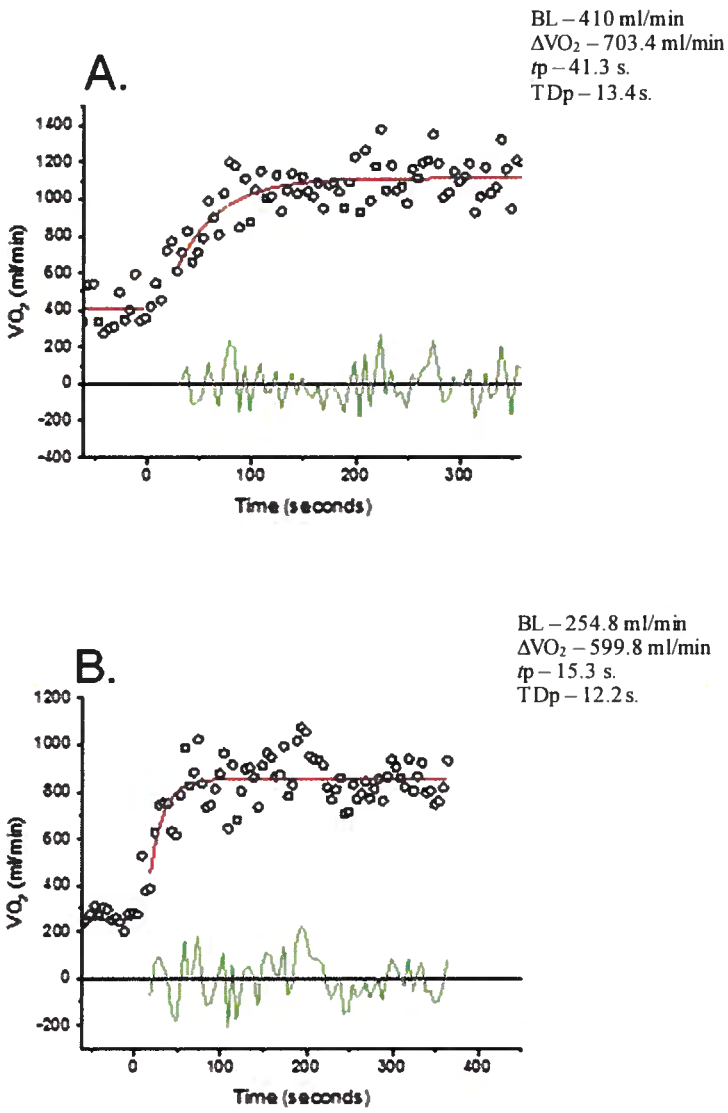

Figure 3 Graph (A) depicts pulmonary VO_2 on-kinetic response of a representative chronic motor-incomplete spinal cord injured (miSCI) participant during 6-minutes of constant work-rate (CWR) treadmill walking at 1.2 mph prior to completing overground locomotor training. Graph (B) depicts pulmonary VO_2 on-kinetic response of a representative reference group participant during 6-minutes of constant work-rate treadmill walking at 3.0 mph. Pulmonary VO_2 on-kinetic profiles were modeled according to Eq. 2.

Near-Infrared Spectroscopy (NIRS)

Muscle oxygenation indices were obtained using a continuous wave NIRS (Oxymon MK-III, Artinis Medical Systems, The Netherlands) with spatial resolution. The NIRS device consists of 3 LED transmitters and 1 high sensitivity PIN diode for the receiver. The 3 transmitters each emit 2 wavelengths (760 nm and 850 nm) of light at 3 separate transmitter– receiver distances (30 mm, 35 mm, and 40 mm). As a default set up to maximize penetration all data analysis was conducted on the 40 mm transmitter–receiver channel. The NIRS system was calibrated prior to each data collection using the calibration bin supplied by the manufacturing company. The calibration program calculates gain coefficients for each possible gain and power setting. Following the calibration procedures the NIRS optode was placed on the belly of the left lateral gastrocnemius muscle to assess changes in muscle oxygen concentrations. To account for adipose thickness, which has been shown to influence the accuracy of the NIRS recordings, a skinfold measurement was obtained at the site of NIRS optode placement.[40] The NIRS signal was analyzed with an algorithm using the modified Beer-Lambert law.[41] The primary variable of interest was relative deoxygenated myoglobin/hemoglobin concentration [HHb]. Other variables assessed by NIRS technology included relative oxygenated myoglobin/hemoglobin [O_2Hb], total myoglobin/hemoglobin [tHb], and difference in oxygenated-deoxygenated myoglobin/hemoglobin concentrations [Hbdiff]. Tissue saturation index (TSI) was calculated as the ratio of [O_2Hb]/[tHb].

Resting Arterial Occlusion Test

Prior to the CWR treadmill tests each participant underwent an arterial occlusion assessment to determine the oxygenation capacity of the left lateral gastrocnemius muscle as this is a central muscle required for locomotion and easily accessible given its superficial location.[40,42–45] With the optode in place, the participant was placed in a seated position and fitted with a blood pressure cuff at the level of the thigh just above the knee and on the same leg as the NIRS optode. The cuff was rapidly inflated to ≥220 mm Hg to completely occlude venous and arterial blood flow and desaturate the muscle hemoglobin/myoglobin. Complete hemoglobin/myoglobin desaturation was operationally defined as the observance of a sustained plateau (at least 30 seconds) in [O_2Hb], [HHb] and the TSI with minimal change in [tHb] (figure 4).

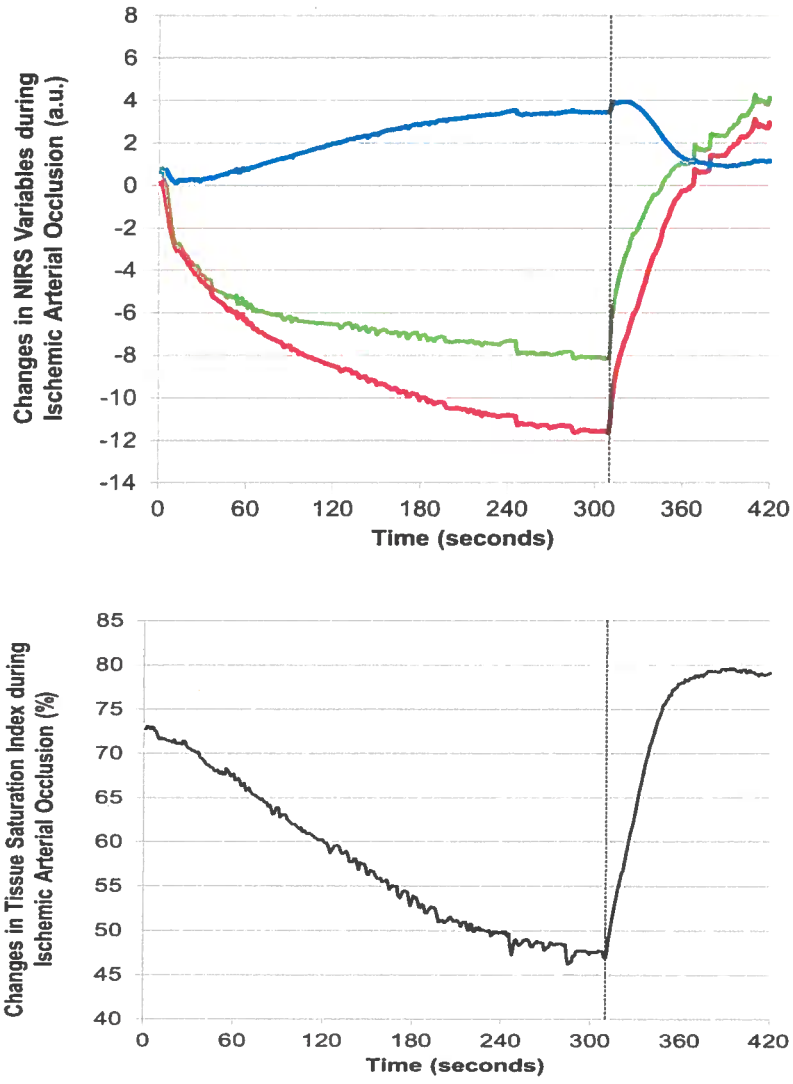

Figure 4 Top: Graph depicting an arterial occlusion assessment of the left gastrocnemius muscle using near-infrared spectroscopy (NIRS) in a representative participant with chronic motor-incomplete spinal cord injury (miSCI). Tracings show relative changes in oxygenated (red trace, [O2Hb]), deoxygenated (blue trace, [HHb]), and total (green trace, [tHb]) myoglobin/hemoglobin concentrations. Bottom: Graph depicting absolute changes in tissue saturation index (TSI) of the left lateral gastrocnemius muscle during arterial occlusion assessment in the same representative participant with miSCI.

Skeletal muscle deoxygenation capacity was determined by assessing the amplitude change from the onset of cuff inflation to the end of the occlusion test. The time to reach

50% of the plateau of $[HHb]_{total}$ was calculated ([HHb] ½ time) to determine the rate of Hb desaturation during arterial occlusion. Following the onset of a plateau in muscle deoxygenation, the pressure in the cuff was rapidly deflated allowing for blood reperfusion to muscle of interest.[42] During muscle reperfusion NIRS assessment of muscle reoxygenation was also measured.

Data Analysis

Differences in fatigability measures, VO_2 on-kinetics, and [HHb] were analyzed using Student's t-test. Linear regressions were used to determine pair-wise relationships between fatigability, *t*p and [HHb] ½ time. Statistical significance was set at a level of $p<0.05$ for two-tailed hypotheses. All values are expressed as means ± SD. All statistical analyses were performed using SPSS version 19 (IBM, Inc.).

CHAPTER THREE

Results

Over the course of a two year period, twelve individuals were screened for participation in the study. One individual was excluded based on the preliminary phone screening and three individuals were excluded based on in-person evaluations for eligibility. Eight individuals completed the in-person screening, signed the informed consent form, and were enrolled into the study.

Baseline Characteristics

Eight individuals with chronic miSCI and classified according to the AIS as C & D were enrolled in the study at baseline. Four individuals in the miSCI group were community ambulators while three individuals used a manual wheelchair and one individual used a power-assist manual wheelchair for community ambulation. Of the four individuals who were primary ambulators, one individual walked independently, one individual used a four-point cane, one individual used a single loftstrand, and one individual used a sled walker. The miSCI group included seven males and one female with a mean age of 38.4

± 17.8 years and a mean BMI of 25 ± 4.5 kg/m^2. Seven (87.5%) of the eight subjects had cervical level injuries and one 12.5%) had a thoracic level injury (table 2).

Table 2 Chronic motor-incomplete spinal cord injury group participant characteristics (N=8).

Gender	
Male	7
Female	1
BMI (kg/m^2) (mean ± SD	25 (4.5)
Age (years) (mean ± SD)	38.4 (17.8)
Race/ethnicity	
White	5
Hispanic/Latino	2
Black/African American	1
Etiology of injury	
Fall	1
Motor vehicle accident	2
Diving	3
Sports/Recreation	1
Vascular Injury	1
Time since injury, years (range)	2 to 5
AIS Classification	
C	6
D	2
Level of injury	
Cervical	7
Thoracic	1
Mobility aids used for walking	
Walker	3
Crutches (bilateral axillary)	3
Four Point Cane	1
None	1
Primary mode of community locomotion	
Wheelchair	5
Walker	2
Four Point Cane	1

Abbreviations: AIS, American Spinal Injury Association Impairment Scale; BMI, body mass index

In addition, eight untrained non-injured and otherwise healthy participants were enrolled to serve as a reference group (table 3). The reference group included seven males and

one female with a mean age of 34.6 ± 11.3 years and a mean BMI of 26 ± 4.2 kg/m^2. There were no significant differences between groups for age or BMI (age p=0.622; BMI p=0.660).

Table 3 Reference group participant characteristics (N=8).

Gender	
Male	7
Female	1
BMI (kg/m^2) (mean ± SD)	26 ± 4.2
Age (years) (mean ± SD)	34.6 ± 11.3
Race/ethnicity	
White	5
Asian American	1
Middle Eastern Decent	2

Abbreviations: BMI, body mass index

Fatigability

All eight participants of the miSCI group and the reference group were included in the analysis of fatigability, perceived fatigability, and performance fatigability. Individuals in the miSCI group walked at a significantly slower self-selected walking speed compared to the reference group (0.96 ± 0.39 vs 2.89 ± 0.53 mph; p<0.0001). Fatigability was calculated according to Eq.2. Individuals with miSCI were more fatigable than the reference group (6.62 ± 4.86 vs 1.87 ± 0.98; p=0.017) (figure 5).

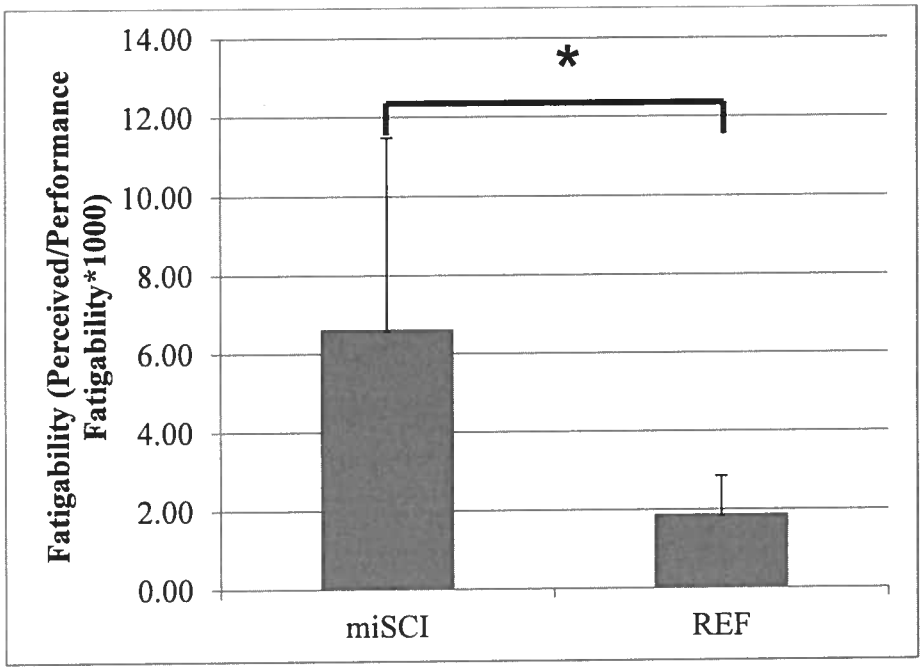

Figure 5 Differences in fatigability between chronic motor-incomplete spinal cord injured and reference groups during bout 2 of the constant work-rate (CWR) treadmill test. Fatigability was calculated as the ratio of perceived fatigability divided by performance fatigability (seconds) multiplied by 1000 (Eq. 1). * Significant difference ($p < 0.05$).

After treadmill walking, miSCI reported significantly greater perceived fatigability scores than the reference group (5.75 ± 0.71 vs 3.38 ± 1.77; $p=0.006$) (figure 6). Of the participants included in the miSCI group, all 8 participants (100%) reported feeling more tired after completing walking bout 2 compared to only 3 participants (37.5%) in the reference group. The remaining participants of the reference group (62.5%) reported feeling "neither tired nor energetic" or "more energetic" after walking bout 2.

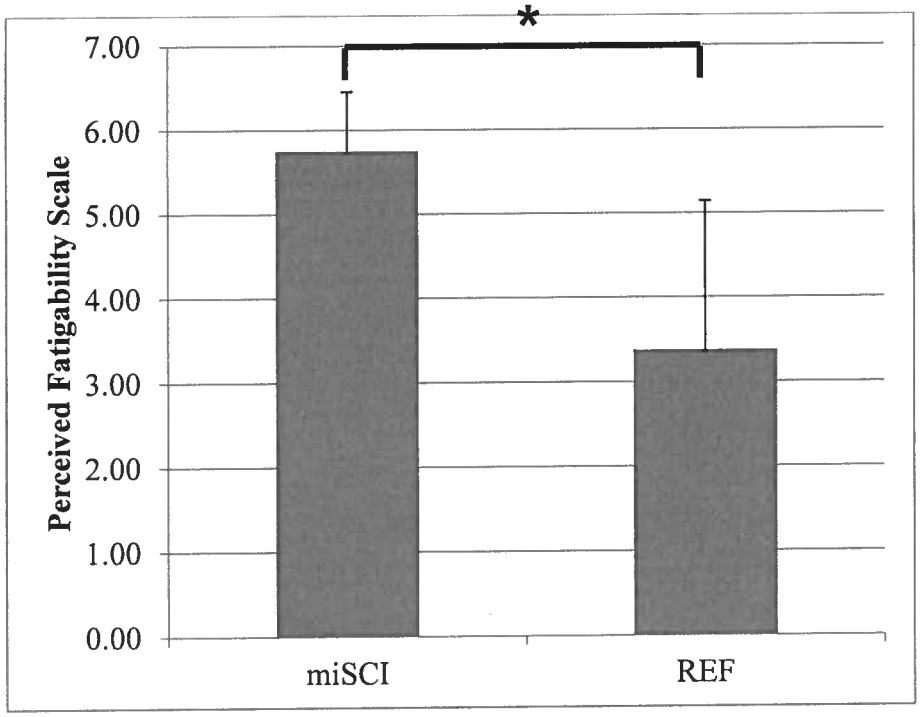

Figure 6 Differences in perceived fatigability between chronic motor-incomplete spinal cord injured and reference groups assessed using the fatigability scale (table 1) immediately following the completion of bout 2 of the constant work-rate (CWR) treadmill test. * Significant difference ($p < 0.05$).

The miSCI group demonstrated significantly greater performance fatigability compared to the reference group (1153.38 ± 529.47 vs 1800 ± 0.00 seconds; p=0.011) (figure 7). Two participants (25%) in the miSCI group were able to complete the entire 30-minutes (i.e. 1800 seconds) of treadmill walking compared to all 8 participants (100%) of the reference group.

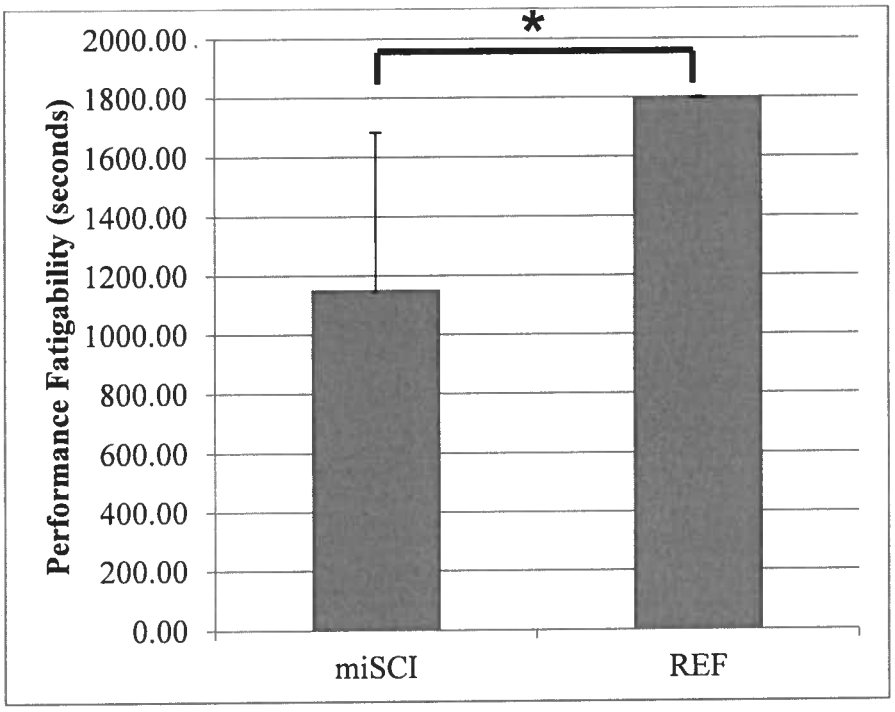

Figure 7 Differences in performance fatigability between chronic motor-incomplete spinal cord injured and reference groups. Performance fatigability was determined as the time spent walking during bout 2 of the constant work-rate (CWR) treadmill test.
* Significant difference ($p < 0.05$).

VO_2 on-kinetic Parameters

Analysis of pulmonary VO_2 kinetic parameters are presented in table 4. Compared to the reference group, the miSCI group had a significantly slower *t*p (41.2 ± 7.67 vs 23.3 ± 6.48; $p<0.0001$). There was no difference in ΔVO_2 between groups (612.73 ± 127.89 vs 744.56 ± 173.86 ml/min; $p=0.106$).

Table 4 Pulmonary VO_2 on-kinetic parameter estimates during bout 1 of constant work-rate (CWR) treadmill walking.

Parameter	miSCI	Reference	p-value
BL (ml/min)	339.6 (69.2)	329.7 (63.9)	0.771
ΔVO_2 (ml/min)	612.7 (127.9)	744.6 (173.9)	0.106
***t*p (s)**	41.2 (7.7)	23.3 (6.5)	0.000 *
TDp (s)	14.7 (22.5)	12.3 (11.3)	0.794
Speed (mph)	0.96 (0.39)	2.89 (0.53)	0.000 *

Abbreviations: BL, baseline pulmonary VO_2; ΔVO_2, VO_2 amplitude change; *t*p, time constant; TDp, time delay; ml/min, milliliters per minute; s, seconds; mph, miles per hour. * Significant difference ($p < 0.05$).

Pearson correlation determined a significant relationship between fatigability and *t*p ($r = 0.56$; $p = 0.012$). Fatigability values were then plotted as a function of the corresponding *t*p and a regression line was drawn. The calculated regression line for fatigability plotted as a function of the corresponding *t*p is shown in figure 8. A linear relationship with a positive slope was observed, suggesting that the level of fatigability and decrease in *t*p during the rest-to-work transition were associated ($p = 0.024$). 31% of the variability in fatigability was attributable by differences in *t*p in this model.

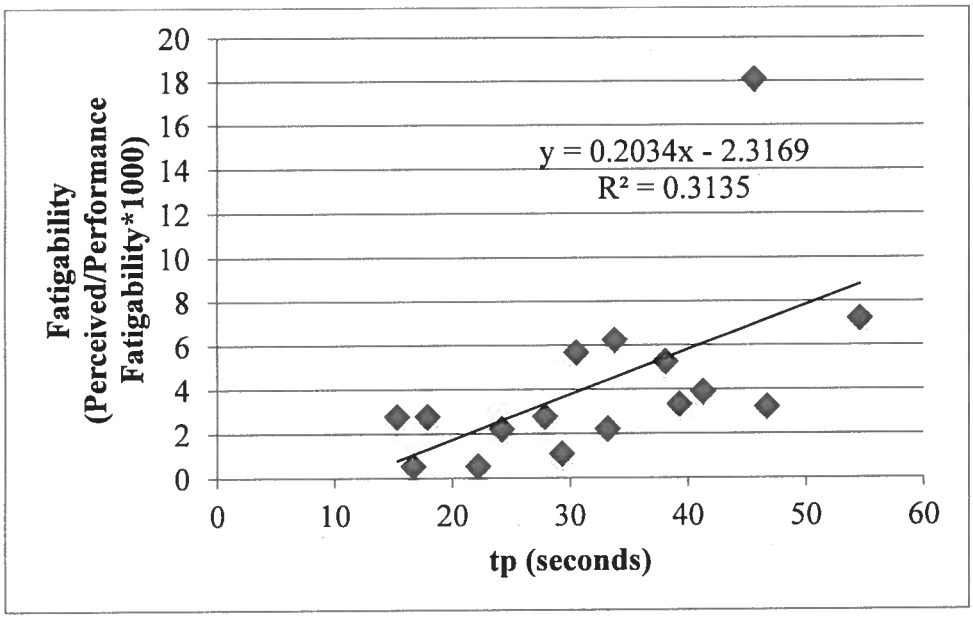

Figure 8 The relationship between fatigability and phase II pulmonary VO_2 time constant (τp) in eight individuals with miSCI and eight able-bodied reference participants. Fatigability was calculated as ratio of perceived fatigability divided by performance fatigability (seconds) multiplied by 1000 (Eq. 1). τp was determined using a mono-exponential model during bout 1 of the constant work-rate (CWR) treadmill test (Eq. 2).

To account for the potential presence of an outlier (data point 45.6, 18.1), a linear regression analysis was performed while excluding the outlier. With the suspected outlier removed the pearson correlation revealed a significant relationship between fatigability and τp ($r = 0.647$; $p = 0.005$). A linear relationship with a positive slope was observed, suggesting that the level of fatigability and τp during the rest-to-work transition were associated ($p = 0.009$). 41.9% of the variability in fatigability was attributable by differences in τp in this model. Given that the removal of the suspected outlier did not alter the trend of the regression, only the analysis including all data points will be discussed.

Muscle Deoxygenation

Due to the absence of the arterial occlusion test, one participant from the reference group (REF_006) was excluded from the analysis of $[HHb]_{total}$, [HHb] ½ time, and ATT. There was a significant difference in [HHb] ½ time between groups (185.9 ± 28.7 vs 157.9 ± 18.9 sec., p=0.047) (table 5). There were no significant differences in $[HHb]_{total}$ or ATT between groups (9.7 ± 5.7 vs 10.7 ± 5.0 a.u., p=0.725;1.7 ± 0.8 vs 1.5 ± 0.5 cm, p=0.558).

Table 5 Resting muscle deoxygenation parameter estimates of the left lateral gastrocnemius during arterial occlusion.

Parameter	miSCI	Reference	p-value
$[HHb]_{total}$ (a.u.)	8.9 ± 5.8	10.7 ± 5.0	p = 0.521
[HHb] ½ time (sec)	185.9 ± 28.7	157.9 ± 18.9	p = 0.047*
ATT (cm)	1.7 ± 0.8	1.5 ± 0.5	p = 0.558

Abbreviations: $[HHb]_{total}$, relative change in left lateral gastrocnemius muscle deoxygenation during arterial occlusion; [HHb] ½ time, time to reach 50% of the plateau in $[HHb]_{total}$; ATT, adipose tissue thickness; a.u., arbitrary units; sec, seconds; cm, centimeters. * Significant difference ($p < 0.05$).

A linear regression analysis was performed to determine the relationship between *t*p and resting [HHb] ½ time. A significant correlation between *t*p and resting [HHb] ½ time ($r = 0.771$; $p < 0.0001$) was observed. In Figure 9, *t*p values were plotted as a function of the corresponding resting [HHb] ½ time and a regression line was drawn. A linear

relationship with a positive slope was observed ($p = 0.001$). 59% of the variability in *t*p was explained by resting [HHb] ½ time in this model.

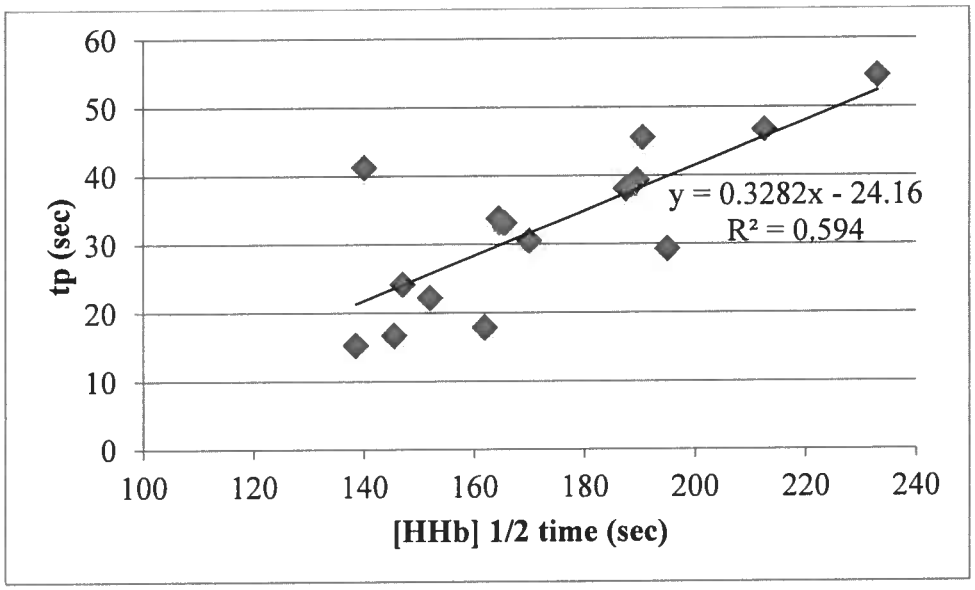

Figure 9 The relationship between phase II pulmonary VO_2 time constant (*t*p) and resting muscle deoxygenation halftime ([HHb] ½ time) of the left lateral gastrocnemius in eight individuals with miSCI and seven able-bodied reference participants. *t*p was determined using a mono-exponential model during bout 1 of the constant work-rate (CWR) treadmill test (Eq. 2). Resting [HHb] ½ time was calculated as the time to reach 50% of the plateau in muscle deoxygenation of the left lateral gastrocnemius during arterial occlusion at rest.

CHAPTER FOUR

Discussion

The primary findings of this study were in support of the proposed hypothesis showing that individuals with chronic miSCI had significantly greater levels of fatigability compared to the able-bodied reference group. Additionally, the chronic miSCI group also demonstrated slower pulmonary VO_2 on-kinetics and resting [HHb] ½ time. The relationship between fatigability and VO_2 on-kinetics and resting [HHb] ½ time suggests that individuals with chronic miSCI may experience elevated levels of fatigability during walking that might be partially explained by cardiorespiratory limitations.

To the best of our knowledge fatigability, as defined in the present study, has not been previously investigated within the context of walking in individuals with chronic miSCI. Preferred walking speed is suggested to be selected based on the minimization of energy expenditure.[46–49] SCI results in an increased metabolic cost of walking as compared to non-injured individuals placing greater strain on the cardiorespiratory system during such activity.[50–52] In the current study there was no difference observed in metabolic cost (i.e., ΔVO_2) of walking between groups despite the chronic miSCI group selecting slower walking speeds. These findings demonstrate that individuals with miSCI select a

preferred walking speed similar in metabolic cost compared to non-injured individuals. Furthermore, irrespective of the similarities in metabolic cost of walking between the groups, those with miSCI reported much greater perceived and performance fatigability.

Our results regarding VO_2 on-kinetic profiles in chronic miSCI during self-selected treadmill walking are in agreement with previous reports demonstrating prolonged VO_2 on-kinetics in individuals with SCI.[53,54] Similarly, the reference group had a VO_2 on-kinetic profile in line with values previously reported in healthy young individuals during moderate-intensity activity (i.e. below the anaerobic threshold).[32,55–59] Of the available evidence on VO_2 on-kinetics post SCI, slowed VO_2 on-kinetics seems to be related in part to alterations in skeletal muscle.[53,54] For example, faster VO_2 on-kinetics were observed in response to voluntary arm exercise compared to leg cycling exercise of paralyzed muscle using functional electrical stimulation (FES) in paraplegics.[54] Therefore, skeletal muscle atrophy, reductions in skeletal muscle oxidative capacity, and changes in skeletal muscle fiber type characteristics as have previously been reported following SCI may all contribute to the observed prolonged VO_2 on-kinetics and fatigability in the present study.[1,25,28,30,60–63]

In the current study, a direct relationship between fatigability severity and the speed of *t*p was observed. These findings were in support of the hypothesis proposed by Grassi et al. that slowed VO_2 on-kinetics provide a biomarker of exercise intolerance and fatigability during moderate-intensity activity.[31] It is generally accepted that the rate at which the

pulmonary, cardiovascular and skeletal muscle bioenergetic systems can respond during rest-to-work transitions is controlled by the bioenergetics of contracting muscle during moderate-intensity exercise in healthy individuals.[64–67] Therefore, it is thought that the transition rate (i.e. *t*p) is not limited by oxygen delivery. Conversely, in populations with chronic illnesses, *t*p may become limited by impairment of one or all of the systems involved in cardiorespiratory function.[67] Irrespective of the mechanism, individuals are likely to experience more severe fatigability when *t*p is prolonged. Therefore, interventions capable of enhancing the processes associated with the delivery and utilization of oxygen at the onset of physical activity may aid in the development of fatigue resistance in the chronic miSCI population.

While VO_2 on-kinetics has been used to make inferences regarding skeletal muscle metabolic control, NIRS technology provides a non-invasive measure of changes in localized skeletal muscle oxygen concentrations.[40,44,45,68] Using NIRS technology combined with arterial occlusion and FES, Erikson et al. observed reduced mitochondrial capacity in individuals with SCI AIS A & B compared to non-injured individuals.[30] Similarly, we found prolonged resting [HHb] ½ time of the left lateral gastrocnemius muscle during complete arterial occlusion in the chronic miSCI group compared a non-injured reference group. These data provide a direct measure of skeletal muscle oxygenation and imply that skeletal muscle oxidative capacity may have been reduced in this group of chronic miSCI. Furthermore, the direct linear relationship between *t*p and resting [HHb] ½ time observed in the present study provides additional evidence for the

potential influence of reduced rate of skeletal muscle oxygen utilization on VO_2 on-kinetics.

CHAPTER FIVE

Limitations

The primary limitation to this study was the small sample size which included highly motivated individuals with chronic miSCI who were ambulatory preventing the generalizability of our findings to the SCI population as a whole. Given the high motivation levels of the participants enrolled in our study, the measures of fatigability may be difficult to interpret in the greater SCI population. Another limitation to the study was the absence of pulmonary VO_2max testing which prevented our ability to control for the intensity at which each participant was walking at on the treadmill. VO_2 capacity has been shown to influence pulmonary VO_2 on-kinetics with higher VO_2max being associated with faster VO_2 on-kinetic profiles.[69] Despite the inability to control for exercise intensity, it was assumed that the intensity of the 6-minute treadmill walking bout fell within the moderate domain (i.e. below anaerobic threshold) given the lack of the presence of a rise in VO_2 despite no increase in work-rate (i.e. slow component) in all but one chronic miSCI participant (participant ABR_004).[67]

CHAPTER SIX

Conclusion

This study demonstrated the relationship between fatigability and chronic miSCI using both perceived and performance fatigability measures during the walking. These individuals living with chronic miSCI appeared to have higher levels of performance and perceived fatigability. The results suggest that poor cardiorespiratory function may be a mediator of fatigability and demonstrate that cardiorespiratory function measures can be used as physiological markers of fatigability in this population. Furthermore, reduced skeletal muscle oxidative capacity is implicated as a potential contributing mechanism to the observed slowed VO_2 on-kinetics.

APPENDIX

Dissertation proposal

Title: Characterization of Cardiorespiratory Function and Walking Fatigability in People with Incomplete Spinal Cord Injury

Muscle fatigue is defined as the decrease in force or power production in response to contractile activity.[23] Following spinal cord injury (SCI) individuals are more fatigable than able-bodied individuals.[1,11,10] It is suggested that fatigue following SCI occurs as a result of impaired contractile function and a reduction in muscle oxidative capacity.[23] In addition, severe physical deconditioning is also experienced as a consequence of the acquired sedentary lifestyle after injury.[70] This posits cardiorespiratory function as a potential variable of interest for intervention to reduce fatigability. Measuring the kinetics of oxygen uptake (VO_2 on-kinetics) at the transition from rest to activity is a method used to assess cardiorespiratory function.[67] The slower the on-kinetic profile the greater the oxygen deficit and more substrate-level phosphorylation which has also been suggested as a primary mechanism of peripheral fatigue.[21] Following SCI, individuals are reported to experience slower VO_2 on-kinetics when compared to their able-bodied counterparts.[53] This slowing of VO_2 on-kinetics in the SCI population may contribute to

an increase in fatigability if present during walking. Therefore, my broad objective is to better understand of relationship between indices of cardiorespiratory function and walking fatigability in people who have incomplete SCI. I also seek to understand if this information might advance rehabilitation approaches aimed at improving walking performance and reducing fatigability.

No studies, to my knowledge, have investigated VO_2 on-kinetics in response to complete weight-bearing volitional walking in individuals with SCI. I will address this informational gap through an investigation of cardiorespiratory adjustments during volitional treadmill walking in persons with incomplete SCI. I will first characterize the responses of VO_2 on-kinetics and muscle oxygenation during treadmill walking in persons with incomplete SCI and a healthy comparison group. Lastly, I aim to determine the subsequent impact of the relationships of VO_2 on-kinetics and muscle oxygenation on peripheral and perceptual aspects of fatigue in persons with incomplete SCI.

Research Question

How does motor-incomplete SCI affect cardiorespiratory function and fatigability?

Specific Aim: "Characterize VO_2 On-Kinetics, Muscle Oxygenation, and the Severity of Fatigability during Self-Selected Pace Treadmill Walking."

Hypothesis 1.a: *Individuals with iSCI will demonstrate slower VO_2 on-kinetics during a 6-minute constant work-rate treadmill test compared to a healthy non-SCI comparison group.*

Hypothesis 1.b: *Individuals with iSCI will demonstrate slower muscle deoxygenation kinetics during a 6-minute constant work-rate treadmill test compared to a healthy non-SCI comparison group.*

Hypothesis 1.c: *Individuals with iSCI will demonstrate greater perceived fatigability severity during a time to exhaustion treadmill test compared to healthy non-SCI comparison group.*

Hypothesis 1.d: *Individuals with iSCI will demonstrate reductions in walking time to exhaustion compared to healthy non-SCI comparison group.*

Methods

Population: Participation of human subjects will be approved by an institutional review board prior to the initiation of the study. All participants will be advised of potential risks and benefits of their participation. Written inform consent will be obtained for all participants prior to enrollment in the study. Inclusion criteria will consist of participants with incomplete SCI grade AIS C or D according to the American Spinal Injury Association Impairment Scale classification. Participants will be included if between the ages of 18-66, have sustained an injury at the T10 level or higher, at least one year post injury, the ability to take at least one step independently with or without assistive walking

devices, the ability to stand for 5 continuous minutes with or without assistive devices, and the ability to safely walk on a treadmill. Participants currently prescribed antispasticity medications will be eligible for inclusion. Exclusion criteria will include complete SCI persons grade AIS A and B, any significant orthopedic complications, spasms or contractures preventing locomotion, have participated in an intensive training program within the previous six months, any history of ischemic heart disease, known cardiovascular, pulmonary, or metabolic diseases, severe psychiatric disease, use of medications that may limit exercise capacity, antiretroviral therapies, illicit drugs, tobacco use, or pregnancy. Participants will be asked to refrain from engaging in any structured exercise activities at least 48 hours prior to the exercise testing session and during their time enrolled in the intervention.

Experimental Procedures: Participants will be asked to report to the Functional Performance Laboratory at George Mason University for two evaluation sessions lasting about 3 hours. Each participant will be asked to fast for at least 12 hours prior to arriving to the Functional Performance Laboratory. Following the completion of the informed consent and inclusion into the study, a health history and physical activity recall questionnaire will be completed. Participants will then undergo standard assessments for height, weight, percent body-fat, and resting blood pressure. Participants will then complete a thigh arterial occlusion assessment to determine the maximal capacity of muscle oxygen utilization of the lateral gastrocnemius. After the thigh arterial occlusion assessment, standard measurements of pulmonary gas exchange and lateral

gastrocnemius oxygen utilization will be obtained during a 6-minute constant work-rate and time to exhaustion treadmill test.

Thigh Arterial Occlusion Test: Prior to the exercise bout each participant will perform an arterial occlusion assessment to determine the maximal oxygen utilization capacity of the muscle. The participant will be placed in a supine position and fitted with a blood pressure cuff at the level of the thigh just above the knee and on the same leg as the NIRS optode. The cuff will be inflated to >220 mm Hg to occlude arterial blood flow and desaturate the muscle hemoglobin to a level of zero oxygenation. Complete deoxygenation of the hemoglobin is operationally defined as the observance of a sustained plateau (30 seconds) in oxygenated hemoglobin [O_2Hb] and deoxygenated hemoglobin [HHb] concentrations. Following complete deoxygenation, the pressure in the cuff will be released allowing for blood reperfusion of the lower the leg.[42] During this time, NIRS assessment of muscle reoxygenation will be measured. The maximum physiologic capacity of muscle oxygen utilization will be calculated by assigning a value of 0% to the lowest value achieved by arterial occlusion of the thigh and the highest value during subsequent hyperemia a value of 100%.

Treadmill Walking Protocol: Each participant will perform two bouts of walking at a self-selected walking speed with a 6 minute rest in between bouts. The walking speed selected by the participant that best represents their preferred walking speed on the treadmill will be determined during a familiarization period. The familiarization period

will consist of having each participant walk at a variety of speeds and determining which speed best represents what they consider to be their most comfortable speed. The first walking bout will be performed for 6-minutes to assess VO_2 on-kinetics and muscle deoxygenation. Following the 6 minute rest, each participant will complete a second walking bout to exhaustion at their self-selected walking speed. Volitional exhaustion will be determined by the participant as the point at which they can no longer sustain the walking speed or when the test has reached a maximum of thirty minutes in duration. All treadmill walking tests will be performed on a standard treadmill. Prior to completing the treadmill walking test to exhaustion, gas exchange will be collected while the participant stands or sits statically as tolerated for 3 minutes. This information will be used to calculate the net metabolic cost by subtracting the resting energy cost from the energy cost obtained during treadmill walking.[71]

Gas Exchange: Pulmonary gas exchange will be measured continuously using breath-by-breath open circuit spirometry (Medgraphics, Cardio 2 Ultima, Medical Graphics Corp, St. Paul, MN). The principal outcome measures for the treadmill walking protocol will be VO_2, carbon-dioxide production (VCO_2), and respiratory exchange ratio (RER). Heart rate (HR) will be measured at rest and during exercise by 12-lead electrocardiography (ECG).

Near-Infrared Spectroscopy (NIRS): Muscle oxygenation indices will be obtained using a continuous wave NIRS (Oxymon MK-III, Artinis Medical Systems, The Netherlands).

The NIRS device consists of 3 LED transmitters and 1 high sensitivity PIN diode for the receiver. The 3 transmitters each emit 2 wavelengths (760 nm and 850 nm) of light at 3 separate transmitter– receiver distances (30 mm, 35 mm, and 40 mm). As a default set up to maximize penetration we will perform all data analysis on the 40 mm transmitter–receiver channel. Muscle oxygenation will be measured in the lateral gastrocnemius and will include amplitude changes of deoxygenated and oxygenated hemoglobin/myoglobin ([HHb] and [O_2Hb], respectively) from rest to volitional exhaustion during the treadmill walking test. Total tissue hemoglobin ([tHb]) concentration will be calculated as the sum of [O_2Hb] and [HHb], whereas the hemoglobin concentration difference ([Hb-diff]) will be determined by subtracting [HHb] from [O_2Hb]. To account for adipose thickness a skinfold measurement will be obtained at the site of optode placement.[72]

Perceived Fatigue and Fatigability Severity Scales: The perceived fatigability severity of each participant will be assessed by asking them to rate their level of tiredness before and at the completion of the treadmill walking test to exhaustion. Perceived fatigability severity will be calculated by dividing the participant's perceived rating of change in tiredness by the time walked in seconds during the treadmill test. A higher score will indicate a greater fatigability severity.[16]

Fatigue Scale Items (Before Walking Test)	Score	Fatigability Scale Items (After Walking Test)
Extremely tired	7	Extremely more tired
Somewhat tired	6	Somewhat more tired
A little tired	5	A little more tired
Neither tired nor energetic	4	Neither more tired nor energetic
A little energetic	3	A little more energetic
Somewhat energetic	2	Somewhat more energetic
Extremely energetic	1	Extremely more energetic

Statistical Analysis: Changes in VO_2 kinetics, muscle oxygenation, and fatigability severity will be analyzed by comparing variables across the walking bout using a two-way ANOVA with repeated measures. Tukey's post hoc analysis will be performed if significant differences are found. Statistical significance will be set at a level of $p<0.05$. All values will be expressed as means ± SD.[72,73] All statistical analyses will be performed using SPSS version 21 (IBM, Inc.).

Review of Literature

Traumatic spinal cord injury occurs when the spinal column is damaged as a result of an insult. In the United States of America approximately 17,000 new spinal cord injury (SCI) cases are reported each year with an estimated 282,000 people currently living with an SCI.[74] Of those 282,000 estimated cases, 66% of them are classified as incomplete spinal cord injuries (iSCI). The primary cause of injury is vehicle crashes followed by falls, acts of violence, and sports. Despite the advancements in medical care for individuals with SCI, the life expectancy is still significantly lower than that expected for non-spinal cord injured persons. The leading causes of death include pneumonia and septicemia with rising increases in mortality rates for endocrine, metabolic and nutritional diseases, accidents, nervous system diseases, musculoskeletal disorders and mental disorders. In additional to the concerns associated with increased risk of secondary complications reported in this population, individuals living with SCI endure significant annual health care and living expenses.[74]

SCI is classified according to the severity of the injury. The International Standards of Neurological Classification of Spinal Cord Injury (ISNCSCI) is the currently recommended guidelines for spinal cord severity categorization.[33] Under the ISNCSCI the American Spinal Injury Association (ASIA) Impairment Scale (AIS) classifies SCI severity into 5 categories, AIS A; AIS B; AIS C; AIS D; and AIS E. According to the AIS, AIS A are individuals considered to be complete injuries which includes no sensory

or motor function in the sacral segments S4-5. AIS B includes individuals with sensory but no motor preserved below the neurological level of injury and includes the sacral segments S4-5 and no motor function is preserved more then three levels below the motor level on either side of the body. An individual is categorized as AIS C when motor function is preserved below the neurological level of injury and more than half of the key muscle functions below the neurological level of injury have muscle grades less than 3. AIS D encompasses individuals with motor function preservation below the neurological level and at least half of the key muscle functions below the neurological level of injury have a muscle grade of greater than 3. AIS E is the final classification and includes all individuals that when tested with ISNCSCI sensation and motor function are graded as normal in all segments and the patient had prior deficits.[33]

Fatigue and Fatigability

Fatigue is a complex phenomenon defined as a disabling symptom in which physical and cognitive function is limited by interactions between performance fatigability and perceived fatigability.[14,16,17] Perceived fatigability is an increase in feelings of exhaustion, tiredness, or lack of energy [15,16,17,14] and performance fatigability represents decrements in physical performance of a task with respect to time, intensity or frequency of activity.[16,17,14] Most often performance fatigability is used to assess fatigue in healthy populations.[20,22,23,75,76] It has been commonly assumed that the onset of fatigue in healthy and athletic populations is directly related to physical and not psychological factors.[77]

Conversely, perceived fatigability uses self-reported measures of fatigue which is often used when is typically used to assess fatigue in clinical populations.[2–5,8,9,12,13,78] The use of self-report methods to assess perceived fatigability eliminates the potential concern of subjecting individuals with chronic illness and or disease to physically exhausting activities. While qualitative approaches eliminate such concerns they do not allow for direct assessments of physiological variables implicated as contributing to fatigue.

Individuals with SCI have a high risk of experiencing fatigue and have been shown to be susceptible to experiencing excessive tiredness when performing extended tasks (2-3 hours).[8] Severity of fatigue was reported to be greater in individuals with incomplete spinal cord injury when assess using the Fatigue Severity Scale (FSS).[4] Freixes et al. reported 5 of 26 patients (19.2%) with AIS D who were community ambulatory and in outpatient reported fatigue using the FSS. Furthermore, fatigue in SCI has been demonstrated to have a close relationship with depression, pain, and hopelessness.[5] Similarly, pain, weakness, fatigue, and memory loss have been identified as symptoms most closely associated with patient functioning in persons with SCI.[3]

Fatigue has been reported as being greatest among individuals with SCI who are younger (those between ages of 40 to 65) and had a shorter duration of disability.[2] The authors attempted to explain this finding by suggesting that younger individuals with SCI perhaps live a more active lifestyle or even a lifestyle that exceeds their energy levels.[2] Fatigue was significantly related to continuing to work and to the number of hours worked. It

was also shown that fatigue has a number of negative effects on health problems, disability problems, perceived temporal disadvantage, and ultimately on quality of life.[2]

Skeletal muscle fatigue in SCI is suggested to result as a combination of impaired contractile function and a lower oxidative capacity as a result of chronic disuse.[23] Neural factors beyond the injury and impaired blood flow do not appear to be primary mechanisms for muscle fatigability in this population.[23] In chronically paralyzed human soleus muscle it was suggested that the source of the fatigue was within the contractile mechanism and not attributable to neuromuscular transmission compromise.[1] Qualitative histochemical analysis showed greater than 90% of the sampled chronically paralyzed soleus muscle was comprised of type II fibers and had reduced oxidative capacity. It was concluded that fatigability, relaxation properties, and histochemical analysis supports that the chronically paralyzed soleus muscle functions and stains qualitatively as a composite of type IIB muscle fibers. Conversely, within 6 wks of paralysis, the fatigability and relaxation property changes were minimal in the human soleus muscle as would be expected in a predominantly slow muscle.[1]

Extending the work of Shields, fatigue of the right triceps surae muscle of thirteen individuals with complete SCI using neuromuscular electrical stimulation at 30-hz (2 s on 2 s off) composed of three series of 5 trains was assessed. Spinal excitability was assessed using the H-reflex, muscle excitability was assessed using the M-wave, muscle contractile properties were assessed using mechanical response parameters, and torque

evoked NMES. The results of this study indicated significant fatigue development which was attributable to impaired cross-bridge force-generating capacity without modification of spinal excitability nor muscle excitability.[11]

Pulmonary VO_2 on-kinetics

Oxygen uptake at the rest-to-work transition (VO_2 on-kinetics) is dependent on the interactions of the pulmonary, cardiovascular and skeletal muscle bioenergetic systems.[67] Oxygen (O_2) moves from the environment into the lungs where it can then diffuse into the blood stream to be transported to working muscle(s) for energy production (i.e. adenosine triphosphate (ATP) synthesis). VO_2 on-kinetics within the moderate-intensity domain (i.e. below the anaerobic threshold) is suggested to be controlled by skeletal muscle metabolism and not limited by O_2 delivery.[34,64,67,79,80] However, in diseased populations this relationship may shift towards O_2 delivery becoming a primary limitation to VO_2 on-kinetics.[67] Peripheral factors influencing VO_2 on-kinetic profiles may include but is not limited to motor unit recruitment, cardiorespiratory fitness, and skeletal muscle oxidative capacity.[31,56,69,81,82]

VO_2 on-kinetics is calculated using raw breath-by-breath data collected during constant work-rate exercise. The data is then analyzed using a curvilinear least squares fitting procedure with a mono-exponential model.[34,35] The tri-phasic VO_2 on-kinetic response is determined by the time constant (τp), time delay (TDp), and amplitude (ΔVO_2)

characteristics of the rise in VO_2 to a steady state or asymptote. A mean response time can be estimated algebraically the time taken to reach 63% of the ΔVO_2 and *t*p, can be estimated by subtracting the time delay (phase 1) from the mean response time.[34] Phase I of the response has been identified as the "cardiodynamic response" and reflects an initial, bolus increase in venous return due to initiation of the muscle pump in addition to muscle oxygen utilization.[35–37] The phase 2 time constant (*t*p) is used as the primary measure of VO_2 on-kinetics to reflect muscle oxygen utilization.[32,35,59,67]

Cardiorespiratory Function in SCI

Cardiorespiratory fitness levels are a known precursor of mortality.[83] Individuals who demonstrate moderate fitness levels increase protective mechanisms on predictors of mortality.[83] Similarly, compromised cardiovascular health among the leading causes of death among SCI.[74,84] In addition, altered cardiorespiratory function is likely to contribute to fatigability during activity given the previously reported elevations in metabolic cost.[50,51] Furthermore, SCI is associated with impaired pulmonary function, reduced cardiorespiratory fitness, alterations in skeletal muscle fiber type characteristics, skeletal muscle atrophy and reduced oxidative capacity all potentially influencing VO_2 on-kinetics.[28,62,63,70,85,86]

VO_2 on-kinetics in SCI has rarely been studied. Moreover, the methods to investigate VO_2 on-kinetics in SCI primarily used functional electrical stimulated muscle

contractions and upper extremity exercise.[53,54,87–90] The findings of these studies show a prolonged VO_2 on-kinetic profile in those with SCI compared to able-bodied controls.[53] To better understand potential mechanisms contributing to the slowed on-kinetic VO_2 responses in those with SCI Barstow et al., compared voluntary exercise (i.e. upper extremity exercise) to FES stimulated exercise (i.e. lower extremity exercise) in individuals with paraplegia.[54] The voluntary upper extremity exercise demonstrated a higher peak heart rate and VO_2 and faster VO_2 on-kinetics compared to FES lower extremity exercise.[54] This led the authors to conclude that slowed VO_2 on-kinetics during FES exercise is the result of some characteristic of the injury such as reduced muscle mass or deconditioning of the remaining muscle mass.[54]

In a feasibility study, Jack et al. conducted cardiopulmonary exercise testing using a CWR treadmill walking protocol with body-weight support in two individuals with chronic miSCI.[88] Due to an inability to obtain steady-state in VO_2, VO_2 on-kinetic parameters could not be accurately obtained.[88] This was the only study to our knowledge which has attempted to investigate VO_2 on-kinetic parameters during treadmill walking in individuals with chronic motor-incomplete SCI (miSCI).[88] Despite the potential value of VO_2 on-kinetic measures, it was found that accuracy in obtaining key parameters was limited potentially preventing the utility of VO_2 on-kinetics in this population.[88]

Near-infrared spectroscopy (NIRS)

NIRS provides noninvasive and continuous monitoring of the relative concentration changes of oxygenated, deoxygenated, and total myoglobin/hemoglobin ([O_2Hb], [HHb], and [tHb] respectively).[40,45,68,91] This technology is also capable of providing absolute changes in tissue oxygen saturation (tissue saturation index, TSI). It is suggested that NIRS measurements primarily reflect changes in the small arterioles, capillaries, and venules and thus any change in [HHb] specifically are presumably a consequence of change in O_2 extraction.[92,93] Therefore, NIRS provides a valuable measurement of localized muscle oxygenation.

Muscle oxygenation indices are obtained using a continuous wave NIRS (Oxymon MK-III, Artinis Medical Systems, The Netherlands) with spatial resolution. The NIRS device consists of 3 LED transmitters and 1 high sensitivity PIN diode for the receiver. The 3 transmitters each emit 2 wavelengths (760 nm and 850 nm) of light at 3 separate transmitter– receiver distances (30 mm, 35 mm, and 40 mm). As a default set up to maximize penetration all data analysis was conducted on the 40 mm transmitter–receiver channel. The NIRS system was calibrated prior to each data collection using the calibration bin supplied by the manufacturing company. The calibration program calculates gain coefficients for each possible gain and power setting. The NIRS signal is analyzed with an algorithm using the modified Beer-Lambert law.[41]

Several studies have used NIRS to investigate skeletal muscle oxygenation in clinical populations.[42,86,94–98] For example, O_2 extraction has been shown to be impaired in

individuals with metabolic myopathies.[94] Using NIRS technology in combination with repeated ischemic occlusion, individuals with SCI have been shown to experience reductions in skeletal muscle oxidative capacity.[86]

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BIOGRAPHY

Jared M. Gollie graduated from Allentown Central Catholic High School in 2001 where he played football and competed on the powerlifting team. He received his Bachelor of Science degree from Wesley College in 2007 where he also continued his football career. He received his Master of Science degree from East Stroudsburg University in 2011. He was employed as a sports performance coach/director at Velocity Sports Performance in Allentown, PA from 2007-2011 and a site director at Explosive Performance in Herndon, VA in 2012. Jared has coached and trained hundreds of individuals including athletes at all levels and clinical populations.