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Comparison of Two Different Sprint Interval Training Work-to-Rest Ratios on Acute Metabolic and Inflammatory Responses

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Comparison of Two Different Sprint Interval Training Work-to-Rest Ratios on Acute Metabolic and Inflammatory Responses

A dissertation proposal submitted in partial fulfillment of the degree of Doctor of Philosophy at Virginia Commonwealth University

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List of Major Abbreviations

ACE – Arm crank ergometry

AMPK – AMP-activated protein kinase

BLC – Blood lactate concentration

DXA – Dual X-ray absorptiometry

GLUT4 – Glucose transporter 4

HIT – High-intensity interval training

IL-6 – Interleukin 6

IL-10 – Interleukin 10

OGTT – Oral glucose tolerance test

SCI – Spinal cord injury/injured

SIT – Sprint interval training

S_i – Insulin Sensitivity

TAB – Tabata training consisting of 20 sec sprints with 10 sec recovery for 4 min.

TNF-α - Tumor necrosis factor alpha

$VO_{2\ Peak}$ – Peak oxygen consumption measured in either $L \cdot min^{-1}$ or $ml \cdot kg^{-1} \cdot min^{-1}$

WIN – Wingate training consisting of maximal 30 sec Wingate sprints with ~4 min recovery.

W:R – Work-to-Rest ratio.

ABSTRACT

COMPARISON OF TWO DIFFERENT SPRINT INTERVAL TRAINING WORK-TO-REST RATIOS ON ACUTE METABOLIC AND INFLAMMATORY RESPONSES

By Christopher R. Harnish, Ph.D.

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High intensity exercise is believed to yield greater results on health and human performance than moderate intensity exercise. Extensive research indicates that not only do high-intensity interval training (HIT) and sprint interval training (SIT) produce significant improvements in cardiovascular fitness and disease, they may be more effective at improving long-term metabolic function, including insulin sensitivity (S_i), by producing more mitochondria. Moreover, compliance rates for HIT and SIT participation are reported to be the same or better than traditional moderate intensity exercise. Because lack of time is often cited as major hindrance to exercise participation, SIT is also seen as a time efficient option to improve health and performance. It does appear, however, that repeated sessions of SIT are needed before overall improvements can be measured. SIT protocols employing maximal 30 sec sprints with ~5 min rest [a 1:9 work-to-rest ratio (W:R)], have garnered much of the research focus, while those using minimal rest periods, like Tabata which uses 20 sec sprints and 10 sec rest (2:1 W:R), have been ignored. This may omit a possible SIT option that could influence acute and chronic adaptations. The role of inflammatory cytokines on Si remains an area of continued research. While endurance exercise is thought to create an overall anti-inflammatory environment that stimulates improvement in Si, SIT is often viewed as pro-inflammatory. However, few studies have provided significant insight into cytokine release following SIT, and none have explored its impact on Si. In addition, the impact of W:R on cytokine remains speculative at best.

Therefore, the examination of the effect of different sprint protocols of similar total work (kJ) on performance, metabolic function, and inflammatory response may provide valuable insight into these adaptive processes.

CHAPTER 1

INTRODUCTION

Exercise is an effective treatment for many of modern society's chronic diseases, yet, exercise remains an underutilized component of disease treatment. In a brief review, Colberg and Grieco (2009) discussed the central role physical activity can and should play in both the prevention and treatment of diabetes. Exercise can be effective in reducing body fat (Sigal et al. 2004; Volek et al. 2005; Thorogood et al. 2011); however, it is far more effective at improving many of the components of metabolic syndrome, including insulin sensitivity (Sigal et al. 2004; Earnest 2008; Colberg and Grieco 2009; Hawley and Gibala 2009). Insulin sensitivity (S_i) and glucose effectiveness, or the ability to uptake glucose into the cell, are driven by a number of factors that include translocation of glucose transporter 4 (GLUT4) inside the cell membrane, and capacity and mitochondrial density (Bournat and Brown 2010).

It is generally believed that high intensity activity may yield greater positive health outcomes than traditional moderate intensity endurance activity. Individuals engaging in greater levels of high-intensity leisure activities actually improve cardiovascular fitness to a greater extent than lower intensity activity (Talbot et al. 2000), decreasing one's risk for disease (Wisloff et al. 2009). Early work by Dudley et al. (1982) eloquently demonstrated enhanced endurance performance in response to increased intensity. In fact, high-intensity training has been shown to reverse long-term cardiac damage (Wisloff et al. 2009), and may yield greater improvements in mitochondrial function and GLUT4 expression. Despite the clear efficacy of exercise for improving health and fitness in a variety of populations, participation in exercise or physical activity remains low, with lack of time being a commonly reported reason (Trost et al. 2001). Thus, researchers and professionals have sought to develop more time efficient exercise strategies that may yield the same results in less time.

The strong relationship between intensity and improved health and human performance via high-intensity interval training (HIT), as well as a growing body of research, indicates that HIT

provides a more powerful stimulus for the improvement of health and fitness (Hawley and Gibala 2009; Earnest 2008). In the past decade, research using HIT and sprint interval training (SIT) have shown great promise in not only improving endurance performance to equal or greater levels than endurance training (Wisloff et al. 2009; Burgomaster et al. 2008; Gibala et al. 2006; Stepto et al. 1999; Acevedo et al. 1989), but also enhancing fat metabolism (Swart et al. 2009), and glucose tolerance (Babraj et al. 2009). It comes as little surprise to sports scientists, who have known for years that peak athletic performance demands maximal intensity exercise. Yet, contemporary exercise advice (ACSM 2009) has recommended similar guidelines to the general public for decades. Some of the reluctance has come from a fear that high intensity intervals were dangerous for high-risk patients (e.g., those with cardiac disease). However, even in post-infarction heart failure patients, exercise intensities greater than 90% peak heart rate were shown to be safe, and compliance rates for such training has been high among a range of populations (Gibala 2011; Wisloff 2011; Wisloff et al. 2009).

Although the metabolic and cardiovascular response to SIT (8-30 sec maximal efforts interspersed with recovery), might not seem as effective as endurance training, this model has been shown to be equal or superior to high volume endurance exercise (Whyte et al. 2013, 2010; Trilk et al. 2011; Brestoff et al. 2010; Richards et al. 2010; Babraj et al. 2009; Burgomaster et al. 2008). In 1996, Tabata et al. demonstrated that just *six weeks* of training using 20 sec sprints with 10 sec rest produced significant improvements in $VO_{2\ Max}$ and anaerobic power. Stepto et al. (1999) later showed that among trained cyclists, 30 sec sprint intervals improved 40 km time trial performance as much as 4 min $VO_{2\ max}$ intervals; both were superior to other intervals used. Since that time, researchers (Burgomaster et al. 2008, Gibala et al. 2006) have demonstrated that supra-maximal 30 sec Wingate SIT produce similar acute metabolic/biochemical changes in the trained musculature as more traditional endurance training. Subsequent data from these researchers has shown that from a cell signaling perspective, SIT is more closely related to endurance than strength training, acting as a

potent stimulus for PGC-1α expression by up regulating AMPK and p38 MAPK signaling pathways (Gibala et al. 2009).

Based on the preponderance of research currently, it is apparent that how hard one exercises (i.e., intensity) strongly influences the adaptive process. This is common knowledge to athletes and coaches, who have long used interval training for peak performance. Unfortunately, adoption of optimal training methods for the general and special populations has lagged. Nonetheless, it is widely accepted that optimal endurance performance requires training at or near maximal intensity (Laursen 2010). In addition, the W:R can have a dramatic impact on both cardiovascular, muscular, and endocrine response to exercise (Ziemann et al. 2011; Gray et al. 1993; Hakkinen and Pakarinen 1993). For example, Tabata et al. (1996) utilized a 2:1 W:R in their 6-week SIT program to produce significant improvements in aerobic and anaerobic fitness. Follow-up research (Tabata et al. 1997) indicated that this 20 sec sprint program achieved maximal stimulation of both aerobic and anaerobic capacity, which was significantly higher than a 1:4 W:R using 30 sec Wingate sprints. Thus, mitochondrial ATP production should be higher using the 2:1 Tabata protocol. This latter point is important, as ATP turnover is believed to be a key variable in mitochondrial biogenesis, aerobic enzyme production and acute metabolic improvements (Thyfault 2008), and may drive long-term adaptations (Gibala et al. 2009, Coffey and Hawley 2007). The former premise was supported by Whyte et al. (2013) who demonstrated that a single maximal 200 sec extended sprint significantly improved 24-hr insulin sensitivity, whereas a single session of four Wingate sprints of similar kJ expenditure did not.

Presently, research indicates that six or more bouts of SIT are needed to produce significant improvements in performance and S_i (Whyte et al. 2013, 2010; Trilk et al. 2011; Brestoff et al. 2010; Richards et al. 2010; Babraj et al. 2009; Burgomaster et al. 2008). It remains unclear whether a single bout of SIT using a low W:R, like that proposed by Tabata et al. (1996), could improve acute S_i or other performance markers, as many of the mechanisms for such a response remain undefined.

For example, Burgomaster et al. (2008) showed that six weeks of SIT produced similar improvements in lipid and carbohydrate oxidation and mitochondrial biogenesis compared to endurance training encompassing ten-times the total work expenditure (225 kj vs. 2250 kj). More recently, researchers have shown that 2-weeks of 30 sec Wingate SIT with ~5 min rest (1:9 W:R) improves metabolic function in obese women (Trilk et al. 2011), young adults (Brestoff et al. 2010; Richard et al. 2010; Babraj et al. 2009), and obese men (Whyte et al. 2010). Only White et al. (2013) have shown an acute improvement in S_i, but that was following a maximal 200 sec continuous effort. If ATP flux is a critical factor, then one could surmise that the Tabata protocol (Tabata et al. 1997 and 1996) would also result in an improvement in S_i. It also raises questions about the mechanisms for chronic SIT adaptations.

It has been suggested that SIT adaptations are short lived and represented early adaptations. Two unrelated studies addressed this issue, and in doing so, validated the *Overload Principal* in untrained and trained individuals. For example, Nordsborg et al. (2010) compared the molecular response via alterations in mRNA PGC-1α following HIT in both untrained and trained (1 yr training and $VO_{2\ Peak}$ 55 ml.kg-1.min-1) individuals. Trained participants did HIT sessions at 85% of the untrained $VO_{2\ Peak}$ power. As expected, training at the same absolute power did not yield any significant changes in the trained group, while 85% of each group's max (i.e., same relative power) showed significant increases in mRNA PGC-1α. Although not surprising, another interesting finding was that lactate levels for trained individuals were significantly lower at the same absolute workload. The latter finding brings into question the role of homeostatic disruption to elicit exercise adaptations, as well as the role of reactive oxygen species (ROS), like H_2O_2, and lactate accumulation, implicating both in the up-regulation of PGC-1α (Lira et al. 2010; Hashimoto et al. 2007). Finally, further support for SIT impact on endurance adaptations were seen in even highly trained cyclists ($VO_{2\ peak}$ ~70 $ml{\cdot}kg^{-1}{\cdot}min^{-1}$), who, after completing a single session of SIT, saw gene expression in several key mitochondrial markers, supporting the notion that it is the relative intensity

of training (i.e., near the individuals "max") that elicits improvements (Niklas et al. 2010). This relative response may have important training implications for non-ambulatory populations, including persons with spinal cord injury (SCI), who suffer from a multitude of cardiovascular and metabolic ailments. Training research among those with SCI is severely deficient; for additional information on SCI please refer to Chapter 2, and for an extended review of SCI please refer to Appendix A.

The implications of homeostatic disruption suggest that the exercise inflammatory response could play an important role in exercise adaptations. Endurance exercise is generally considered to be anti-inflammatory (Petersen and Pedersen 2006) in the sense that on balance, anti-inflammatory cytokines like IL-6 and IL-10 exceed inflammatory cytokines like TNF-α (Ropelle et al. 2010; Pedersen and Fischer 2007; Petersen and Pedersen 2005), and that the release of IL-6 is proportional to the intensity and muscle mass utilized during training (Fischer et al. 2006). Further, IL-10 has been proposed as a major influence on S_i at rest (Staczkowski et al. 2005), and Steensberg et al. (2003) have shown that IL-6 infusion enhances IL-10 release.

Alterations in inflammatory cytokines (e.g., IL-6, IL-10, and TNF-α) have been implicated as mediators of glucose regulation at rest (Harnish et al. 2005; Staczkowski et al. 2005, Pedersen et al. 2001), as well as during and after exercise (Brandt and Pedersen 2010; Hong et al. 2009; Pedersen and Fischer 2007; Fischer et al. 2006; Petersen and Pedersen 2005; Febbraio and Pedersen 2002; Pedersen et al. 2001). Moderate to high intensity endurance exercise is known to be a potent stimulus for IL-6 release from muscles (Febbraio and Pedersen 2002), but less is known about short duration maximal or sprint exercise. For example, a 2-fold increase in IL-6 was seen in exercise as short as 6 min at $VO_{2\ max}$ (Nielsen et al. 1996), and following run sprint training (Meckel et al. 2011, 2009) Figure 1 summarizes the current proposed impact of muscle-derived IL-6 on GLUT-4 and overall

glucose uptake. As indicated, IL-6 is believed to both stimulate GLUT-4 activity directly, as well as stimulate IL-10 release, which itself may improve S_i (Steensberg et al. 2003).

In contrast to endurance exercise, SIT has been described as more pro-inflammatory (Meckel et al. 2011, 2009; Nemet et al. 2009). If this is correct, it might help explain the lack of acute improvement in S_i. In general, the literature regarding the inflammatory cytokine (e.g., IL-6, IL-10, and TNF-α) response following SIT appears inconclusive. For example, Meckel et al. (2011; 2009) showed that IL-6, considered pro-inflammatory by these researchers, peaked 1-hr after run sprint training, while Brestoff et al. (2010) showed inconclusive results for IL-6 and TNF-α. Whether inflammatory cytokines influence acute improvements in S_i following SIT remain to be seen, as no study to date has examined this possible mechanism. Additionally, W:R can dramatically impact metabolic stress, cardiovascular demand, and endocrine response during and following exercise (Ziemann et al. 2011; Tabata et al. 1997; Gray et al. 1993; Hakkinen and Pakarinen 1993). Little is known about the impact of W:R on cytokine release.

In spite of the large body of evidence supporting the efficacy of long-term SIT, questions remain regarding the mechanisms for SIT adaptations, as well as the acute (i.e., 1 – 24 hr post) response following SIT. In particular, W:R may influence acute adaptations, as well as the inflammatory response. Therefore, it would be valuable to examine the effect of different sprint protocols of similar total work (kJ) on performance, metabolic function, and inflammatory response.

In order to further evaluate SIT, we performed two separate studies to examine if SIT could be applied to upper extremity training, and a second to ascertain if an alteration in W:R could clarify some of the possible mechanisms for acute SIT. In the first study (see Chapter 2) , a group of men with chronic spinal cord injury engaged in 2 weeks of arm crank sprint training. Positive influence of metabolic factors could be critically important in improving the health of this population. In a follow-up study (see Chapter 3), energy expenditure was matched between Wingate SIT and 5 min

of Tabata training using 20 sec of sprinting with 10 sec of recovery. In this latter study, we sought to explore whether the compressed W:R would improve S_i, and whether those changes were related to inflammatory cytokines, cited as a key player in endurance training improvements in S_i.

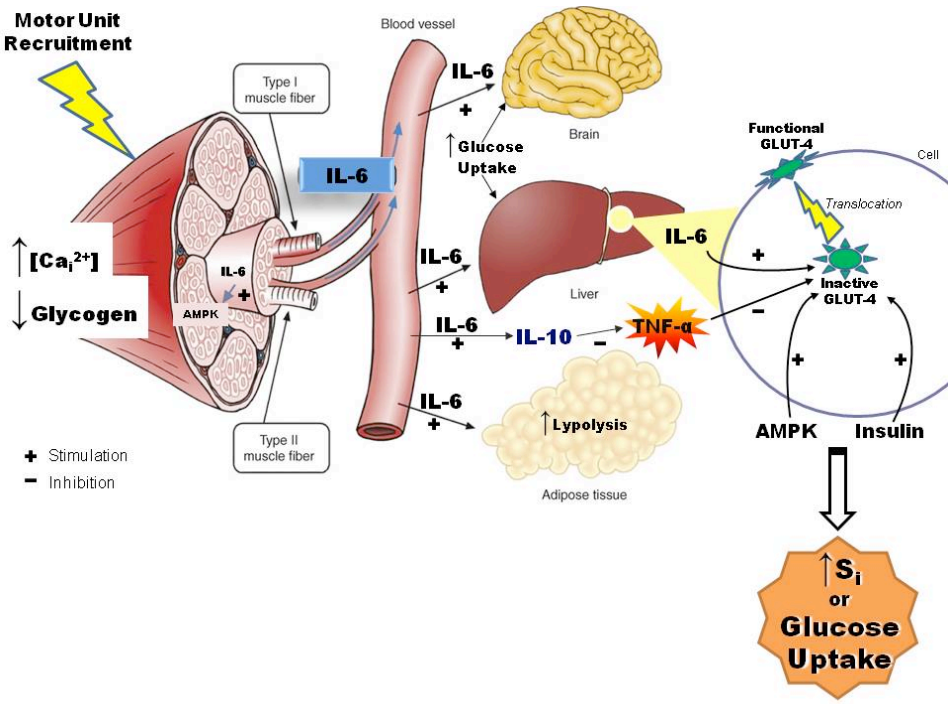

Figure 1. Schematic summary of the initiation of muscle-derived IL-6 release and the subsequent role that IL-6 plays in various organs that lead to enhanced glucose uptake. IL-6 promotes GLUT-4 activation in the brain, liver, and even skeletal muscle, as well as promoting IL-10 production. IL-10 blocks TNF-α and macrophage constituents, which interfere with GLUT-4 (Adapted from Febbraio and Pedersen 2002; Pedersen and Fischer 2007).

CHAPTER 2

The effects of two weeks of arm crank sprint interval training in men with chronic spinal cord injury (SCI)

Research conducted at the Hunter Holmes McGuire VAMC, Richmond, VA

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ABSTRACT

The purpose of this study was to examine the performance and metabolic effects of two weeks of sprint interval training (SIT) in men with spinal cord injury (SCI). Eight males aged 47 (44, 56.8) yrs, 180.8 (2.4) cm tall, 85.1 (6.9) kg, and a peak 2 min power output of 90 (60, 135) W with chronic SCI, T1-T10 completed three OGTT's - baseline, 2 weeks later (Pre), and 48 hrs Post training, with corresponding 24 hr dietary recall during each. Six SIT sessions over 2-weeks were performed on a Monark 891E ACE. Subjects cranked against 3.5% body mass for 30 sec, completing 4 sprints session 1, then 5, 5, 6, 6, and 7 sprints in the final session. All data are presented as medians (Q1, Q3), and a Wilcoxon test (α=0.05) was used to test for significant pre and post session changes. Dietary analysis indicated subjects consumed 1907 (1288, 2751) kcal, consisting of 50.5 (38.7, 57.8)% CHO and 31.0 (26.3, 37.9)% Fat. Work during the first four sprints of each session increased (p=0.13) from 23.0 (18.4, 26.3) to 25.7 (19.8, 32.1) kJ between the first session and last. AUC for either glucose or insulin did not significantly change and were and highly variable. ISI-Cederholm insulin sensitivity (Si), was 151.6 (145.2, 176.0) baseline, 179.2 (162.7, 190.8) Pre, and 165.2 (141.0, 202.3) Post. Plasma NEFA area under the curve was significantly improved (p=0.008), however. In conclusion, two weeks of ACE SIT was effective at reducing NEFA in men with SCI, but did not improve insulin sensitivity. These data indicate that ACE SIT may be an effective adjunct training modality for those with SCI and other non-ambulatory populations.

Key Words
Spinal cord injury, sprint interval training, insulin sensitivity, arm crank ergometry, OGTT

INTRODUCTION

More than 6 million (~2%) Americans are living with a spinal cord injury or disorder (4). Numerous studies have shown that up to half of persons with spinal cord injury (SCI) are obese, with nearly 70% of persons with SCI exhibiting two or more components of Metabolic Syndrome (6,8,9,18). Poor glucose and insulin regulation, as well as dyslipidemia, are also common (25). Due to the close relationship between metabolic syndrome and both obesity and blood sugar management, mitigating either or both of these conditions is a priority for many populations, including SCI. Little is known, however, on the impact of specific ACE interventions among SCI.

Upper extremity training is effective at improving central and peripheral fitness, and may transfer to lower extremity fitness (2,23). Although training the upper extremities does improve force production and endurance of the muscles trained, intensity appears to be a critical factor in upper extremity fitness and transfer to lower extremity fitness (23). Nevertheless, the data are sparse for SCI training interventions, particularly high-intensity protocols. Moreover, the potential metabolic benefits of SIT could provide substantial benefit to the myriad of metabolic disorders common among SCI.

Exercise can be effective in reducing body fat (24) and improving many of the components of metabolic syndrome, like insulin sensitivity (5,7,13). The link between improved mitochondrial function and glucose transporter (GLUT) 4 expression led Earnest (7) to hypothesize that high-intensity interval training (HIT) provides a more powerful stimulus improving insulin sensitivity than moderate aerobic exercise, relating specifically to the aerobic metabolic processes (e.g., aerobic glycolysis, beta oxidation, and mitochondrial biogenesis). Moreover, greater levels of high-intensity leisure activities improve cardiovascular fitness, decreasing one's risk for disease (22,26).

Results by Gibala and others (1,3,10) show the powerful endurance-like impact that sprint interval training (SIT) has on oxidative capacity and metabolic function. For example, Burgomaster et al. (3) showed that six weeks of SIT produced similar improvements in lipid levels, carbohydrate

oxidation, and mitochondrial biogenesis compared to endurance training encompassing ten-times the total work expenditure (225 kJ vs 2250 kJ). More recently, Babraj et al. (1) showed that six sessions of SIT improved insulin sensitivity by 37%, as well as a significant reduction in non-esterified fatty acids (NEFA). Unfortunately, many populations lack adequate ambulation necessary to effectively utilize leg ergometry (12), and may be limited to upper extremity exercise, with arm crank ergometry (ACE) being common.

The purposes of this study were to examine the efficacy of six sessions of ACE SIT on sprint performance and metabolic factors, including insulin sensitivity and plasma NEFA's. We hypothesized that ACE SIT would improve insulin sensitivity (ISI-Cederholm), reduce plasma NEFA,'s and improve repeated Wingate performance from pre-regimen levels in men with SCI.

METHODS

Experimental Approach to the Problem

The experimental protocol (Figure 1) was similar to previous SIT studies (1,3,10). Due to difficulty in recruiting and transporting persons with SCI, we utilized a two-week control period where two separate oral glucose tolerance tests (OGTTs) were compared when lifestyle and activity were unchanged. During this two-week period, subjects performed baseline and pre-training (Pre) OGTT with 24 hr dietary recall, and DXA body composition analysis. Within this two-week contol period, subjects were familiarized with ACE Wingate training no less 5 days prior to the second OGTT to prevent any possible effect on blood test. Once completed, each participant began their sprint training within 36 hrs after the Pre OGTT. The sprint training took place over a period of 2 weeks with a total of six training sessions. A final post training (Post) OGTT was performed between 48 and 60 hrs of the final training session. Utilizing this protocol, we surmised that baseline and Pre blood variables would not change, while those same variables would change -- as shown in other studies (1,3,10) -- after six sessions of SIT. Enrollment and testing began in June 2010 and were concluded approximately 18 mo later.

Subjects

All experimental protocols were reviewed and approved by the McGuire VAMC institutional review board and comply with the Declaration of Helsinki. All participants were actively recruited through word of mouth, flyers and call lists, with individuals being both veterans visiting the Hunter Holmes McGuire Veterans Administration Medical Center (VAMC) and individuals living in the greater Richmond, Virginia (USA) Community. Subjects were enrolled in the study following completion of the McGuire IRB approved informed consent document. A detailed medical history and ACSM risk factor assessment was performed for all participants and each subject was reviewed by a board-certified physician. Only individuals considered paraplegics (i.e., T1–L2) AIS-A through D for 3 months or longer were considered for the study. Individuals classified as High Risk based on established American College of Sports Medicine criteria, persons with known orthopedic limitations, diabetes mellitus (fasting glucose > 126 or HgbA1c > 7.0), hypothyroidism, renal disease, uncontrolled autonomic dysreflexia, recent (within 3 months) deep vein thrombosis, or pressure ulcers > Grade II were excluded from participation. Twelve sedentary men with T1 – T10 SCI initiated the study, with eight completing the entire protocol; these eight were aged 47 (44, 56.8) yrs, 180.8 (2.4) cm tall, 85.1 (6.9) kg, and a peak 2 min power output of 90 (60, 135) W. The study was conducted over the course of 18 months.

Procedures

Subjects were instructed to maintain their usual diet throughout the study and to consume similar meals the day before each OGTT; a standard 24 hr dietary recall form for the day prior to the OGTT were used to instruct subject's on maintaining their dietary habits and used for later comparison; subjects were also instructed to consume 8-16 oz of water prior to their arrival for testing. During the pre-training control period, each subject completed one to $VO_{2\ Peak}$ testing was used to assess physical readiness and determine maximum 2 min power after the first OGTT. Testing was performed using a Lode upper extremity ergometer (Electro-Med Corporation, Flint, MI).

Subjects performed the test in their own stabilized wheelchair with appropriate seating, trunk support, leg wraps, abdominal binder and protective hand mitts provided. Each subject cranked at 70 RPM against no resistance for 3 min before work rate was increased by 15 W every 3 min until volitional exhaustion was reached. VO_2 and HR were measured continuously using a Cosmed K^4b^2 (Rome, Italy) and stored for later analysis. Subjects were familiarized with the training protocol no less than 5 days prior to training to mitigate any influence on the Pre OGTT.

Sprint training was performed using a mechanically braked Monark 891E arm crank ergometer (ACE) (Monark Exercise AB, Sweden) while sitting in their own stabilized wheelchair with appropriate seating, trunk support, leg wraps, abdominal binder and protective hand mitts provided. Following 10 min of unloaded warm-up at 30-50 rpm, each subject cranked as fast as possible for 30 sec against a resistance equivalent to 0.035 kg/kg (3.5%) body weight; this resistance was tested during the pilot phase of this study and has been shown to be suitable for thoracic level persons with SCI (14). Subjects cranked while being provided with vigorous verbal encouragement throughout each sprint. Peak and mean power (W) and total work (kJ) were recorded using the software provided with the ergometer. Each sprint was followed by ~5 min of rest or slow reverse pedaling. The initial training session included four sprints progressing to five sprints in sessions 2 and 3, six sprints in sessions 4 and 5, and finally seven sprints in the final session. Sessions were separated by at least 48 hrs, but no more than 72 hrs (i.e., one weekend). During sessions 1 and 6, 5 µl blood lactate samples were taken from the subject's earlobe using a small plastic lancet and immediately analyzed using a Lactate Scout Analyzer (EKF diagnostic sales GmbH, Barleben/Magdeburg). Samples were taken prior to training, after sprint 1, 4 and 7 (during session 6), and 1 and 3 min post exercise. Each training session lasted approximately 30 min. Due to the increase in the number of sprints performed during training, the relative improvement in overall sprint work capacity was compared using the total kJ expenditure

All OGTT were performed between 0800 and 1000 hours, and each subject's tests were conducted at the same time (± 5 min) of the first test. Subjects refrained from performing any strenuous physical activity for a period of 72 hrs prior to baseline and Pre OGTT, and arrived at the laboratory following at least a 12 hr overnight fast. Venous blood samples (~10 ml) were collected by venupuncture before ingestion, and at 60, 90 and 120 min after ingestion of 75 g glucose (NOW Foods, Bloomingdale, IL) dissolved in 100 ml of water. Plasma was separated by centrifugation (15 min at 7000 rpm) and stored at -20°C until analysis of glucose, insulin, and NEFA concentrations. Plasma glucose concentrations were measured using an auto-analyzer glucose oxidase method, while plasma insulin concentrations were determined by ELISA (R&D Systems, Inc, Minneapolis, MN). Plasma NEFA concentrations were determined by a colorimetric assay (Wako Chemicals, Germany) using a modified protocol. Briefly, 3.75 µl of plasma samples and standards of known concentration were pipetted into a 96-well plate. 75 µl of color reagent A were added to each well and incubated at 37°C for 10 min. 150 µl of colour reagent B were added and incubated for a further 10 min at 37°C. The plate was then removed from the incubator and allowed to cool to room temperature prior to the absorbance being read at 550 nm. In order to assess normal intra-individual variation in response to an OGTT over a period of several weeks as used in the present study, all subjects performed the initial OGTT prior to any testing in week 0 and compared to the Pre training test at week 2.

Statistical Analyses

Data were analyzed using commercially available software (Jump 11.0, SAS Institute Inc, Cary, NC). Due to the relatively small final sample size, all measurements are presented as medians and quartiles (Q1, Q3), except where noted. Area under the curve (AUC) was calculated using the trapezoidal rule and peripheral insulin sensitivity (S_i) was estimated using ISI-Cederholm.

$$\frac{75000+(G0-G120)*1.15*180*0.19*BW}{120*G_{mean}*\log(I_{Mean})}$$

BW = body weight, G_0 and G_{120} are plasma glucose concentration at 0 and 120 min ($mmol \cdot l^{-1}$), and I_{mean} and G_{mean} are the mean insulin ($mU \cdot l^{-}1$) and glucose ($mmol \cdot l^{-1}$) concentrations during the

OGTT. The Wilcoxon Signed-Rank test (α=0.05) was used to compare AUC values pre- to post-regimen. In these tests we hypothesize a decrease in AUC for each measurement after the sprint interval regimen, against a null hypothesis of no change. For each measurement, the median difference in AUCs and quartiles (Q1, Q3) are reported due to the small sample size. A 5% significance level was used for all tests.

RESULTS

The average work during sprints increased from 5.75 (4.61, 6.86) to 6.13 (4.78, 7.75) kJ the first session and last, or a nearly 7% improvement (p = 0.13). Table 1 shows the median (and IQR) AUC both pre- and post-test (as well as the median differences (and IQR) in absolute measures). AUC changes for either glucose (p = 0.55) or insulin (p = 0.38) failed to show significant changes. ISI-Cederholm 151.6 (145.2, 176.0) baseline, 179.2 (162.7, 190.8) Pre, and 165.2 (141.0, 202.3) Post, also did not show significant changes (0.60); close inspection of the individual data (Figure 2) show large variation between the three OGTT periods. Further, the variability could not be explained by differences in dietary intake. Dietary analysis indicated subjects consumed 1907 (1288, 2751) kcal, consisting of 50.5 (38.7, 57.8)% CHO and 31.0 (26.3, 37.9)% Fat, without significant variations between tests. There was a significant reduction in NEFA (p = 0.008), as the NEFA AUC post intervention was -0.3 units lower than the NEFA AUC pre-intervention (Table 2).

DISCUSSION

The purpose of this study was to evaluate the efficacy of arm crank SIT for paraplegic men. Based on the available research for leg sprinting (1,3,10) and upper extremity training (20,23), we speculated that ACE SIT could improve sprint performance and metabolic factors in men with chronic SCI. While this preliminary study could not find a significant improvement in glucose tolerance or insulin sensitivity, we did see a significant reduction in NEFA. These findings suggest that while SCI may exhibit too much variability in carbohydrate metabolism to make oral glucose tolerance tests sensitive enough for training evaluations, but NEFA measurement may be a useful

alternative in men with SCI. Additionally, the study is an important step in optimizing ACE training for SCI and others, which have long been ignored in lieu of lower extremity training.

As opposed to earlier research, SIT failed to influence carbohydrate metabolism or insulin resistance (1,10). For instance, Babraj et al. (1) reported a coefficient of variation in glucose AUC of less than 5%, whereas we saw as much as a 40% increase in our subjects. Further, our comparative data included four individuals who initiated but did not complete the study, two of which saw an improvement in S_i during the control period. Excluding dietary influences, which were monitored, it is likely that the high day-to-day variability in glucose and insulin response was too great to overcome with upper extremity exercise alone. It is well documented (9,18,20,21,25) that persons with SCI suffer a multitude of metabolic disruptions. It is believed that nearly 70% of persons with SCI suffer from obesity (21), while two-thirds suffer impaired fasting glucose (25). Our subjects reflected typical body fat levels (> 30%) seen after SCI, and ACE has been shown to produce lower work outputs (9). Moreover, other researchers have encountered similar problems using the OGTT (Personal Communication, T. Ryan 2012), and even the intravenous glucose tolerance test (IVGTT) data (unpublished) from our lab suggest that it may not be an ideal test to assess metabolic improvements for persons with SCI.

In contrast to glucose and insulin, the significant reduction in plasma NEFA AUC indicates that blood lipids may be more useful metabolic training marker in persons with SCI (20). Further, our 2-hour trends in NEFA levels relate closely to those published by Babraj et al. (1) follow lower extremity sprints. Elevated plasma NEFA levels have been shown to directly and indirectly impair insulin sensitivity (11,17), and that persons with SCI show elevated NEFA levels (8,26), making reductions an important outcome with training. A reduction in NEFA in the blood could indirectly improve insulin sensitivity (17). Moreover, long-term training utilizing SIT and resistance training could significantly impact factors other than just glucose metabolism. For example, Nash et al. (20) demonstrated that three months of combined aerobic and resistance circuit training significantly

improves both cardiovascular fitness and blood lipid profiles in men with SCI, while Jacobs (15) demonstrated impressive cardiovascular and power enhancements from heavy resistance training alone. Therefore, SIT may afford an additional modality for training and overall improvement in quality of life.

In order to make relative work comparisons, we used the total kJ for the first four sprints of each session. The paraplegics in this study were all untrained males, but showed a high training capacity with an approximate 7% improvement in total sprint work over the course of six sessions. These data, while not significant, showed a consistent increase in work output each training session; the impact of learning is likely minimal considering subjects performed 4 sprints in the first session, and 26 sprints prior to the final training session. These data suggest that men with SCI can tolerate the addition of some SIT, which would improve overall upper extremity power, an important fitness component for wheelchair propulsion and activities of daily living (15,16,19,27). For example, loss of upper extremity strength and power significantly increases one's risk for premature mortality (19), and strength and power have a profound influence on one's ability to perform activities of daily living and wheelchair propulsion (16,27).

Spinal cord injury creates a physiological environment driven by catabolic and inflammatory responses (8,25) that is both complex and deleterious to the individual's health and wellness. Despite the mixed results on "metabolic fitness", at least compared to lower extremity SIT, ACE SIT may be a useful adjunct modality for persons with SCI. Furthermore, it is likely that healthier, non-ambulatory persons could benefit more from ACE SIT (12). In addition, ACE SIT may provide tertiary benefits to activities of daily living. More research is needed to elucidate the effects of longer duration interval programs for those with SCI.

PRACTICAL APPLICATIONS

This study is an important step towards optimizing upper extremity protocols for individuals with or without spinal cord injuries. These findings demonstrate that persons with SCI have a high

work capacity, which, when coupled with the body of literature using combined resistance and cardiovascular training, suggest that broad training prescriptions can be considered for those with SCI. Contemporary research demonstrates the importance of power in overall health and functional ability. SIT can also provide enhanced power for wheelchair propulsion, reducing physical strain and improving one's ability to perform activities of daily living. While exercise-induced metabolic improvements for persons with SCI are variable, SCI training programs emphasizing training to enhance strength and power may ultimately improve long-term participation in daily physical activity, and prove more beneficial over time than endurance focused training programs. Such training could be accomplished via arm crank ergometry, wheelchair sprints, or with the use of circuit resistance training. Strength and conditioning specialists and personal trainers can effectively incorporate high-intensity sprint interval training into programs for persons with SCI , as well as other non-ambulatory populations.

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Table 1: Summary of Pre- and Post-Test Areas Under Curves for glucose, insulin and NEFA. Pre and post intervention ISI-Cederholm results are also shown.

	Pre		Post			Difference		
Measure	**Median**	**IQR**	**Median**	**IQR**		**Median**	**IQR**	**p-value**
Glucose	77	(68, 80)	79	(62, 90)		2.9	(-3 , 8)	0.547
Insulin	143	(99, 258)	139	(96, 171)		-35	(-98, 18)	0.383
NEFA	1.5	(1.1, 1.6)	1.2	(0.5, 1.4)		-0.3	(-0.6, -0.1)	0.008
ISI-Cederholm	169	(149, 194)	170	(147, 201)		-9	(-19, 31)	0.7422

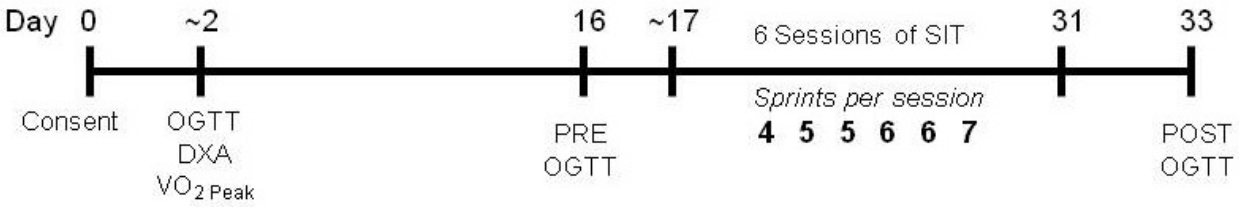

Figure 1. Experimental design for 2 weeks of sprint interval training in individuals with SCI.

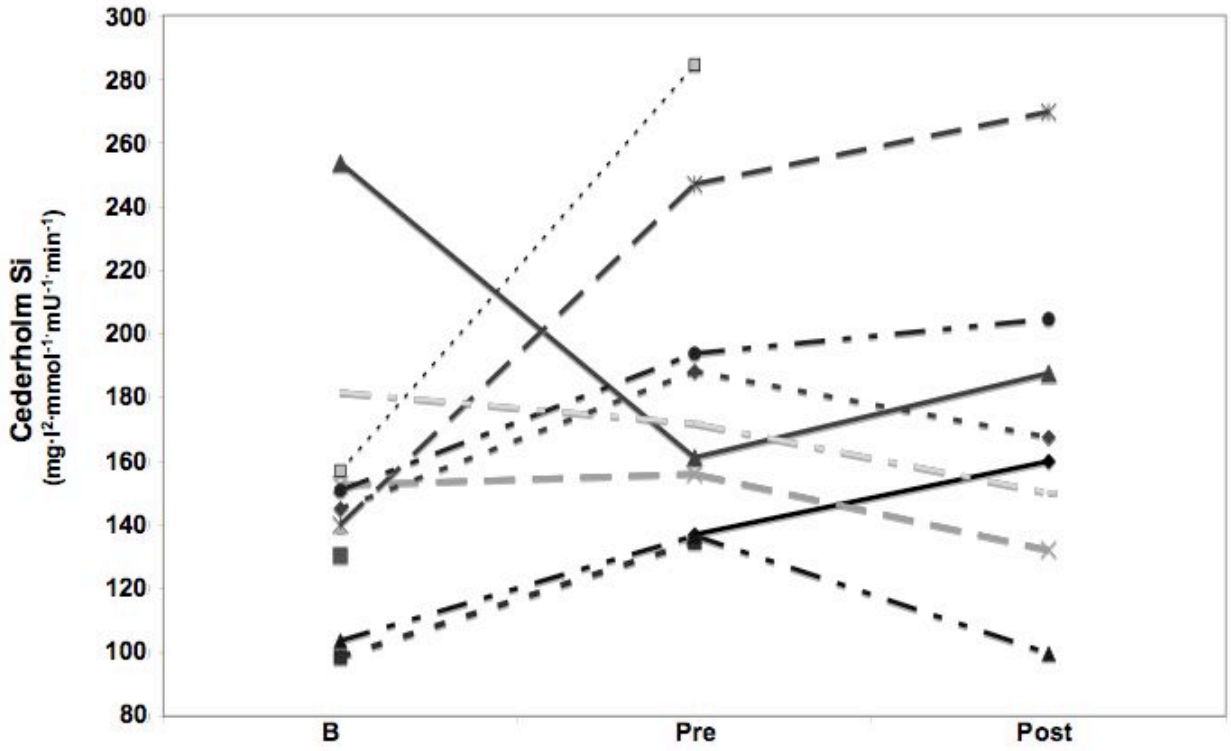

Figure 2. Plot of individual insulin sensitivity for baseline (B), Pre and Post training periods. Of the 12 volunteers, 8 completed all testing, two completed B and Pre and two completed B. The large variation in Si suggests the OGTT may not be a suitable training marker for men with spinal cord injury.

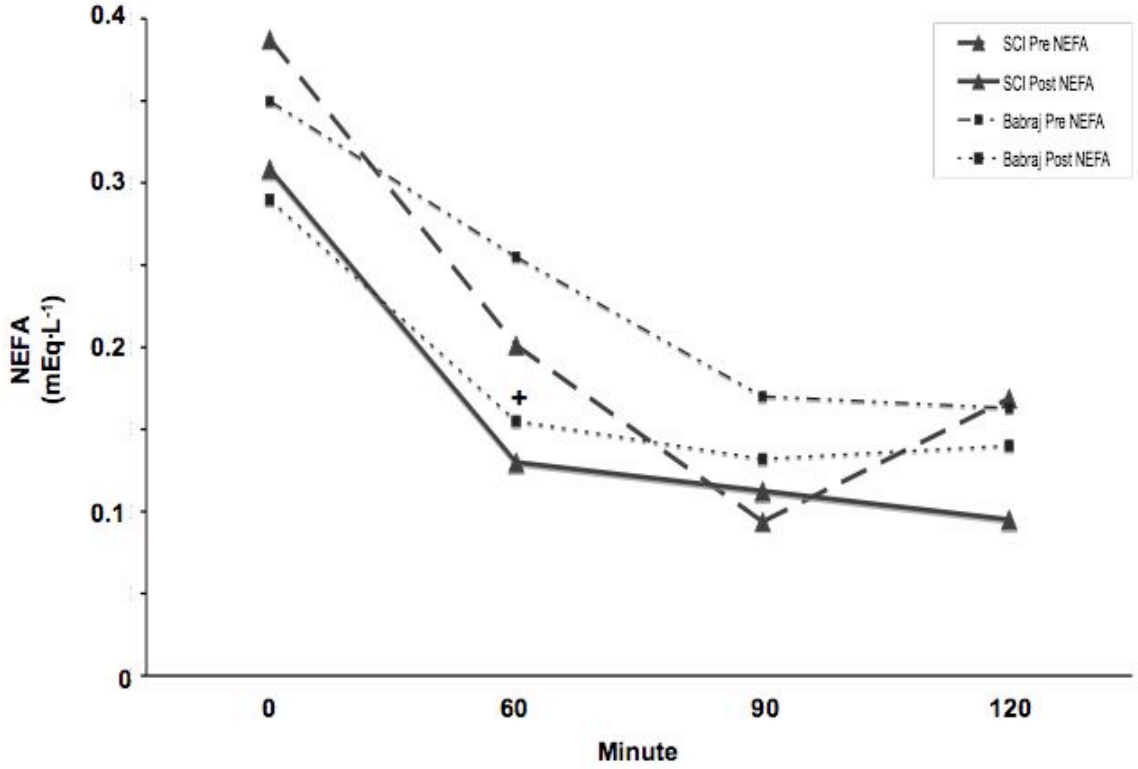

Figure 3. Illustrative comparison of mean NEFA values Pre and Post training for our SCI group (Triangle) and means reported by Babraj et al.[1] (Square)*. Note the parity in NEFA between both groups; our data indicate a significant decrease in AUC, while Babraj et al. reported only a significant drop at 60 min (+). **Adapted with permission.*

CHAPTER 3

Comparison of Two Different Sprint Interval Training Work-to-Rest Ratios on Acute Metabolic and Inflammatory Responses

ABSTRACT

Purpose: The purpose of this study was to compare how W:R influences S_i and inflammatory responses following a single bout of SIT. It was believed that when matched for energy expenditure, SIT using brief rest periods (W:R = 2:1) would elicit an improvement in S_i and larger cytokine response than SIT using long rests (W:R = 1:9). **Methods:** 12 men and 2 women completed a cross-over comparison of two SIT interventions – Tabata (TAB), 10X 20 sec sprints/10 sec rest using 5% of body weight, and Wingate (WIN), 5X 30 sec sprints with ~270 sec rest using 7% of body weight. Baseline measures and oral glucose tolerance tests (OGTT) were repeated one week apart and included IL-6, IL-10, and TNF-α. Blood samples (~10 ml) were taken at baseline, immediately following the training session, 1-hr after each training session, and prior to the 24-hr post-exercise OGTT. All data are presented as means ± SE. Insulin sensitivity (S_i) was estimated using the Cederholm index. The effect of SIT on S_i following SIT sessions at baseline and 24 hr were analyzed using repeated measures ANOVA with post hoc Tukey tests (α=0.05). **Results:** Subjects were 23.8 (±0.9) yrs old, 16.9 (±1.7) % body fat, with a mean $VO_{2\ Peak}$ of 42.0 (±2.0) $ml \cdot kg^{-1} \cdot min^{-1}$. Mean power during WIN was significantly higher ($p<0.0001$), but kJ expenditure between TAB (64.7 ± 3.5) and WIN (68.0 ± 3.5) was similar. S_i 24-hr was suppressed after both SIT sessions, and was significantly lower following WIN ($p=0.031$). There were no significant differences in inflammatory response between TAB and WIN. Neither TAB (1.95 ± 0.30 $pg \cdot ml^{-1}$) nor WIN (1.96 ± 0.30 $pg \cdot ml^{-1}$) produced peak IL-6 levels significantly above baseline (0.85 ± 0.30 $pg \cdot ml^{-1}$). In contrast, resting IL-10 (3.19 ± 0.32 $pg \cdot ml^{-1}$) increased significantly immediately following TAB (5.65 ± 0.35 $pg \cdot ml^{-1}$; $p < 0.0001$) and WIN (5.53 ± 0.33 $pg \cdot ml^{-1}$; $p < 0.0001$), returning to baseline within 1-hr. Similarly, resting TNF-

α (6.21 ± 0.68 $pg \cdot ml^{-1}$) significantly increased immediately following TAB (9.75 ± 0.71 $pg \cdot ml^{-1}$; p = 0.0118) and WIN (9.75 ± 0.71 $pg \cdot ml^{-1}$; p = 0.0118). There was a weak positive relationship (r = 0.24, p= 0.0364) between IL-6 and IL-10, but a strong significant relationship (r = 0.71, p < 0.0001) between TNF-α and IL-10. **Conclusions:** A single bout of SIT, regardless of W:R, may slightly reduce insulin sensitivity 24-hr after training, despite an increase in IL-10, which has been shown to improve insulin sensitivity. Additionally, the release of IL-10 may be mediated by an increase in TNF-α. These data indicate that SIT produces a pro-inflammatory response without acute improvement in metabolic factors, like insulin sensitivity. More research is needed to elucidate the acute and chronic adaptations to SIT.

Key words: SIT, Cytokines, Myokines, Insulin Sensitivity, Wingate, Tabata, OGTT

INTRODUCTION

High-intensity interval training, including sprint interval training (SIT), has been proposed as a more powerful stimulus to improve insulin sensitivity (S_i) than moderate aerobic exercise (Earnest 2008). Repeated sessions of SIT using long rest periods (i.e., low work-to-rest ratio) elicit improvements in endurance performance (Burgomaster et al. 2008), as well as metabolic function (Whyte et al. 2013, Gibala 2011, Brestoff et al. 2010, Richards et al. 2010, Babraj et al. 2009). The underlying mechanisms for these chronic improvements are not fully understood. Moreover, the work-to-rest ratio (W:R) is an important mediator of metabolic, cardiovascular, and endocrine responses during and after interval and resistance training (Gray et al. 1993; Hakkinen and Pakarinen 1993), but has not been studied in relation to S_i.

While acute and chronic endurance exercise improves S_i, it appears that only at least 6six sessions of SIT are needed to improve S_i (Whyte et al. 2013; Brestoff et al. 2010; Richards et al. 2010). For example, Babraj et al. (2009) showed that six sessions of SIT improved insulin sensitivity by 37%, while other groups have reported similar findings among obese men (Whyte et al. 2010) and obese women (Trilk et al 2011). In contrast, a single bout of SIT appears ineffective at improving S_i (Whyte et al. 2013; Brestoff et al. 2010; Richards et al. 2010). Whyte et al. (2013) proposed that the 4-5 min rest periods (1:8-1:10 W:R) used in many studies does not provide sufficient stimulus on the mitochondria and is independent of kJ expenditure. This was supported by data showing that a single continuous sprint of ~200 sec could improve S_i, which furthered Thyfault's hypothesis (2008) that ATP flux is a critical variable for acute S_i improvement. Extrapolating further, one could expect that SIT using brief rest periods could have a similar impact. Early work by Tabata et al. (1996), indicated that just 4 min of 20 sec of sprinting with 10 sec of recovery (2:1 W:R) significantly improve $VO_{2\ max}$ and sprint performance, compared to moderate intensity endurance training, which improved only $VO_{2\ max}$. Despite these impressive findings, follow-up research using *Tabata* training is lacking.

There are many possible mediators of insulin sensitivity and glucose uptake following exercise. Inflammatory cytokines have been implicated as mediators of glucose regulation at rest (Staczkowski et al. 2005; Pedersen et al. 2001;), and following endurance exercise (Pedersen and Fischer 2007; Fischer et al. 2006; Petersen and Pedersen 2005; Febbraio and Pedersen 2002; Pedersen et al. 2001). On balance, endurance exercise is viewed as *anti-inflammatory*, with both IL-6 and IL-10 key players in the post-exercise improvement in glucose uptake (Pedersen 2011). In contrast, SIT has often been viewed as pro-inflammatory (Meckel et all. 2011, 2009; Nemet et al. 2009) with significant increases in IL-6 following training. Therefore, it is unclear whether these inflammatory cytokines are influencing the metabolic changes following exercise. Moreover, it is unclear whether W:R influences either of these factors.

The purpose of this study was to compare how W:R influences S_i and inflammatory responses following a single bout of SIT. It was believed that when matched for energy expenditure, SIT using brief rest periods (W:R = 2:1) would elicit an improvement in S_i and larger cytokine response than SIT using long rests (W:R = 1:9).

METHODS

Participants

A total of 13 men and 2 women were actively recruited for the study. . All subjects were evaluated for safe exercise participation using an ACSM risk factor assessment and informed of the purposes of the study before signing an informed consent document approved by the Virginia Commonwealth University IRB. *Inclusion* criteria included men and women between the ages of 18-35 years old who were minimally active, but had a body fat $\leq$ 25% men and 32% women. *Exclusion* criteria were any person exceeding the body fat cut off, orthopedic limitations preventing full participation in the study, pre-diabetes or diabetes mellitus, reported hypothyroidism, renal disease, and/or anyone considered *High* risk for exercise participation based on current ACSM clinical guidelines.

Experimental Protocol

The experimental protocol (Figure 1) was similar to previous SIT studies, and consisted of a one-week intra-subject control period. During this period subjects performed baseline (B) and pre-training (PRE) oral glucose tolerance tests (OGTT). Subjects then completed two different acute SIT protocols – *Tabata* and *Wingate*, utilizing a cross-over trial design, with each training bout separated by no less than one week. Half the subjects completed the *Tabata* first, while the other half completed the *Wingate* first. All exercise took place using a mechanically braked Monark Peak Bike (Monark Exercise AB, Sweden). Blood samples (~10 ml) were taken immediately following, and 1 hr after each training session, as well as 24 hr after exercise; this corresponded to the initial resting sample prior to the post-exercise OGTT.

Dietary Control

Each subject was asked to complete a 3-day dietary recall form prior to completing any blood analysis. Dietary analysis were performed by a registered dietician for later comparison, and subjects were asked to pick one day within the recall and repeat those meals the day before each OGTT, recording the meals for those days. Additionally, each participant completed all training sessions after a 12-hr fast, including alcohol and caffeine, and they abstained from significant activity 24-hr prior to all exercise sessions and OGTT's.

Preliminary Testing and Evaluation

On the initial assessment day (Day 3) and during the OGTT, subjects completed body composition analysis using bioelectrical impedance analysis (RJL Quantum IV, RJL Systems, Inc., Clinton Township, MI), where subjects lay supine for a period of 20 min to allow body fluids to equilibrate across the body. During this time small electrodes were placed on right ankle and wrist. Body composition was then estimated using web based software (RJL Interactive Online BIA, RJL Systems Inc., Clinton Township, MI). Following the initial OGTT, physiologic testing included bicycle $VO_{2\ peak}$ testing. Testing was completed on the Monark bike which was equipped with an

SRM power meter (SRM Service Center, Inc., Colorado Springs, CO); peak and mean power (W) were measured for each stage. VO_2 and HR were measured continuously using a Parvo OneMax system (Parvo Medics, Salt Lake City, UT) and Polar HR monitor (Polar Electro Inc., New Success, NY), respectively. Subjects were instructed to pedal at their preferred cadence throughout testing. The initial workload was set at 1.5 KP with an approximate work rate of 100 W, increasing by 0.5 KP every 2 min until volitional exhaustion was reached, or the subject could not maintain their chosen cadence.

Exercise Protocols

All SIT sessions began between 0700 and 0900, and each subject's sessions took place at the same time of the morning. All sprint bouts began with a 10 min unloaded warm-up at ~70 rpm. Subjects then pedaled against a resistance equivalent to 7% (0.07 $kg \cdot kg^{-1}$) body mass for Wingate sprints, and a slightly lower 5% (0.05 $kg \cdot kg^{-1}$) body mass for Tabata. The former resistance has been shown to produce optimal power output and reliable measurement (Foster et al. 1995), while the latter was shown to be optimal during pilot data work prior to the study. Subjects were instructed to pedal as fast as possible for ~2 sec before the load is applied and to continue to crank while being provided with vigorous verbal encouragement throughout each sprint. The *Wingate* protocol consisted of a total of five 30 sec sprints with approximately 4 min recovery (i.e., very slow unloaded pedaling), while those completing the *Tabata* protocol were asked to exercise for a total of 5 min, sprinting for 20 sec and recovering for 10 sec, completing a total of ten sprints in that time. Table 1 summarizes the two sprint protocols.

Peak and mean power (W), as well as total work (kJ) were measured and stored using the SRM power meter and downloaded for later analysis using commercially available software (Training Peaks 3.0, Training Peaks, Boulder, CO). Blood lactate samples (5 µl) were measured from the fingertip using a small plastic lancet prior to exercise, immediately following, 1 min and 3 min

after exercise, and analyzed using a Lactate Scout Analyzer (EKF diagnostic sales GmbH, Barleben/Magdeburg). Each sprint session lasted between 15 and 30 min with warm-up.

Blood Analysis

Hemoglobin concentration ($g \cdot dL^{-1}$) and hematocrit (%) - using the micro-hematocrit method, were measured in duplicate and then used to estimate percentage changes in PV (Dill and Costill 1974). An indwelling venous catheter was inserted to allow for convenient blood draws. Blood samples (~10 ml) were collected together using gray top sodium fluoride tubes (OGTT) and gold top serum-separator tubes (cytokines) throughout testing and then centrifuged after each session at 4000 rpm for 15 minutes at 4^{o}C. Separated plasma was immediately removed and stored in capped 1.5 mL polypropylene tubes frozen at -80^{o}C until later analysis.

Oral Glucose Tolerance Tests

OGTT were completed following insertion of a catheter. Blood (~10 ml) was drawn before, as well as 30, 60, 90 and 120 min after ingestion of a 75% Glucola drink (Fisher Science Inc., Philadelphia, PA). Plasma glucose concentrations ($mg \cdot dl^{-}1$) were measured using the auto-analyzer glucose oxidase method, while plasma insulin concentrations ($mU \cdot L^{-1}$) were determined by ELISA (R&D Systems, Inc, Minneapolis, MN).

Inflammatory Markers

Inflammatory markers of interest included IL-6 (IL-6 B), IL-10 (IL-10 B), and TNF-α (TNF-α B) measured during baseline testing periods, as well as following each bout of SIT. At baseline, samples were analyzed from the blood taken at minute 0. On SIT days, 10 ml of blood was taken prior to, immediately following exercise (P) and 1 hr later (P 1). A final cytokine measurement was taken prior to the OGTT ~24 hrs after the SIT bout (P 24). Plasma concentrations of IL- 6, IL-10, and TNF-α were determined using interleukin-specific Humakine ELISA kits (R&D Systems, Minneapolis, MN), each completed according to manufacturer's instructions.

Coefficients of variation (CV) for baseline *Cederholm* insulin sensitivity measures was 4.8%, while IL-6, IL-10, and TNF-α were 9.9%, 6.1%, and 6.6%, respectively.

Statistical Analysis

Data were analyzed using commercially available software (Jump 13.0, SAS Institute Inc, Cary, NC). All data are presented as means ± SE. Area under the curve (AUC) was calculated using the trapezoidal rule, while the Cederholm index, which represents peripheral insulin sensitivity, was calculated using the formula:

$$\textit{Cederholm Si} = \frac{75000 + (G_0 - G_{120}) \times 1.15 \times 180 \times 0.19 \times BW/120 \times G_{mean} \times \log(I_{mean})}{1000}$$

BW = body weight, G_0 and G_{120} are plasma glucose concentration at 0 and 120 min (mmol·l^{-1}), and I_{mean} and G_{mean} are the mean insulin (mU·l 1) and glucose (mmol·l^{-1}) concentrations during the OGTT.

All exercise responses were analyzed using repeated measures ANOVA with *post hoc* Tukey tests. A 2X2 model was used to assess pre to post exercise response to the OGTT, including AUC and S_i. Dependent t-tests were run to compare change in S_i following *Tabata* and *Wingate* SIT from baseline and at 24-hr. A 2 X 4 model was used to determine the effect of SIT on IL-6, IL-10, and TNF-α. Finally, Pearson's correlation coefficients were calculated to examine the relationships between S_i and changes in cytokine response.

RESULTS

Fifteen subjects completed both sprints sessions, with one subject unable to complete 24 hr follow-up after the wingate session due to inclement weather. Subjects were 23.8 (±0.9) yrs old, 180.0 (±2.7) cm tall, weighed 78.5 (1.6) kg, were 16.9 (±1.7) % body fat, with a mean $VO_{2\ Peak}$ of 42.0 (±2.0) ml·kg^{-1}·min^{-1} at 237.0 (±14.6) W. Dietary analysis indicated our participants consumed a diet consisting of 2077.5 ± 132.3 kcal from 81.9 ± 8.0 g of fat, 243.2 ± 14.4 g of carbohydrate, and 93.2 ± 6.8 g of protein. Table 1 provides a summary comparison of SIT session variables. Of specific note, the percentage of VO_{2Peak} power was significantly higher ($p < 0.001$) during WIN (196.8 ±

4.2%) compared to TAB (95.6 ± 4.2%); . However, there were no differences in total kJ expenditure ($p = 0.5152$) or blood lactate ($p = 0.8307$) between SIT sessions.

Insulin Sensitivity (S_i)

Baseline S_i for all subjects was 75.9 (± 1.0) $mg \cdot I^{2} \cdot mM^{-1} \cdot mU^{-1} \cdot min^{-1}$. Table 1 summarizes pre and post OGTT data for both SIT sessions using an intent-to-treat analysis. As noted above, one subject was unable to complete 24 hr post testing, including OGTT, after WIN training. These data indicate that S_i was significantly reduced ($p = 0.031$) after WIN (n=14), while S_i after TAB was consistently (n=12 of 15), though not significantly lower ($p = 0.144$). There were no differences between sprint sessions ($p = 0.6723$) and AUC for neither glucose nor insulin were significantly impacted (see Table 1).

Inflammatory Cytokine Response

Plasma cytokine levels of IL-6, IL-10 and TNF-α were measured in all 15 subjects during pre OGTT (baseline), and TAB test sessions, however, only 14 subjects of 15 subjects were measured 24 hrs after WIN. Overall findings showed that both TAB and WIN lead to significant increases in IL-10 and TNF-α, but not IL-6 (see Figure 2). IL-10 (Figure 1 B) increased significantly immediately following TAB ($p < 0.0001$) and WIN ($p < 0.0001$), returning to baseline within 1-hr. Similarly, TNF-α (Figure 1 C) increased significantly immediately following TAB ($p = 0.0118$) and WIN ($p = 0.0118$), followed by a significant drop after both TAB ($p=0.0013$) and WIN ($p=0.0077$). All cytokines returned to baseline levels 24-hr after exercise. Results of all significant Pearson correlations are summarized in table 2. There was a strong inverse relationship between S_i B and IL-6 B ($r= -0.65$, $p=0.0090$). There was, however, no relationship between cytokine increases after exercise and and S_i 24-hr after exercise. While IL-6 was not related to either IL-10 or TNF- α, IL-10 and TNF-α were positively related ($r=0.71$, $p<0.001$) .

DISCUSSION

The purpose of this study was to compare how W:R influences insulin sensitivity (S_i) and inflammatory responses following a single bout of SIT. When matched for energy expenditure, SIT using brief rest periods (TAB) was expected to elicit an improvement in S_i, partly due to a larger cytokine response. Furthermore, the improvement in S_i would be proportional to cytokine release. However, these data indicate that neither SIT protocol improved S_i 24-hr after exercise; S_i actually decreased significantly following WIN. While both protocols significantly increased IL-10 and TNF-α concentrations immediately following exercise, IL-6 did not change significantly. Finally, there was no significant relationship between any of the measured cytokines and S_i P 24, but there was a strong positive relationship between TNF-α and IL-10.

SIT and Insulin Sensitivity

A major finding of this research was that neither TAB nor WIN SIT improved S_i P 24, indicating that W:R does not influence S_i in healthy young adults. In the present study, insulin sensitivity was actually significantly decreased by 5% following WIN, while 5 min of TAB decreased S_i, albeit non-significantly, by 3.6% 24-hr after exercise. This finding was consistent among subjects in both SIT trials, with only 3 of 15 subjects actually improving S_i following TAB. Close examination of these data show that 2 of 14 subjects had 15% or greater decrease in S_i following WIN. Interestingly, the subject with the largest decrease in S_i, ~15% following TAB and 20% following WIN, also had the highest body fat at 24.8%. However, no other differences, including diet, were noted between subjects, and removal of these outliers did not reverse the trend towards reduced S_i.

The lack of improvement following TAB was unexpected because kJ expenditure was similar to that of the extended sprint reported by Whyte et al. (2013). There, S_i improved significantly 24-hr after exercise, while WIN SIT did not improve in that study, or others (Brestoff et al. 2010, Richards

et al. 2010). These researchers suggested that the key factor for acute improvements in S_i may be ATP turnover (Thyfault 2008), which would be maximal during the ~200 sec continuous time trial used in their study. It was this premise that influenced our choice of the *Tabata* SIT intervention. As reported by Tabata et al. (1997), 4 min of the 20 sec work to 10 sec rest ratio maximally stimulated oxygen consumption and anaerobic capacity; peak VO_2 in the final 10 sec of the 4 min Tabata was similar to their subjects' $VO_{2\ max}$, as was the accumulated O_2 deficit. In order to match kJ expenditure in our study, our TAB SIT session lasted an additional 50 sec (i.e., two 20 sec sprints), with a total duration exceeding Whyte's extended sprint, and likely maximally stimulating mitochondrial ATP production. Therefore, kJ expenditure and ATP turn-over may not be critical factors at play. Of particular note, however, Whyte et al. (2013) enrolled overweight and obese male subjects, while we studied healthy young adults, who were relatively lean (body fat % = 16.9). Nonetheless, the outlier showing the greatest drop in S_i following TAB also had the highest body fat at nearly 25%. Therefore, it appears that changes in S_i following a single session of SIT are complex and warrant further investigation.

SIT impact on the inflammatory response

A second important finding of this study was that W:R does not differentially effect inflammatory cytokine release following SIT. In addition, we noted that IL-10 release is not dependent on IL-6, but that increases in IL-10 immediately following SIT are directly proportional to TNF-α ($r=0.71$, $p<0.001$). To our knowledge, this is the first study to show such a response following exercise. For example, prior research by Meckel et al. (2011, 2009) and Nemet et al. (2009) reported that running sprint exercise significantly increased IL-6 1-hr after exercise, but does not influence IL-10 (Nemet et al. 2009) in trained men and women. In contrast, Brestoff et al. showed that a session of five Wingate sprints (1:9 W:R) did not alter IL-6 or TNF-α release after exercise in recreationally active men and women. In the present study, SIT using a disparate W:R produced a similar inflammatory response (Figure 2) that contrasted changes seen during endurance

exercise. Specifically, endurance exercise is viewed as *anti-inflammatory* on balance, with a large increase in IL-6 immediately following exercise, followed later by IL-10, and little if any change in TNF-α (Febbraio and Pedersen 2002). The combined increase in IL6 and subsequently IL-10 have been implicated in the improvement in S_i following exercise (Pedersen 2001; Steensburg et al. 2003), however, direct evidence for this is absent from the literature.

A major premise of cytokine release following endurance exercise is that IL-6 is released directly from the muscle, making it a myokine (Pedersen 2011), and that this release from the muscle influences its anti-inflammatory role. Further, IL-6 is believed to be a stimulant to IL-10 release, which is a known inhibitor of TNF-α (Dhingra et al. 2009; Steensburg et al. 2003; Armstrong et al. 1996). The current study suggests that SIT, regardless of W:R produces a more *pro-inflammtory* response, with nearly a 60% increase in TNF-α immediately following exercise, as well as a similar increase in IL-10. This finding is important for two reasons. First, it shows that IL-10 can increase following intense exercise independent of IL-6, and second, it suggests that IL-10 may increase in response to TNF-α. The latter is supported indirectly by the fact that both IL-10 and TNF-α increased significantly immediately following both SIT sessions, followed by a significant decrease in TNF-α 1-hr after exercise, and that IL-10 levels were strongly related (r=0.87) to TNF-α immediately following both SIT sessions. As indicated, IL-10 is a potent mediator of TNF-α (Dhingra et al. 2009; Armstrong et al. 1996), and may have little influence on S_i following SIT. This pro-inflammatory response, though transient, may be an important stimulus for long-term adaptation, much like transient increases in cortisol and growth hormone are to muscle remodelling (Häkkinen and Pakarinen 1993), or reactive oxygen species (ROS), like H_2O_2, and lactate accumulation are to mitochondrial biogenesis (Lira et al. 2010; Hashimoto et al. 2007).

SIT: Inflammation and Glucose Regulation

Presently our understanding of cytokine release following exercise is largely based on endurance exercise studies, which propose that *anti-inflammatory* cytokines contribute to an acute

improvement in S_i (Pedersen 2011, Brandt and Pedersen 2010, Petersen and Pedersen 2006; Steensberg et al. 2003, Febbraio and Pedersen 2002), as outlined in Figure 3. Our data indicate that SIT does not have an acute impact on IL-6 release, nor does acute SIT influence on S_i, regardless of W:R. Additionally, there was no relationship between cytokine release and S_i, suggesting that inflammatory cytokines do not play a significant role in the improved S_i seen in SIT studies of at least 2-wk (Trilk et al. 2011, Richards et al. 2010, Whyte et al. 2010, Babraj et al. 2009). Therefore, similar to studies examining endurance performance following SIT (Laursen 2010; Burgomaster et al. 2008), metabolic improvements after SIT may follow a different set of cellular pathways than endurance training. For example, Coffey and Hawley (2007) outlined four distinct signals for mitochondrial biogenesis and improved glucose regulation, including mechanical stretch, increased intramuscular calcium concentration, reduced muscle ATP concentrations, and an increase in ROS, or other disruptions to muscle homeostasis. While all of these are likely involved in SIT adaptations, the last would support the role of inflammatory cytokines in this process; however, far more work is needed before direct conclusions can be drawn.

The results presented here are a preliminary attempt to elucidate the inflammatory response following SIT and its possible role in the chronic training improvements reported from a variety of sprint protocols. These data, while intriguing, are based on a relatively healthy population of college age adults. The fact that these data seem to contrast those of Meckel et al. (2011, 2009), who studied sprint training in elite athletes, indicates that population characteristics and fitness level likely influence inflammatory and metabolic responses to SIT. The results in the present investigation demonstrate the need for examining a number of mechanisms in various populations to better understand the possible health benefits of SIT.

In conclusion, sprint interval work to rest ratio has no apparent impact on insulin sensitivity or inflammatory responses 24-hr after training in healthy young males. It would appear that repeated bouts of SIT over at least 2 weeks are needed to improve insulin sensitivity. These data indicate that

the inflammatory response following SIT is very different from that of endurance training, which indicates a largely anti-inflammatory effect. SIT failed to produce a significant increase in IL-6 release, but instead showed a strong response from TNF-α and IL-10, which both peaked rapidly after exercise and returned to baseline within 1-hr. It would appear that following SIT, the latter two cytokines follow a release pattern more similar to that seen during sepsis (Fischer et al. 2006; Dhingra et al. 2009; Armstrong et al. 1996) than endurance training. In this sense, SIT may be considered pro-inflammatory. It is not known whether this seemingly pro-inflammatory response serves as a stimulus for positive adaptation.

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Tables and Figures

Table 1. Comparison of *Tabata* and *Wingate* protocols and exercise session data, including pre and post OGTT data. Data are presented as means (± SE). Note, only 14 of 15 subjects completed Wingate SIT. * Denotes significance.

	Tabata	**Wingate**		
Workload (% Body Mass)	5	7		
# of Sprints	10	5		
Work/Recovery (sec)	20/10	30/270		
W:R	2:1	1:9		
			P-value *Pre-Post*	**P-value *Between Sessions***
Mean Power (W)	223.2 (17.1)*	457.8 (17.1)*	N/A	< 0.0001
% $VO_{2\ Peak}$ Power	95.6 (4.7)*	196.8 (4.7)*	N/A	< 0.0001
Energy (kJ)	64.7 (3.5)	68.0 (3.5)	N/A	0.515
BLC (mM)	12.8 (0.7)	12.6 (0.7)	N/A	0.831
HR (bpm)	180.7 (2.4)	173.9 (2.4)	N/A	0.054
		OGTT Data		
S_i – *Cederholm* ($Mg*I^2*mM^{-1}*mU^{-1}*min^{-1}$)				
Pre-training	75.9 (1.0)			
Post-training	73.2 (1.0)	72.1 (1.0)*	TAB 0.144 WIN 0.031*	0.672
Glucose AUC				
Pre-training	444.1 (17.99)			
Post-training	426.3 (17.99)	429.3 (18.63)	TAB 0.766 WIN 0.836	0.993
Insulin AUC				
Pre-training	91.9 (14.47)			
Post-training	79.5 (14.47)	87.2 (14.98)	TAB 0.818 WIN 0.927	0.973

Table 2. Summary of significant Pearson correlation coefficients. No other significant relationships were observed. Note, B= baseline; P = immediately post exercise; P24 = 24 hr post exercise.

Independent Variable	Dependant Variable	r	p-value
IL-6	S_i	r= 0.24	0.0364
IL-6 B	S_i	r= - 0.65	0.0090
TNF-α	IL-10	r= 0.71	<0.0001
Tabata			
TNF-α P	IL-10	r= 0.87	0.0025
TNF-α P24	IL-10	r= 0.76	<0.0475
Wingate			
TNF-α P	IL-10	r= 0.87	0.0021

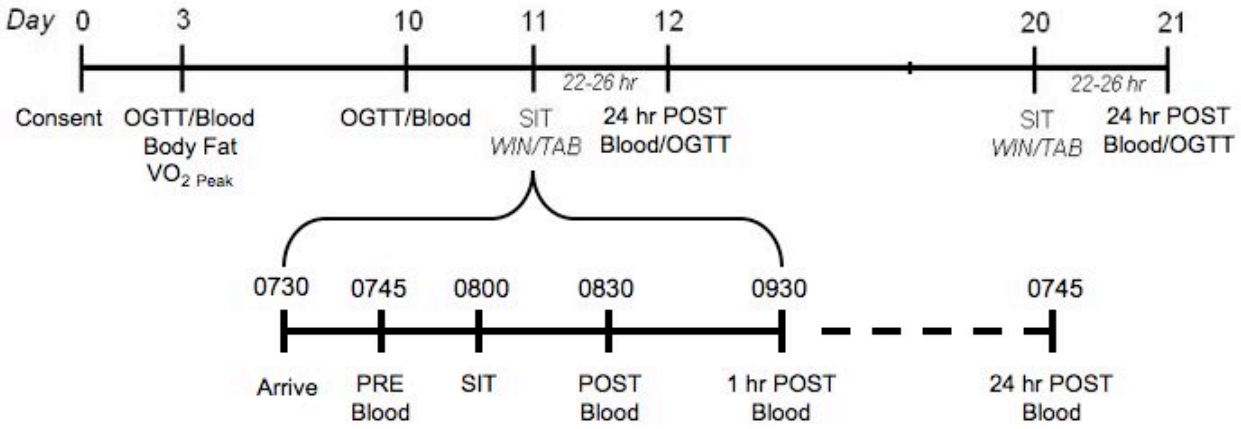

Figure 1. Graphic summary of the experimental design for the study. Note: OGTT=oral glucose tolerance test; SIT=sprint interval training; TAB=Tabata short recovery exercise; WIN=Wingate long recovery exercise.

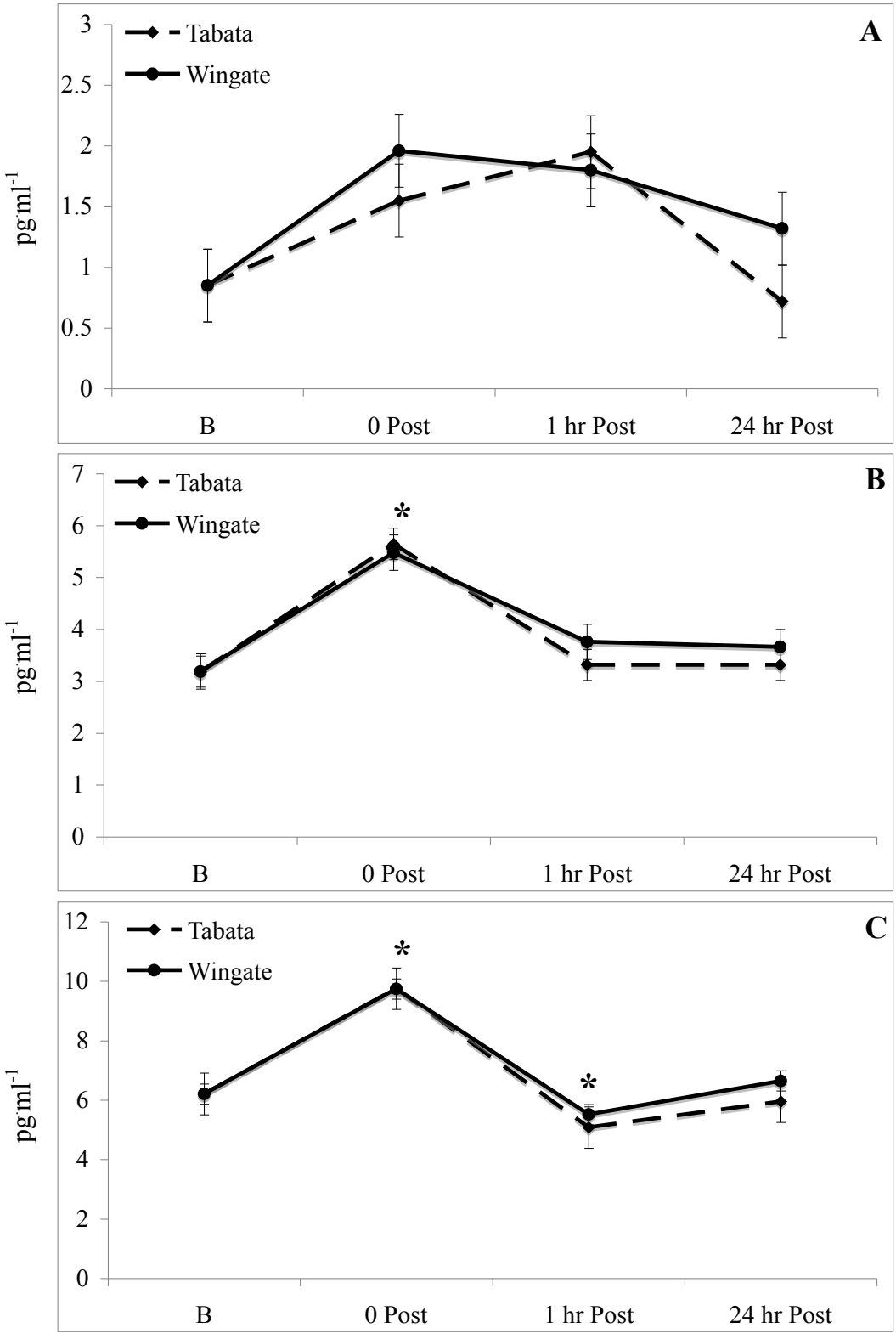

Figure 2. The effect of sprint interval training on IL-6 (A), IL-10 (B), and TNF-α (C). IL-10 increased significantly immediately following *Tabata* ($p<0.0001$) and *Wingate* ($p<0.0001$). Similarly, TNF-α increased significantly following *Tabata* ($p=0.0118$) and *Wingate* ($p<0.0118$), then dropped sharply 1 hr after exercise ($p=0.0013$ and $p=0.0077$, respectively). * Denotes significance from prior time period.

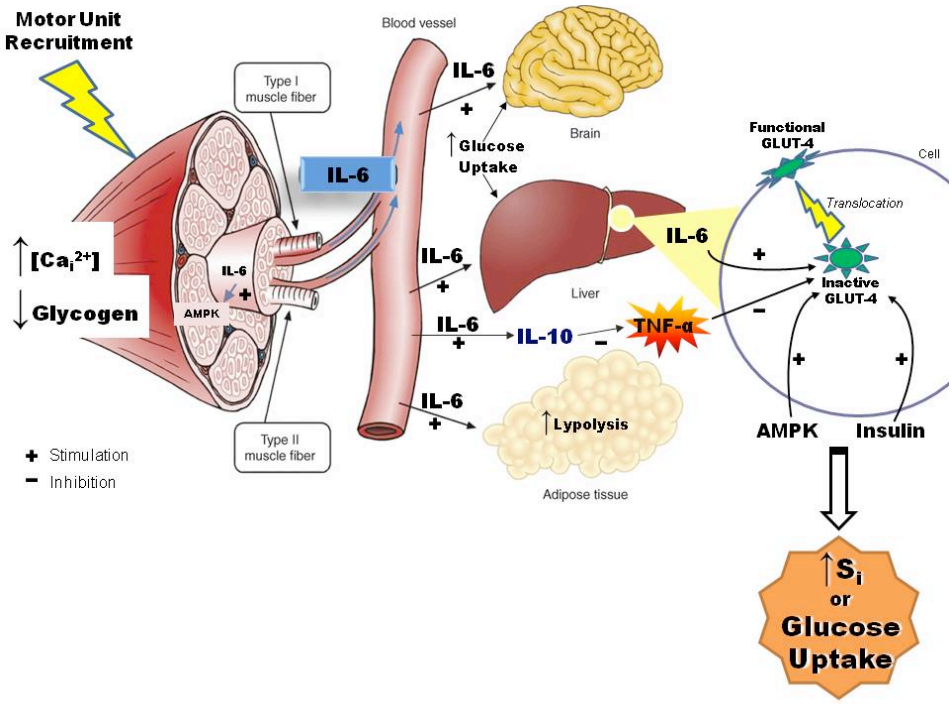

Figure 3. Schematic summary of the initiation of muscle-derived IL-6 release and the subsequent role that IL-6 plays in various organs that lead to enhanced glucose uptake. IL-6 promotes GLUT-4 activation in the brain, liver, and even skeletal muscle, as well as promoting IL-10 production. IL-10 blocks TNF-α and macrophage constituents, which interfere with GLUT-4 (Adapted from Febbraio and Pedersen 2002; Pedersen and Fischer 2007).

CHAPTER 4

DISSERTATION CONCLUSIONS

Historically, physical activity and health researchers have focused on the benefits of aerobic endurance activity. More recently, investigators have sought to examine alternative forms of physical activity, including HIT.The revelations regarding low volume, high-intensity interval exercise, including sprint interval training, represent a major paradigm shift in our perspective on optimal, as well as, minimal exercise prescription requirements. Further examination of HIT, and specifically SIT, will enhance our understanding of the underlying mechanisms related to both acute and chronic adaptive processes. In the two studies presented here, SIT was studied over the course of 2-wk in persons with spinal cord injury, as well as for a single session among healthy adults. While these studies yielded mixed results, our findings provided important information regarding applications for SIT and future research.

Among persons with SCI, 2-wk of SIT failed to alter the profound disruption of glucose metabolism within this population. However, we were able to demonstrate a significant reduction in blood lipids (NEFA) linked to insulin resistance. Subjects in this study tolerated training well, indicating that additional SIT research is needed on optimal application of SIT for non-ambulatory populations, including persons with SCI. Furthermore, it is unclear whether the improvement threshold for upper extremity SIT differs from lower extremity, further supporting the notion that far more research is needed on the application of high intensity training for all special populations.

As a follow-up study, we explored the role that W:R plays on the acute SIT effects on metabolic and inflammatory responses. Research in this area has been sparse and inconclusive, with some researchers (Meckel et al. 2011, 2009) indicating that SIT increases acute (pro) inflammation. Our findings indicate that sprint interval inflammatory response is similar for disparate W:R. Additionally, neither insulin sensitivity nor inflammatory responses differ between W:R protocols

24-hr after exercise. It appears that at least 2 weeks of SIT are needed to improve insulin sensitivity. Based on the available data, the inflammatory response following SIT differs from endurance training, and could be considered pro-inflammatory. More research is needed to elucidate whether the inflammatory responses seen in our research plays a significant role in the long-term adaptation to sprint training.

Future Directions

Taken together, the research presented here indicates that far more research is needed to understand the acute impact of SIT on both the metabolic and inflammatory responses among different populations. It is unclear how individual physiology among various special populations may impact the adaptive processes of training. In addition, more research is needed to expound on whether or not, and if so how the post-SIT inflammatory response influences metabolic and performance adaptations. Data here and elsewhere indicate that SIT has many more revelations to reveal in the years to come.

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APPENDICES

Appendix A. Review of Literature

Spinal cord injury and sprint interval training

Recent statistics indicate that there are approximately spinal cord disorders and injuries is close to 6 million Americans[2], which accounts for nearly 2% of the U.S. population. While difficult to fathom, the true costs spinal cord injuries (SCI) are far greater to the overall quality of life of those with SCI who face a milieu of health and daily activity problems, as well as staggering care costs; lifetime costs range from $800,000 to over $5 million for patients in their mid-20's[2,3]. Of significant concern is the prevalence of metabolic syndrome (MtS) among SCI patients secondary to obesity[4-8], which no doubt contributes significantly to the cost of care in SCI. Because of the close relationship between MtS both obesity and blood sugar management, addressing either or both of these must be a priority in treating MtS among SCI. Individuals with SCI, however, have little influence over their development of CVD, obesity or MtS, making management seemingly insurmountable.

Exercise is a useful tool in the reduction of body fat[9] and an effective means for improving or reversing many of the constituents of metabolic syndrome, including glucose effectiveness and insulin sensitivity[10-13]. Yet, fewer than 50% of American's meet current ACSM recommendations for physical activity[14] – recognize that ACSM recommendations are for risk factor reduction, not weight loss. Unfortunately, if able-bodied obese individuals find exercise a daunting task, the person with SCI may find exercise frustrating and limited at best, and nearly impossible at worst due to physical and physiological limitations of the injury. Nonetheless, exercise must remain an important component to managing risk factors and enhancing SCI quality of life. Greater understanding of the acute and chronic exercise training responses are needed in SCI, with emphasis on modalities focused on improving overall functionality for SCI and metabolic improvement. Therefore, the purpose of this review is to summarize the literature on spinal cord injury health consequences,

contemporary exercise research on available modalities, and potential applications of emerging able-bodied training research.

Spinal Cord Injury in the U.S.: Demographics

Spinal cord injury accounts for nearly a quarter of all paralysis in the U.S., with more than half of those injuries caused by some type of accident (see **Figure 1** for details) and nearly equal representation among men and women. While 80% of all persons are considered "White", evidence suggests that SCI may be disproportionately represented among minority groups. The average age for SCI is 52 years with the average time since injury approximately 16 years with more than a third of SCI under the age of 40[2], indicating that many individuals have the potential for a long life of care post injury (**Table 1**). Not surprisingly, as post-injury life expectancy increases so does cost of care. Current estimates lifetime costs vary among different cohort groups[3,15-17], and can range from more than $800,000 to over $5.4 million for patients in their mid-20's[3,15-17]

The breadth of these estimates reflects the range of injury severity and care needs among SCI. For example, the single year cost for a cervical level complete (i.e., no motor function below the injury level) can be as much as five times higher than those for an individual with an incomplete lumbar injury[16]. In the first year alone, cost of care averages more than $520,000, and can be as high as $1,000,000. These costs burden both the medical system, as well as for the individual, both of which influence quality of care. Consider that the U.S. Census Bureau indicates that the 2009 Median household income was $49,777, while 80.1% of SCI report an income of less than $50,000. In fact, at least half of all SCI live below federal standards for poverty ($22,350). New data suggest that the impact of SCI on income is closely linked to employment following injury. For example, individuals with SCI show a $25,000 drop in income on average, which is directly attributed to a 70% increase in unemployment following injury.[18] Thus, it is possible for SCI to quickly move an individual from the median to poverty. One cannot overlook the link between MtS, and any of its

components, particularly obesity, and poverty[19]. Whether or not the latter issue can be addressed, it must be acknowledged when trying to exact health improvements among SCI and reduce MtS.

Metabolic Syndrome and SCI

Cardiovascular disease (CVD) remains the leading cause of death in the United States, accounting for more than 27% of the reported deaths in 2005[20]. The staggering toll heart disease plays within healthcare often overshadows the complex interaction of underlying factors typically referred to as the metabolic syndrome[21]. Despite a clear consensus on the definition or clinical diagnosis of MtS among leading organizations (see **Table 2** for a comparison), the overlap is considerable and includes obesity, poor glucose regulation/insulin resistance, hypertension, dyslipidemia (e.g., high triglycerides or low HDL)[22], with cardiovascular disease (CVD) recognized as a major outcome. Additional factors suggested by the Adult treatment Panel III (ATPIII) report also include increased systemic inflammation, typically marked by elevated C-reactive protein levels (CRP) and a prothrombotic environment, characterized by elevated plasminogen activator inhibitor (PAI)-1[22,23]. The latter two are often ignored in the clinical assessment of MtS due to the difficulty and cost of measuring them and their close relationship to obesity; both CRP and PAI-1 are synthesized by adipose tissue, so as body fat increases, so do CRP and PAI-1. In fact, the exact role obesity plays in development of CVD or other components of MtS, most notably insulin resistance, is nearly impossible to assess because of the intricate relationship obesity has with each component. For example, obesity is known to cause insulin resistance through a cascade of interactions, while insulin resistance often exacerbates obesity[23]. Taken together, one can understand how obesity alone plays a multi-factorial role in MtS and supports the premise that obesity may precede MtS[24]. Moreover, MtS is strongly related to the development of diabetes and CVD[25], both of which show increased prevalence among SCI. However, the relationship between MtS and SCI is not quite so clear.

Compared with able-bodied individuals, those with SCI exhibit increased rates of obesity[26-28], hypertension[26-28], insulin resistance or diabetes[7,8,25,29,30], systemic inflammation[4,6], and ultimately CVD[31-33]. Yet, the individual prevalence of MtS among SCI does not appear higher than able-bodied[25], which on the surface might seem counter intuitive until one examines the data closely and suggests that certain components of MtS may have a greater impact on the development of CVD among SCI and should be examined accordingly. Chief among these is obesity, which, based on its complex interaction within the body has multifarious outcomes.

Obesity and SCI

It is now believed that more than one third of the U.S. adult population is obese[34], which may be far less than SCI obesity rates[26-28]. Sources vary widely, however, with data by Weaver et al.[26] indicating that 31% of SCI veterans were classified as obese, while Rajan et al.[27] reported that as many 66% of SCI are obese. One reason for the disparity may be the use of BMI, which grossly underestimates body fat in this population[7,26]. Disregarding BMI data are difficult, due to their ubiquity, but dual x-ray absorptiometry (DXA) data by Spungen et al.[28] supports these numbers and that age has a significant impact on body fat; individuals over the age of 40 have significantly more body fat than those under 40. Unfortunately, a clear understanding of body composition and metabolic syndrome among SCI are still not entirely clear, with a reassessment and adjustment of current body composition methodologies. Nonetheless, increased body fat is a trademark for SCI, with the typical new SCI gaining nearly 14 kg of fat in the first two years of injury[35]. Thus, addressing MtS among SCI cannot be separated from addressing the increase in body fat because in addition to the obesity-MtS link, increased fat mass will promote insulin resistance and hypertension, and further limit functional ability to complete either exercise or activities of daily living (ADL), as well as encourage dyslipidemia (**Figure 2**)[1].

Disordered Carbohydrate Metabolism

There are many indications that SCI do not metabolize and regulate carbohydrate as effectively as able-bodied[1,8,29,30,32]. For example, early research often relied on small sample sizes making definitive conclusions difficult, while recent data have shown that more than a third and as many as two-thirds of SCI may exhibit impaired fasting glucose [1,32], while those exhibiting frank diabetes ranges from 15 – 22%[29,30,36], which is three-fold higher than the general population. As is seen in many instances among SCI, level and completeness of injury influences carbohydrate metabolism (e.g., complete tetras fair worse than other SCI), as does age [1,32]; age related increases may ultimately relate to continued increases in fat mass, as demonstrated in the general population[37]. However, the underlying mechanisms for the development of metabolic disorders in SCI have not been fully elucidated. For example, as depicted in Figure 1, SCI appears to promote insulin resistance and pancreatic/β cell by itself, as well as in conjunction with the reduction in activity, development of obesity, loss of muscle mass, and inherent changes in the paralyzed muscle[38,39] which may by itself alter carbohydrate metabolism[40]. Therefore, all the potential factors influencing development of carbohydrate disorders in SCI should be considered.

Adipose tissue, no longer considered inert tissue, is involved in the modulation of the metabolic function in the body by releasing non-esterified fatty acids (NEFAs), hormones, and as previously mentioned, CRP, all of which have a unique impact on insulin resistance and are all believed to be elevated by obesity[41]. Of those above, NEFAs may be the single most important factor for altering insulin sensitivity, with insulin resistance developing within hours of NEFA infusion [41]. Normally associated with fasting, obese individuals release excess amounts of NEFAs despite higher insulin levels, which should actually suppress lipolysis. The influx of NEFAs into the muscles further enhance insulin resistance, possibly by increasing muscle fatty acid metabolites, like diacylglycerol, which in turn inhibit insulin signaling, as well as interfering with the insulin receptors which are involved in the activation of glucose transporter isoform 1 (GLUT-1) and GLUT-4[23,41-43]. While the exact mechanisms are poorly understood, NEFAs also appear to interfere with the

compensatory feedback loop for insulin secretion, and act synergistically with elevated glucose to have a glucolypotoxic effect on β cells[41].

SCI fill a unique niche here, because they can develop insulin resistance and obesity separately. Worse still, the disruption or cessation of the autonomic nervous system in SCI can further exacerbate pancreatic/β cell function by disrupting normal insulin release[41], which could partly explain the rapid development of insulin resistance in SCI. Additionally, peripheral changes in the paralyzed muscle may also impact carbohydrate metabolism disorders.

Following SCI, it is difficult to point to one single change or event that ultimately influences metabolic function. One often does not consider, or perhaps cannot fathom the minute control the central nervous system (CNS) exhibits over the entire body, including maintenance of the tight control of the organs, or the role of muscle tone and hence mass. Chronic SCI is far more than loss of walking ability; it can mean the loss of nearly half the metabolic "engine" and glucose repository, namely the lower extremity musculature. The loss of muscle and increase in fat seems to occur as readily, though to a lesser magnitude among incomplete injuries as it does in completes[39], greatly limiting the metabolic role that leg muscle plays in glucose metabolism. Following injury there is a preferential atrophy of Type II fibers, followed by Type I fibers with a continual infiltration of intramuscular fat in just the first three months. as an injury persists, muscle fiber conversion takes place. While the precise time line (e.g., < 6 mo vs. > 6 mo) is still unclear, data indicate that muscles atrophy and shift to a fiber-type composition made up of mostly Type IIx fibers[38,39,44], with only rare exceptions escaping this fate[45]. Again, such changes seem mundane on the surface, but may play a larger role in the overall life of SCI.

Higashiura et al.[40], demonstrated the postive linear relationship between Type I fibers and insulin sensitivity, and the negative linear relationship between Type II muscle fibers and insulin sensitivity. In conjunction with the sweeping changes seen in SCI, fiber conversion more likely

limits lower body training effectiveness, but could exacerbate insulin resistance in SCI[46-48]. Thus, it is not surprising that SCI have a different risk pattern for MtS than the able-bodied[25].

Hypertension in SCI: Still a silent killer

Hypertension has long been termed the "silent killer" in the United States and has a profound influence on the development of CVD (Grundy 04). Nearly two-thirds of the population develops hypertension by age 60[49], with the prevalence of HBP among obese individuals six times higher than normal weight individuals[50]. The prevalence among SCI is believed to be much higher[1,8,26]. For example, a recent report by Weaver et al.[26], indicates that nearly 60% of SCI may be at least borderline hypertensive, with nearly half those considered hypertensive. Worse still, diabetic SCI are more than twice as likely to be hypertensive[1]. Again, the inter-relationships between obesity, diabetes and hypertension is extremely complex, but the role that proinflammatory elements like CRP, released by adipose tissue, have on vascular function are important to recognize when working with SCI. Further, the role that autonomic dysfunction, including baroreflex dysfunction, among SCI further complicates systemic blood pressure (BP) control at rest and during exercise by limiting the hemodynamic response and predisposing SCI to uncontrolled shifts in BP. Of the range of abnormalities, the most dangerous is autonomic dysreflexia (AD)[8,33].

Characterized by hyper responsive sympathetic outflow in response to a noxious stimuli (e.g., distended bladder, cut or fracture, burn) below the SCI, AD should be considered dangerous, or life-threatening, and requires immediate treatment[51]. Fairly common in SCI of Thoracic level six or above, uncontrolled AD can limit one's ability to safely perform activity or exercise training. Moreover, sharp fluxuations in blood pressure will have obvious detrimental effects on health, including cerebral vascular events. Nonetheless, AD and hypertension are two distinct conditions, where AD is mediated by SCI, while hypertension is strongly influenced by the development obesity following SCI.

Dyslipidemia and Cardiovascular Disease

Ultimately, the impact of MtS on any population is typically an increased risk for developing CVD. While commonsense suggests that SCI should have a much higher prevalence of CVD than able-bodied individuals, the literature indicates this may not be the case. For example, Myers et al.[33] reported a much higher prevalence of CVD among SCI than ambulating populations, suggesting that paraplegics (para) have a 70% greater risk for CVD and that 65% of para's suffer from "silent ischemia". However, in a far reaching review, Wilt et al.[1] unraveled much of the confusion surrounding CVD in SCI and support the suppositions of Liang et al.[25] that the absolute risk of specific factors varies between SCI and able-bodied. In fact, it appears that two overwhelming factors influence CVD development among SCI, dysfunctional carbohydrate metabolism and obesity.

One cannot overlook the impact of blood lipid disorders in SCI, particularly increased LDL cholesterol (LDL), and extremely low HDL cholesterol (HDL).[25,32,33] For example, Bauman and Spungen (2008) reported that as many 40% of SCI have an HDL less than 35 mg/dL, compared with 10% in the general population, and that HDL was inversely related to triglyceride levels. Interestingly, both obesity and low HDL were found to be the only significant risk factors for developing MtS in SCI[25], while the relative risk for developing CVD may be similar between SCI and able-bodied[1]. The former observation is interesting when one considers that obesity increases NEFAs, and NEFA levels play a significant role in modulating blood lipids.[43,52]

Pro-inflammatory Environment: The final denominator

Of all the factors influencing MtS, systemic inflammation component is increasingly seen as the missing link between MtS and atherogenesis[53]. The interrelationship between obesity and this subclinical inflammation relates to adipose tissue's release of inflammatory molecules like CRP, tumor necrosis factor (TNF)-α, IL-1, and IL-6, which also interfere with insulin action[53]. The interelationship between obesity and insulin resistance is further muddled after spinal cord injury. For example, IL-1, IL-6 and TNF-α rapidly increase within hours after SCI but may serve both an

inflammatory and neurotrophic response[54,55]. Further, chronic SCI have been shown to exhibit subclinical inflammation[7,8,56] which may be involved in a proregenerative response in SCI[56]. Nonetheless, the proinflammatory cyctokine linkage to MtS and the high rates of MtS among SCI, may necessitate controlling this response to alter the prevalence of MtS in SCI.

Exercise as Medicine

It could be said that exercise is an effective treatment for many of modern society's ills. As with any drug, it has risks associated with it, but probably carries far greater benefits than negative side effects. Yet, exercise remains an underutilized component of disease treatment. For the SCI patient, exercise may be the most important treatment to maintain long-term health and independence. The prevalence of MtS among SCI demands a potent treatment of some of the major constituents like diabetes and hypertension. In a brief review, Colberg and Grieco[11] discussed the central role physical activity can and should play in both the prevention and treatment of diabetes. Of particular importance are the increases in glycogen synthase in response to aerobic training, while GLUT4 expression has been shown to increase following both aerobic[11] and resistance training[57]. In addition, resistance training (RT) increases muscle mass, allowing for a larger repository for glucose uptake. Further, improvement in insulin resistance and/or type 2 diabetes is independent of weight loss, because exercise decreases both visceral and intramuscular fat, both of which exacerbate insulin resistance[58]. Most intriguing, however, is the role that intensity may play in reversing many of the components of MtS.

It has also been proposed that the degree of mitochondrial biogenesis can have an impact on managing, or even reversing insulin sensitivity and the progression of diabetes[12]. Due to the link between improved mitochondrial biogenesis and function with GLUT4 expression, Earnest[12] has hypothesized that high intensity interval training (HIT) provides a more powerful stimulus improving insulin sensitivity than traditional moderate aerobic exercise related specifically to the metabolic processes (e.g., aerobic glycolysis, beta oxidation, and mitochondrial biogenesis). The

efficacy for high intensity training has been shown in a variety of populations[13,59-69], which has been shown to reverse heart disease cardiac damage[69], promote insulin sensitivity, and perhaps reverse diabetes[13,70].

In the past decade, research among able-bodied persons using HIT and sprint interval training (SIT) have shown great promise in not only improving endurance performance to equal or greater levels than endurance training[61-63,65,69,71-82], but also enhancing fat metabolism[82], glucose tolerance[83] and vascular function[68]. It comes as little surprise to sports scientists, who have known for years that peak athletic performance demands maximal intensity exercise. Yet, contemporary exercise advice[84] have recommended similar guidelines to the general public for decades. Some of the reluctance has come from a fear that high intensity intervals were dangerous for high-risk patients (e.g., those with cardiac disease). As indicated earlier, however, even in post-infarction heart failure patients, exercise intensities greater than 90% peak heart rate were not only safe, but were also more effective at improving $VO_{2\ peak}$, and actually shown to reverse left ventricular remodeling[69,85]. Some would argue, however, that high intensity training actually discourages participation and compliance. However, recent data suggest the opposite. For example, Gibala reported[86] that HIT has been successfully used in a range of populations, including persons with diabetes and MtS, as well as men and women over the age of 65. Wisloff indicates that many individuals prefer HIT to continuous training because of the reduced time commitment, and clearly defined session objectives and end-point.[87]

Endurance exercise is part of an effective treatment for CVD and obesity. Therefore, HIT could indeed be a critical factor in reversing the MtS. Perhaps such a statement is bold, but for a population that has very limited exercise capacity to start with and a high risk for overuse injury of the shoulder, short, high intensity work bouts may provide a means to mitigate or reverse risk, while building overall work capacity. Of greatest interest are data from a series of studies from McMaster

University[61-66,68,72,73] indicating that low volume sprint interval training (i.e., 30 sec Wingate Sprints) yields results comparable to that of traditional submaximal endurance training.

Early work by Dudley et al.[88] eloquently showed enhanced endurance performance in response to increased intensity. Since then, data from both endurance athletes and untrained individuals have shown that HIT – intervals of 1 – 5 min - are an effective[12,69,82] and often necessary tool for improving exercise performance[74-78,81,82,89]. Although the metabolic and cardiovascular response to Wingate sprints seemed to contradict an endurance adaptation, Stepto and Hawley[81] showed that among trained cyclists, 30 sec intervals improved 40 km time trial performance as much as 4 min $VO_{2\ max}$ intervals; both were superior to other intervals used. However, this paper stood in isolation for nearly a decade before data by Burgomaster, Hughes et al.[63] and Gibala et al.[65] both indicated that supramaximal Wingate SIT produce similar initial metabolic/biochemical changes in the trained musculature[63] as long-term endurance performance [61,65] as more traditional endurance training. Subsequent data from these researchers has shown that from a cell signaling perspective, SIT is more closely related to endurance than strength training, acting as a potent stimulus for PGC-1α expression by up regulating AMPK and p38 MAPK signaling pathways[72], all of which are closely tied to endurance adaptation[90], including mitochondrial biogenesis[80], insulin sensitivity[70], and even fiber type transformation[70,91,92]. Not surprisingly, improvement in endurance characteristics are inherently linked to improvement in insulin sensitivity and glucose tolerance, and indeed, this is what we see following just 2 weeks of SIT training in several populations.[83,86,93,94]

Questions arise whether such high intensity work is realistic for many individuals. In light of this, Gibala's group[67] proposed a less taxing training regiment using 1 min intervals at $VO_{2\ Peak}$ wattage followed by 75 sec of recovery completed 8 – 12 times. Total training time was less than 30 min and subjects reported none of adverse effects, like nausea, sometimes reported following SIT. After 2 weeks (6 sessions total) subjects improved performance about 10%, as well as increased mitochondrial enzyme content (~35%), markers of biogenesis (~30%), and GLUT4 content (119%),

putting it on par with endurance and SIT adaptations. Moreover, Gibala has indicated that HIT has been effective and shown good compliance across many populations.[86]

Another question that arose from Gibala's work[13], was whether sprint training adaptations were short lived and represented early adaptations. Two unrelated studies addressed this issue and in doing so, validated the *Overload* principal in untrained and trained individuals. For example, Nordsborg et al.[95] compared the molecular response via alterations in mRNA PGC-1α following HIT in both untrained and trained (1 yr training and $VO_{2\ Peak}$ 55 $ml \cdot kg^{-1} \cdot min^{-1}$) individuals. Trained participants did HIT sessions at 85% of the untrained $VO_{2\ Peak}$ power and 85% of their Peak power. As expected, training at the same absolute power did not yield any significant changes in the trained group, while 85% of each group's max (i.e., same relative power) showed significant increases in mRNA PGC-1α. Another interesting finding, not surprisingly, were lactate levels for trained individuals were significantly lower at the same absolute workload. The latter finding brings into question the role of homeostatic disruption to elicit exercise adaptations, as well as the role of reactive oxygen species (ROS), like H_2O_2, and lactate accumulation, implicating both in the up-regulation of PGC-1α[70,96]. Finally, further support for SIT impact on endurance adaptations were seen in even highly trained cyclists ($VO_{2\ peak}$ ~70 $ml \cdot kg^{-1} \cdot min^{-1}$), who, after completing a single session of SIT, saw gene expression in several key mitochondrial markers, supporting the notion that it is the relative intensity of training (i.e., near the individuals "max") that elicits improvements[97]. This relative response may have important training implications for persons with SCI.

To review, high intensity training appears to provide a useful and potentially powerful tool for endurance and metabolic change in a number of populations. While not entirely clear, it does appear that the relative intensity and perhaps contribution of motor unit recruitment[13,65,72,95,97] may relate to the underlying mechanisms for these changes. Support for the motor unit recruitment theory (i.e., activation of high threshold Type IIa/x fibers) is provided first, by lactate data[95-97], indicating that higher blood lactate concentration (BLC) may induce greater PGC-1α mRNA. For example

expression following exposure to 10 mM lactate, with even further expression after 20 mM exposure. In actuality, 20 mM increased many hundreds of genes involved metabolism and mitochondria, several fold more than 10 mM. Further, lactate was shown to activate H_2O_2 production[96], a ROS, another regulator of PGC-1α. How specifically either ROS or lactate influence this regulation is open to some debate, but ROS are believed to be linked to AMPK's promotion of PGC-1α[70], while lactate may signal a need for improved oxidative metabolism[98], or enhanced lactate transport into the mitochondria. Moreover, ROS are functionally essential to endurance adaptations[70], and perhaps increased BLC is as well.

Exercise in SCI: Potential vs. Possible

For able-bodied obese individuals, exercise may seem a daunting task that yields mixed results, while for SCI, the physical and physiologic limitations they endure may minimize exercise capacity and adaptations outcomes. SCI may exhibit typically display cardiovascular, pulmonary and/or hemodynamic limitations, sarcopenia, autonomic nervous system and endocrine dysfunction, lower limb spasticity, diminished bone density, neurogenic bladder and bowel conditions, and risk for shoulder disabilities[8,51,99-105]. For example, all SCI patients can expect some limitation on maximal aerobic power ($VO_{2\ peak}$) simply due to the a smaller available muscle mass and decreased cardiac preload, secondary to venous pooling; i.e., the engine is smaller and has less available fuel. However, as the level of the injury increases from T-12 and up, greater overall systemic responses occur, further exacerbated by the completeness of the spinal lesion or injury (ASI-A or B versus C or D), and that day to day physical strain during ADL's is proportional to one's level of spinal cord injury[106-108]. Despite the limitations faced by individuals with SCI and related disorders, exercise remains an important component to not only managing health risk factors, but also enhancing one's quality of life.

Physical limitations

It has long been held that the key to long life and health was aerobic endurance exercise. However, training options for persons with SCI are typically limited to either arm crank ergometry, wheelchair training, or less often, functional electrical stimulation (FES) cycling. Unlike the general population, however, SCI activities of daily living (ADL) and aerobic fitness are directly tied to upper body strength[107,109]. Moreover, as the level of the injury increases from T-12 upward (i.e., higher level injury), the greater the strain they suffer. Likewise, individuals may be classified as AIS A or B, where they have no motor function, or AIS C or D, where motor function is preserved (see **Table 3** for more information).[110] Not surprisingly, AIS A and B injuries have greater difficulties than C or D injuries.[107] As individuals with SCI live longer, the risk for shoulder joint dysfunction, injury and/or degeneration increases. Current estimates among SCI persons indicate that between 30 and 100%[99] suffer from shoulder pain at some point in their lives. The cause of such pain can be diverse and may stem from: poor transfer or pushing technique, incorrectly sized wheelchair, inappropriate biomenchanics, inadequate strength, acute or injury, chronic overuse, and/or muscular imbalances between the anterior and posterior musculature. While mild pain may not initially limit activity, over time, functionality will inevitably diminish. Further complicating those factors is the presence of paralysis in the upper extremities for tetraplegics.[99]

Acute Exercise Responses

Acute exercise responses are impacted most by neuroendocrine system, due the nature of the feedforward and feedback systems in the body and the "fight or flight" response. It is no wonder that profound cardiopulmonary changes may be seen following SCI, and, like other problems in SCI, vary by level and completeness of injury. For instance, able-bodied individuals often take for granted the impact sympathetic drive has on heart rate and heart contractility, which ultimately impact cardiac output and VO_2. For SCI of Thoracic (T) level 6 or lower, this generally is not an issue. However, loss of sympathetic drive to the heart becomes more likely from T5 upto T1, with a general loss of cardioacceleration and tone at the cervical level[51,103], where maximum heart rate may

not exceed 100-120 beats. Dela et al.[111] confirmed the importance of the ANS in the early increase in HR for SCI; compared to controls, SCI had a delayed HR increase in response to evoked exercise, as well as a diminsihed catecholamine response, supporting the role of the endocrine system in cardioacceleration. Loss of sympathetic drive to the heart will also limit contractility and stroke volume (SV), explaining part of the decrease in maximal cardiac output. However, decreased venous return appears to be the major determinant for diminishing submax cardiac output and possible exaccerbation of cardiovascular drift[103,111].

Loss of sympathetic tone on the vessels affects blood pressure and venous return, while the loss of the muscle pump may severely limit venous return, thereby forcing a compensatory HR drift in SCI that may not reflect the true intensity of the training session. *Circulatory hypokinesis*[51,112-114] as it has been termed, is common after SCI and results in significant venous statis in the lower extremities, and has been shown to have a significant deletarious impact on cardiac output during upper extremity exercise.[113] Not unlike an athlete training in a hot environment, individuals with SCI must contend with cardiovascular drift at every session. Furthermore, diminished venous return and cardiac output has been shown to limit positive cardiovascular remodelling[114,115], which may diminish the global impacts from arm training and contibute to the difficulty in achieving central adaptation ins SCI[114].

Unlike the cardiac system, separating the role of the central nervous system (CNS) from the ANS for respiration can be difficult. At rest, the breathing is controlled by the respiratory center in the medulla oblongata.[116], while at the initiation of exercise, motor cortex outflow increases ventilation rapidly, with rapid feedback from proprioceptive feedback of the active limbs. The spinal cord, in simplest terms, delivers the information provided by the upper CNS and disruption of the CNS limits pulmonary function in SCI as low as T11. [117] Somatic or motor function below the level of injury will lead to a loss of innervation to accessory muscles like the internal intercostals (T1-T11), transversus abdominus (T2-L1), obliques (T6-L1), and rectus abdominus (T6-T12), while the

diaphram is spared dysfunction up to Cervial (C) level 5.[8,118] Therefore, pulmonary limitations become more pronounced as exercise intensity increases; where able-bodied normally are not limited by maximal pulmonary stress, SCI often will have some breathing limits, in addition to cardiovascular limits.

Breathing may be further complicated after SCI due to an imbalance the ANS, which controls sympathetic and parasympathetic outflow to the broncioloes.[119] While upper thoracic and cervial level injury may be largely reliant on the diaphram for breathing, tetraplegics also showed increased vagal stimulation of the broncioloes, reducing airway caliber and restricting airflow to and from the lungs. Coupled with diminished chest wall and lung compliance, along with a concomitant increase in abdominal compliance, tetraplegics have increase in breathing work.[120]

As already indicated, SCI exhibit lower resting catecholamine levels and a blunted catecholamine response to exercise that is inverse to the level of injury, with norepinephrine (NE) being a good measure of sympathetic nervous activity (SNS) and epinephrine (E) a good measure of adrenal function[121]. In general, catecholamine deficiency or decreased response is most pronounced in SCI above T6 [111,121,122]. The relative impact of this blunting has clear impacts of cardiovascular parameters and blood flow, but also metabolic function, and substrate mobilization and utilization, which may minimize serial impact of training over time (i.e., lower acute leads to reduced chronic adaptation). E and NE are strong mediators of glycogen breakdown and lactate production, but it is unclear how closely they are linked to lactate production in persons with SCI.

Frey et al.[104] have suggested a parallel relationship between lactate and catecholamines after SCI where catecholamine deficiency limited maximal blood lactate concentration (BLC). While this study is often cited as evidence of a blunted lactate response in high level (e.g., above T1) SCI, close inspection of the available literature[104,111,121,123-126] suggests that lactate response in SCI has more to do with available muscle mass and workload. For instance, Frey et al.[104] compared T2 and above with T10-12 individuals during a progressive arm crank test using 3 min stages. Disregarding the

small sample size, one obvious finding is the disparity in maximal workload (30 vs. 90 W), which reflects the difference in upper body strength – a major determinant of arm exercise in SCI [109] – alone would account for the difference in BLC. While it was also clear that neither NE nor E changed in the high-level individuals, it would be unwise to link low BLC with low SNS response. Moreover, data in similar groups during functional electrical stimulation (FES) cycling does not show the same degree of disparity in catecholamine's[123,127] and unpublished data[128] from our laboratory indicate that above T4 SCI exhibit high BLC during FES and ACE. While level of injury may play a role in lactate response, other factors including motor unit recruitment, muscle fiber type and individual drive also play a significant role. Alternatively, venous pooling in the lower extremities could artificially increase BLC by reducing total blood volume in the system. Therefore, far more work is needed to fully elucidate the lactate response for persons with SCI.

One special note must be made regarding the reflexive hypertonicity, or muscle spasticity, below the level of injury in SCI. Spasticity is often a double edged sword, believed to help preserve muscle and bone mass[8,129], but can greatly diminish quality of life and functionality in SCI[8,114]. Fortunately, lower extremity exercise has been shown to reduce spasticity in SCI[130], making exercise an important facet to long-term care.

In summary, disruption of the combined neuroendorine system will impact cardiac response to exercise, as well as the hemodynamic responses. Moreover, pulmonary limitations may impact maximal activity, but probably do not significantly impact training in SCI T10 and below. Finally, it appears that the acute lactate response in SCI is influenced, but not determined by the SNS, and is more likely inflenced by the mode of activity, lower extremity venous stasis and the overall work capacity. Additionally, SCI appear to exhibit a similar lactate elimination as able bodied[125], but may exhibit higher submaximal BLC under certain conditions. Of particular note, is the potential for diminished respiratory buffering capacity in high level para and tetraplegia due to impair ventilatory

capacity and venous pooling. Taken together, these changes can have important implications on how BLC after SCI is interpreted and how exercise should be prescribed for individuals with SCI.

Chronic Exercise Adaptation

Our understanding of the endocrine system's role in exercise adaptation has expanded significantly in the past decade. Many of the acute responses following an individual training session act serially to produce a larger chronic adaptation, whether positive or negative. For example, muscle remodeling following training is a balance of catabolic breakdown (e.g., cortisol) that enables anabolic hormones, like growth hormone and testosterone, to restructure and rebuild a muscle more capable of responding to the stress placed on it. For able-bodied this process functions normally, while in SCI, hormonal disruption may make adaptation more difficult.

As previously discussed, SCI suffer a wide range of neuro-endocrine disruption, which influences acute exercise and chronic training adaptation. Generally speaking, men with SCI can exhibit clinically low testosterone and free testosterone[131], which can have broad impacts on individuals, including limiting strength gains from RT and muscle adaptation and recovery following training[132]. Additionally, growth hormone (GH), and its surrogate measure IGF-1, may be blunted among SCI[131,133,134]. These findings were strengthened recently by Bauman et al.[135], where monozygotic twins displayed divergent GH responses, with SCI twins presenting reduced GH. Clinically and metabolically, this latter finding is probably more important due to the extensive role GH plays in the body at maintaining body weight, blood glucose maintenance during activity, and tissue remodeling/recovery after exercise. Therefore, care must be taken to balance the training stimulus with adequate recovery. The anabolic imbalance may also extend to estradiol, as well, which has been shown to be higher among SCI than their non-SCI twin. The cause is believed to be increased fat mass present in SCI[136]. Nevertheless, it seems unlikely estradiol offers significant protective effect from bone loss. It also highlights the complexity of changes following SCI. Thus, careful consideration must be given to both the short and long-term planning of exercise training in

SCI to account for these alterations. Additionally, more data are needed in elucidating the potential impacts that various training protocols might have on enhancing the endocrine response in SCI.

Exercise Application: Training in SCI

Upper Extremity Endurance Exercise

Without doubt the greatest limiting factor for training SCI is that most are constrained to upper extremity exercise. Whether it be wheelchair pushing, arm crank or hand cycling, or resistance training, arm exercise is the most convenient and cost effective exercise strategy for SCI. Arm crank ergometry (ACE) may offer a conveniant training option for enhancing both cardiovascular fitness and caloric expenditure, despite the relatively small available muscle mass[137]. Moreover, the human shoulder joint is not ideally suited to repetitive endurance activity and arm exercise will often exacerbate overuse issues in the shoulder without appropriate prophylactic resistance exercise is added. In spite of this, numerous studies have support the use of arm exercise as a core part of training SCI, particularly paraplegics.

ACE, and to a lesser extent wheel chair or hand cycling, are probably the most common and easily accessible exercise modalities for wheelchair bound persons and have been studied extensively[103,109,138-151]. Early ACE training has shown varying results, with some showing minimal cardiovascular benefits from 8 weeks of low-moderate intensity training 20 $min \cdot day^{-1}$, 3 $days \cdot week^{-1}$ [152], while other data indicated that 16 weeks of ACE had a significant impact on fitness [151], and that high resistance ACE can also improve upper extremity strength[153]. Upper extremity strength is positively related to endurance performance[109]. Due to the physical limitations faced by increasingly higher injury levels, it has been suggested that level of injury was a major factor affecting ACE improvements[114]. However, most data show significant cardiovascular improvement[103,114,141] following prolonged intensive training, suggesting that a balanced approach to intensity can make the difference between minimal and optimal improvement. For example, de Groot et al. et al. [154] showed that ACE training at 80% heart rate reserve (HRR) was more effective at improving $VO_{2\ Peak}$,

insulin sensitivity, and lipid profiles than 60% HRR. Indeed, data from our lab indicates that motivated SCI training over a period of months can make large improvements in ACE performance. One subject was shown to improve ACE $VO_{2\ Peak}$ by more than 50% in just 5 weeks of training. Thus, SCI can achieve significant improvements with a well designed training program. Additionally, it would appear that simulataneous ACE and FES cycling – referred to as *hybrid* training, can significantly impact the acute exercise response in SCI[155]. It is likely, that the addition of FES to upper extremity exercise mitigates hypokinetic circulation, improving cardiac output.[112] Thus, hybrid training may offer an additonal training or testing tool for individuals with SCI.

Lower Extremity FES Leg Cycle Ergometry

In contrast to upper body exercise, FES training of the legs has both metabolic and performance consequences. Data from FES resistance training (typically leg extensions), saw a 7 – 30 fold increase in force production[156,157], 20-40% increase in thigh cross-sectional area, improved oral glucose tolerance tests (OGTT)[156], and decreased intramuscular fat, which may significantly improve insulin sensitivity[158,159]. Despite its endurance nature, FES cycling provides a weak cardiovascular benefit, but has shown promising results restoring leg muscle mass[156,160]. However, FES training is often even less accessible than either arm crank or wheelchair training options. FES training as a whole, whether it be cycling or leg extension exercise, can have a substantial impact in SCI. Functionally speaking, Lui et al.[161] showed a 3-6% in Torque (Nm) and 2.3% increase in lean mass after just 8 weeks of FES cycling, while Petrofsky et al.[157] saw force (KP) increase 55% after 12 wk of leg cycling. Likewise, Duffell et al.[162] showed significant improvements in FES cycling over the course of one year's training. More importantly, studies support the positive impact FES has on metabolic parameters[163-165]. For example, Mohr et al.[165] showed that a year of FES significantly improved insulin sensitivity and GLUT-4, while more recently, Griffin et al.[163] showed that just 10 weeks of FES cycling improved glucose tolerance tests and reduced inflammatory markers like IL-6 and CRP.

Improvement in insulin sensitivity is typically associated with a reduction in adipose tissue, however, our understanding of muscle fiber typing among SCI, as well as extended training data supports peripheral enhancement of glucose uptake. For instance, after a year of training, Mohr et al.[44] showed a reversal of Type II fibers; prior to training 63% of the muscle was Type IIx and 33% Type IIa, while at the completion of training the breakdown was 32% and 61%, respectively. Even more interesting were data by Crameri et al.[166] showing similar trends in as short as 10 weeks; Type IIa fibers increased from ~25% to nearly 80% by the end of training. These two papers suggest the profound impact FES may have metabolically, improving insulin sensitivity from a route typically unseen in the general population and has important implications for long-term management of SCI. It is unclear what amount of continued FES is needed to maintain these outscomes, however.

Upper Extremity Resistance Training

Few modalities available address the importance of upper body strength in performing ADL.[107,109] Available data among applicable special populations with similar co-morbidities, indicate that RT could be a powerful tool in treating SCI related ailments. For example, Kraemer et al.[167] have shown that older adults still show a high degree of improvement following RT, and that RT may potentiate their diminished endocrine response. While less extensive, RT data from studies using SCI persons suggest that it is an important component for improving strength and overall fitness, likely improve one's ability to perform ADL's and reducing shoulder dysfunction[101,109], _ENREF_6but little is known about its affect on insulin sensitivity. In contrast, upper body (UB) training can often show considerable crossover. For example, both Nash et al.[156] and Jacobs et al.[145,149] have shown impressive improvements in both aerobic (e.g., $VO_{2\ Peak}$), strength, and power (e.g., Wingate) measures following either circuit resistance training or more traditional RT. Most interesting of these, however, is Jacobs [145] study showing that moderate RT is equally effective at improving aerobic fitness and Wingate power as moderate intensity arm crank training, while only RT improved strength measures. This last finding is important, because as Janssen et al.[107] and

Zoeller et al.[109] have shown, upper extremity strength plays an important role in an SCI person's ability to perform ADL. Moreover, Nash et al.[101] indicated that appropriate RT not only improves fitness, but also reduces shoulder pain, which is endemic and debilitating in SCI.

Metabolically, Kirk et al.[168] have shown that even minimal RT can result in a chronic increase in energy expenditure and even increase GLUT-4 content in able bodied subjects.[57] This last finding is important, because other research[169] has suggested that RT only improves glucose disposal due to an increase in muscle mass, and thus creates a larger source of disposal. However, recent data [170] further supports Tabata's[57] work, suggesting that like aerobic training, RT may have an innate ability to improve glucose metabolism. For example, Black et al.[170] showed that acute RT may improve insulin sensitivity in individuals with impaired glucose metabolism. It is unclear what additional influence lower body FES resistance training might have in this population.

Lower Extremity FES Resistance Training

A review of the literature for FES RT among SCI offers promise but also highlights the limitations of FES in SCI. For instance, unlike upper body RT, which may often look very similar to any program in the general population, lower body activity in SCI is often reliant on FES, where the paralyzed musculature is stimulated to either produce or enhance an individual's muscle contractions[156,157,160,161]. Therefore, true resistance training as most are familiar with has not been studied, and has typically been limited to FES leg extensions[156,160] or even FES cycling [157,161]. Further complicating these data are the small sample sizes used, making broad interpretations and recommendations difficult at best. Despite these shortcomings, available data suggests promising results from RT. For example, simple leg extensions have been shown to increase force production upto 30%[156,171] and cross-sectional area 40% [160], while decreasing intramuscular fat of the legs[159] and improving glucose tolerance[156]. Additionally, Petrofsky and Laymon[157] demonstrated that even short-term FES RT can significantly improve FES cycle training. Nonetheless, there are little data on

RT representative of whole leg able-bodied training, nor information on the endocrine repsonse to either upper or lower body RT.

Finally, no research to date has examined the combined impact of upper body RT with lower body FES RT and it is unclear how a more traditional approach to whole body resistance training would influence health or fitness in SCI persons. For example, preliminary data from our lab indicates that ACE caloric expenditure is significantly higher than FES (4.3 vs. 2.5 $kcal \cdot min^{-1}$), but the addition of *hybrid* FES training improves ACE performance in SCI. Whether the combined training would further enhance caloric expenditure of ACE is still unclear, though. It is reasonable to expect significant improvements from combined RT, as well. However, the very nature of SCI makes transporting individuals and retaining them for a three-month training period daunting. Moreover, reduced sympathetic nervous input and hormonal disruptions, particularly clinically low testosterone in men [172], may have broad implications on long-term training adaptations in SCI that alter resistance training outcomes. Thus, much initial work is required.

Practical *Exercise is Medicine* Rx

For physicians, a major tenet of medicine is to *first, do no harm*, perhaps exercise physiologists should adopt the major tenet to *do the most good*. In contemporary society, weight loss is often not just the primary goal, but the only goal for individuals, while research suggests that weight loss may not be needed for improvement in metabolic improvements[58]. In comparison, health professionals have largely focused on cardiovascular or aerobic fitness in an effort to improve cardiovascular function, while ignoring both resistance training and HIT. The belief has been that reducing cardiovascular disease and burning the most calories in an exercise session were of paramount importance. However, for a population suffering from significant metabolic disease that ultimately increases one's risk for CVD, it seems more logical to address and mitigate their risk factors, while improving their functionality – defined here to be the ability to perform ADL and community mobility, and their ability to adhere to a structured exercise program. While it may not be

possible for many with SCI to accrue recommended weekly energy expenditures, expenditures low as 1000 kcals·week^{-1} can lead to significant loss in body fat, despite a divergent cardiovascular response between FES cycling and ACE. Thus, long-term exercise planning may require a multi-modal approach.

As research has shown[145,147,149,173], persons with SCI may actually benefit as much or more by either supplementing endurance training with strength training, or simply using strength training alone. Such a paradigm may improve retention rates and positive lifestyle changes with the goal of adding more cardiovascular training as one makes progress. There is good reason for using one mode of activity to build functional ability or interest, later adding new activities. For example, data among obese adolescents shows a high affinity towards resistance training, with long term compliance near 90%, with significant improvement in insulin sensitivity; many of these participants move on to other traditional endurance activities like cycling and swimming[174]. SCI may be a more complex population, but that may mean greater critical thought on solutions, including using two or more modalities. In particular, increased body weight/fat limits one's ability to perform ADL's and reduces mobility within their community. Added strength enhances wheel chair propulsion and transfer ability, which will improve overall activity, which are important in long-term compliance.

It is a long-held belief that combining endurance and strength training leads to compromised gains in individuals without disability[175-177], and that strength training alone provides no significant cardiovascular benefits, which may not entirely apply to SCI[145]. Thus, it appears that non-traditional modalities may offer similar, if not superior short-term fitness results than modalities like sub-maximal ACE or wheelchair training, while reducing the risk for upper extremity injury[99,109,144]. For the general population, these data offer a powerful tool in managing risk factors and improving endurance capacity in the short-term. In SCI, SIT may prove even more valuable in the short and long-term management of MtS. At present, no data are available on HIT or SIT using ACE, and therefore, the literature is bare with regard to HIT in SCI. Existing data[51,103,146,178] show that Wingate

workloads and power outputs are considerably lower for ACE than they are for leg ergometry and inversely related to the level of the SCI[146,178]. Early work using SIT in our lab[179], suggests that SCI have a high capacity for upper body work and SIT may improve insulin sensitivity, but the overall magnitude may be less than leg ergometry. For example, subjects improved their average work (kj)/sprint by more than 10% after just six sessions, while insulin sensitivity improved by 7%, which are smaller than leg sprint studies.[83,93,94] It is yet unclear from this limited data whether the reduced response is due to lower absolute work rate, the age of the participants – ~50 years, the high degree of obesity – 35% fat, SCI or a combination of any of these factors. However, data by Gibala's group[86] indicates that high intensity leg cycling is an effective training tool among obese, diabetic and elderly populations, suggesting that SCI may achieve more modest improvements.

This brings to light a major limitation of SCI research, which is the heterogeneity of the population, which often makes study design complicated and interpretation of results difficult. For instance, it is as difficult to compare a person with T10 SCI with a person with C5, as it is a T4 complete injury with an ambulatory T4 for any or all of the reasons outlined earlier. Cardiovascular, metabolic, physical mobility and strength all differ, and may even differ between two individuals of equal level and complete injury. Furthermore, the variability in population makes recruitment of adequate subject pools challenging at best, particularly among motor complete, and even more so among cervical level motor complete injuries. Therefore, a great deal of thought must be given to study design, with liberal timelines for data collection. Further complicating research are competing protocols and levels of remuneration, practicality of completion, and subject commitment. All of which will influence the direction of study designs.

Future Directions

21st Century Exercise Rx

One might conclude that persons with SCI are a complex population that should be treated with caution due to the limitations and health issues they face. However, participants at our lab have

proven that with sufficient motivation, SCI are indeed capable of undergoing strenuous training, and making large improvements without large decreases in body fat. Therefore, it would seem that exercise prescription should use both caution and sound training principles that includes long-term planning for training SCI. It also appears that multi-modal training, likely utilizing both lower FES cycling and upper extremity exercise, may yield the greatest overall results, and that appropriate shoulder strengthening can improve shoulder function and reduce shoulder pain [99]. Additionally, both heavy resistance training and circuit resistance training yield impressive results in strength, power, aerobic fitness and even blood lipids[145,147,149,150,173]. Finally, while little data exists, it appears that either HIT or SIT are viable options for training SCI and should be considered for capable individuals. Nonethelss, based on current ACSM guidelines[180] most SCI fall into the moderate risk category influencing early assessment and programming. Thus initial screening and testing are important.

Following a full risk factor assessment, graded exercise testing should be considered based on common ACSM guidelines[180], as well as those absolute and relative contraindications specific to SCI, as summarized in **Table 4**.[181] Training prescriptions should account for individuals goals and risk factor reduction, and consideration should be given to factors limiting recovery to ensure adequate adaptation occurs. Inspite of the broad, often far-reaching health problems among SCI, exercise must be a key component of long-term SCI treatment.

Research

It would seem that research among SCI is nearing a critical mass. Nonetheless, much work needs to be in understanding the optimal training methodology in SCI. While this may prove near impossible due to the heterogeneity of the popular, more data are needed to allow better conclusions on mitigating or reversing MtS in SCI. Specifically, several emerging lines of research warranting further study include:

- Acute effects of SIT or HIT in SCI – it is unknown whether a single session of high intensity training will yield improved insulin sensitivity[182], or whether there are changes in any of the regulatory apparatus from ACE training[73].
- Short-term training effects of ACE SIT in non-SCI populations – clearer understanding is needed on the impact of ACE SIT in upper body limited populations besides SCI.
- Effects of combined, multi-modal training effects in SCI – more work needs to look at the use of simultaneous upper body and lower body activity in SCI, particularly, combined ACE HIT and FES cycling both in acute and long-term training studies and whether combined training presents an increased risk of overtraining.
- The acute and chronic effects of combined RT in SCI – Little is known about the endocrine response to such training, or the long-term benefits. Further, the combined modality may yield changes in body composition that upper or lower body training has not.
- Relationship between fiber type, lactate response and fiber type conversion following FES.
- Development of better maximal and submaximal exercise test methodology, as well as criteria for determining $VO_{2\ Peak}$ in SCI; e.g., utilizing *hybrid* ACE-FES or Nu-Step training system

Persons with chronic SCI face milieu of health problems, many of which center around the development of obesity, metabolic syndrome and ultimately cardiovascular disease. Therefore, the medicinal qualities of exercise offer great potential for treating SCI. Unfortunately, SCI are a highly diverse and challenging population to effectively train, with much still poorly understood. Nonetheless, the challenges of training provide exercise physiologists and clinicians an immense opportunity to both further our understanding of exercise responses and extend our knowledge of exercise in SCI. Furthermore, a great deal more research is needed unravel how best prescribe exercise in this special population.

Table 1. Life expectancy and lifetime costs for spinal cord injury by age group and severity of injury.

		Life expectancy (years) for post-injury by severity of injury and age at injury									
		For persons who survive the first 24 hours					For persons surviving at least 1 year post-injury				
Age at Injury	No SCI	Motor Functional at Any Level	Para	Low Tetra (C5-C8)	High Tetra (C1-C4)	Ventilator Dependent at Any Level	Motor Functional at Any Level	Para	Low Tetra (C5-C8)	High Tetra (C1-C4)	Ventilator Dependent at Any Level
20	58.8	52.6	44.8	39.8	35.3	18.1	53.0	45.5	40.8	36.9	25.1
40	39.9	34.1	27.3	23.1	19.6	8.0	34.5	27.9	23.9	20.8	12.2
60	22.5	17.7	12.7	9.8	7.6	1.8	18.1	13.1	10.3	8.4	3.6

Severity of Injury	Average Yearly Expenses (in 2008 dollars)		Estimated Lifetime Costs by Age At Injury (discounted at 2%)	
	First Year	Each Subsequent Year	25 years old	50 years old
High Tetraplegia (C1-C4)	$801,161	$143,507	$3,160,137	$1,860,390
Low Tetraplegia (C5-C8)	$517,356	$58,783	$1,786,836	$1,131,560
Paraplegia	$292,740	$29,789	$1,055,869	$720,169
Incomplete Motor Functional at Any Level	$236,109	$16,547	$704,344	$510,452

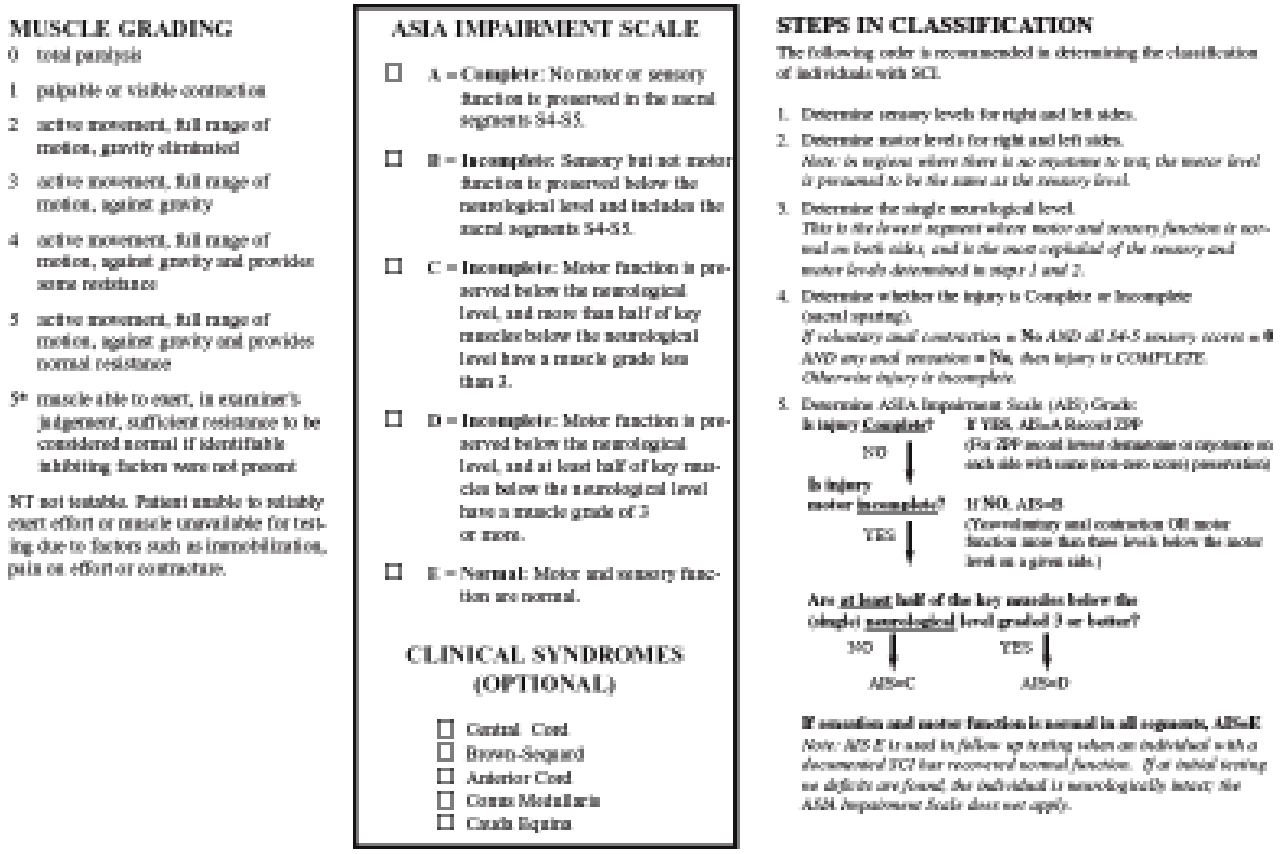
* Adapted from *National SCI Statistical data* [183]

Table 2. Comparison of criteria for determining metabolic syndrome as determined by ATPIII, WHO and AACE. ATPIII and WHO use a strict criteria list, while AACE rely on clinical judgment based on risk factors.[22]

	Obesity	Blood Lipids	Blood Pressure	Glucose	Other
ATP III	Waist Circumference >102 cm (Men) >88 cm (Women)	Triglycerides > 150 $mg \cdot dl^{-1}$ HDL < 40 $mg \cdot dl^{-1}$ < 50 $mg \cdot dl^{-1}$	Systolic ≥ 130 mm Hg ***&/or*** Diastolic ≥ 85 mm Hg	Fasting Glucose ≥ 110 $mg \cdot dl^{-1}$	
WHO	BMI > 30 $kg \cdot m^2$	Triglycerides > 150 $mg \cdot dl^{-1}$ HDL < 35 $mg \cdot dl^{-1}$ < 39 $mg \cdot dl^{-1}$	Systolic ≥ 140 mm Hg ***&/or*** Diastolic ≥ 90 mm Hg	* Type 2 diabetes Impaired fasting glucose Impaired glucose tolerance	Urinary albumin secretion ≥ 20 $\mu g \cdot min^{-1}$ ***Or*** Albumin: creatinine ratio ≥ 30 $mg \cdot g^{-1}$
AACE	BMI > 25 $kg \cdot m^2$	Triglycerides > 150 $mg \cdot dl^{-1}$ HDL < 40 $mg \cdot dl^{-1}$ < 50 $mg \cdot dl^{-1}$	Systolic ≥ 130 mm Hg ***&/or*** Diastolic ≥ 85 mm Hg	Fasting Glucose 110 – 126 $mg \cdot dl^{-1}$ 2 hr post glucose challenge 140 $mg \cdot dl^{-1}$	Family Hx or at risk ethnicity for Type 2 diabetes, hypertension, or CVD Polycystic ovary syndrome Sedentary Advancing age

* Primary criteria plus any two others

Table 3. Overview of neurological assessment form used by the American Spinal Injury Association to classify spinal cord injury impairment.[110]



MUSCLE GRADING

0 total paralysis

1 palpable or visible contraction

2 active movement, full range of motion, gravity eliminated

3 active movement, full range of motion, against gravity

4 active movement, full range of motion, against gravity and provides some resistance

5 active movement, full range of motion, against gravity and provides normal resistance

5* muscle able to exert, in examiner's judgement, sufficient resistance to be considered normal if identifiable inhibiting factors were not present

NT not testable. Patient unable to reliably exert effort or muscle unavailable for testing due to factors such as immobilization, pain on effort or contracture.

ASIA IMPAIRMENT SCALE

☐ A = Complete: No motor or sensory function is preserved in the sacral segments S4-S5.

☐ B = Incomplete: Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5.

☐ C = Incomplete: Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3.

☐ D = Incomplete: Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of 3 or more.

☐ E = Normal: Motor and sensory function are normal.

CLINICAL SYNDROMES (OPTIONAL)

☐ Central Cord
☐ Brown-Sequard
☐ Anterior Cord
☐ Conus Medullaris
☐ Cauda Equina

STEPS IN CLASSIFICATION

The following order is recommended in determining the classification of individuals with SCI.

1. Determine sensory levels for right and left sides.
2. Determine motor levels for right and left sides.
   Note: In regions where there is no myotome to test, the motor level is presumed to be the same as the sensory level.
3. Determine the single neurological level.
   This is the lowest segment where motor and sensory function is normal on both sides, and is the most cephalad of the sensory and motor levels determined in steps 1 and 2.
4. Determine whether the injury is Complete or Incomplete (sacral sparing).
   If voluntary anal contraction = No AND all S4-5 sensory scores = 0 AND any anal sensation = No, then injury is COMPLETE.
   Otherwise injury is Incomplete.
5. Determine ASIA Impairment Scale (AIS) Grade:

Is injury Complete? If YES, AIS=A Record ZPP (For ZPP record lowest dermatome or myotome on each side with some (non-zero score) preservation)

NO ↓

Is injury motor Incomplete? If NO: AIS=B (Voluntary anal contraction OR motor function more than three levels below the motor level on a given side.)

YES ↓

Are at least half of the key muscles below the (single) neurological level graded 3 or better?

NO ↓ AIS=C

YES ↓ AIS=D

If sensation and motor function is normal in all segments, AIS=E

Note: AIS E is used in follow up testing when an individual with a documented SCI has recovered normal function. If at initial testing no deficits are found, the individual is neurologically intact; the ASIA Impairment Scale does not apply.

Table 4. Absolute and relative contraindications to exercise testing for paraplegic and tetraplegic persons. Adapted from *ACSM's Resources for clinical Exercise Physiology*.[181]

Absolute	**Paraplegia**	**Tetraplegia**
Autonomic dysreflexia		√
Severe pressure sore/wound	√	√
Symptomatic hypotension		√
Illness related acute urinary tract infection	√	√
Uncontrolled spasticity/pain	√	√
Unstable fracture	√	√
Uncontrolled environmental heat		√
Inability to safely seat person during testing	√	√
Insufficient range of motion during activity	√	√
Relative		
Asymptomatic hypotension		√
Muscle/Joint discomfort or pain	√	√

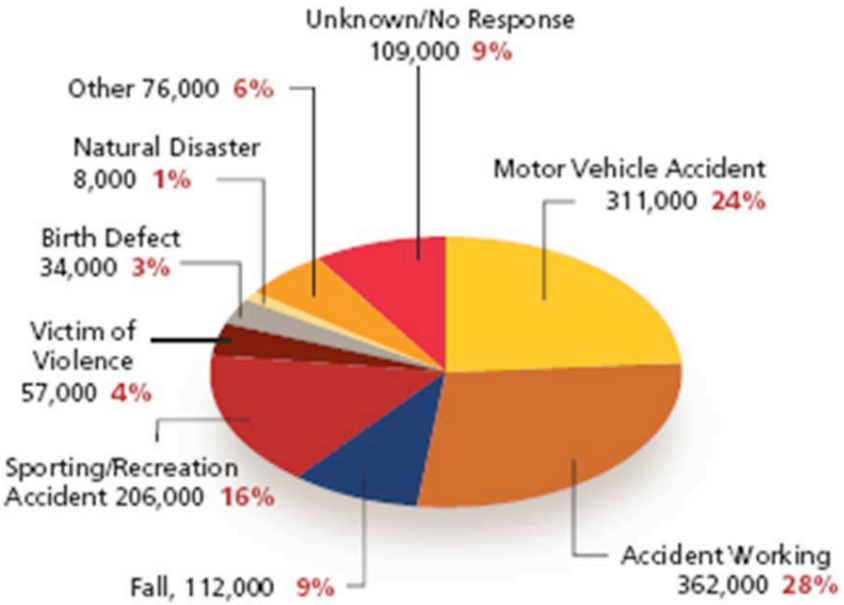


Figure 1. All causes for spinal cord injury.[2]

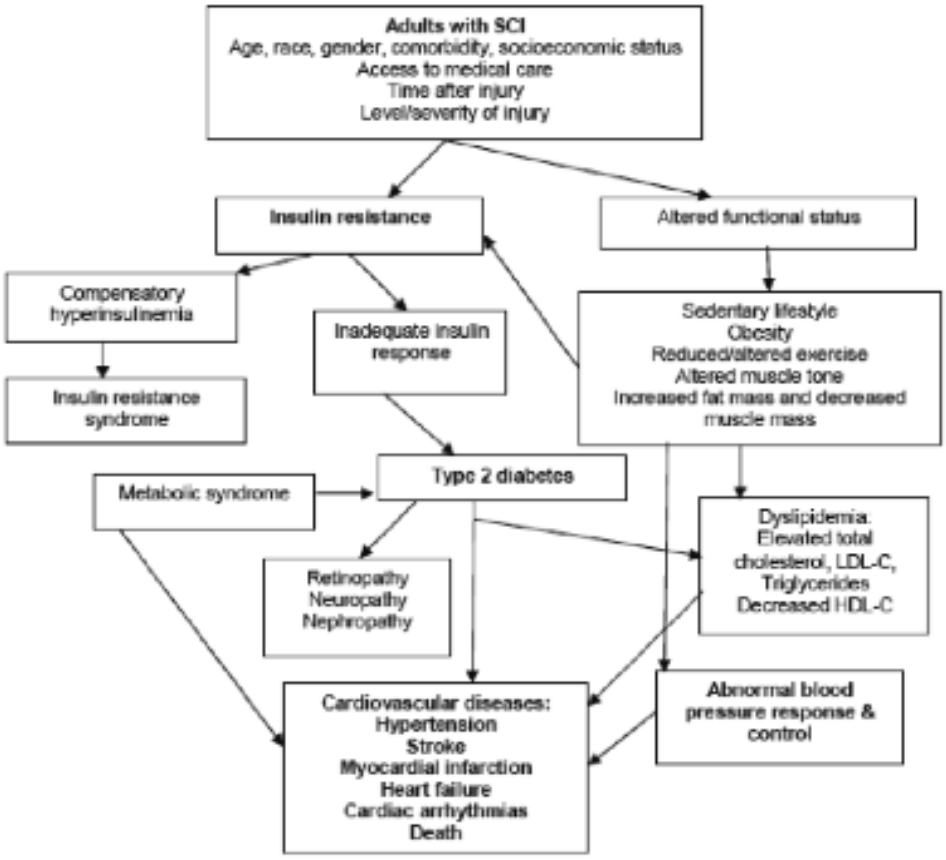


Figure 2. Model present by Wilt et al.[1] for the development carbohydrate and lipid disorders and their contribution to cardiovascular disease among chronic spinal cord injury.

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Appendix B. Pilot Data

All data presented are means ± se. Analyses included both ANOVA with post-hoc Tukey tests, as well as Wilcoxon Sign Rank Tests. Due to the agreement between the aforementioned tests, only ANOVA results are presented.

A total of 12 subjects (females = 4) were used for sprint performance comparison. To accommodate data collection, both males and females were chosen to represent a wide range of abilities. Of the 12 subjects, 8 (3 females) were used for the main analysis comparing a 4 min Tabata with 5 Wingate sprints. The remaining subjects completed most testing, including a 5 min Tabata (identical to Tabata outlined in methods, but session adds an additional 2 sprints), which was used to estimate the additional kJ expenditure for our 8 subjects. From these subjects, it was seen that adding 2 additional sprints increased kJ expenditure 6-8 kJ; the 5 min Tabata estimate uses the lowest value of 6 for the analysis.

The overall findings from the pilot study indicate a 4 min Tabata session will expend a significantly lower amount of kJ (Table 1). However, adding an additional minute to the training adds at least 6 kJ of work and negates this difference. Interestingly, our WIN kJ expenditure compares favorably to data published by Whyte et al. (2012) (61.7± 2.9 kJ). This indicates that using a 5 min Tabata session will allow us to match kJ expenditure with Wingate sessions and maximize the likelihood of a significant myokine response similar to Nielsen et al. (1996).

Whyte et al. (2012) have proposed that energy (ATP) turnover may be the mitigating factor for acute improvement in insulin sensitivity. In their study, the rate of kJ expenditure was 5-6 fold higher for the ~3.3 min "sprint", which is comparative to the data presented here which was ~4 fold higher for Tabata. Thus, if 6 min of VO2 max exercise (Nielsen et al. 1996) increases IL-6, then it is reasonable to expect that a 5 min Tabata (well over 100% relative $VO_{2\ max}$ intensity) will increase IL-6 and improve S_i. Our pilot data (Figures 1 and 2) indicate a consistent and possibly significant increase in IL-10 following 5 min of Tabata training in 5 college age males.

Table 1. Comparison of mean kJ expenditure for 8 subjects following a 4 min Tabata (TAB 4), 5 Wingate (WIN) sprints, or the estimated kJ for a 5 min Tabata (TAB 5 est). *Denotes a significantly higher ($p<0.05$) kJ expenditure from TAB 4; adding 2 additional sprints negates this difference.

SIT	kJ	SE
TAB 4	47.0	3.61
TAB 5 est	53.0	3.61
WIN	61.6	3.61

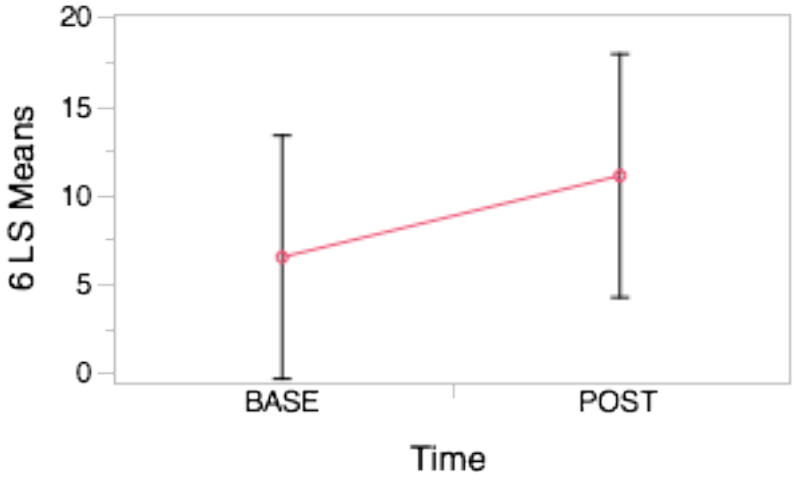


Figure 1. IL-6 at base line and after Tabata training. P = 0.2477

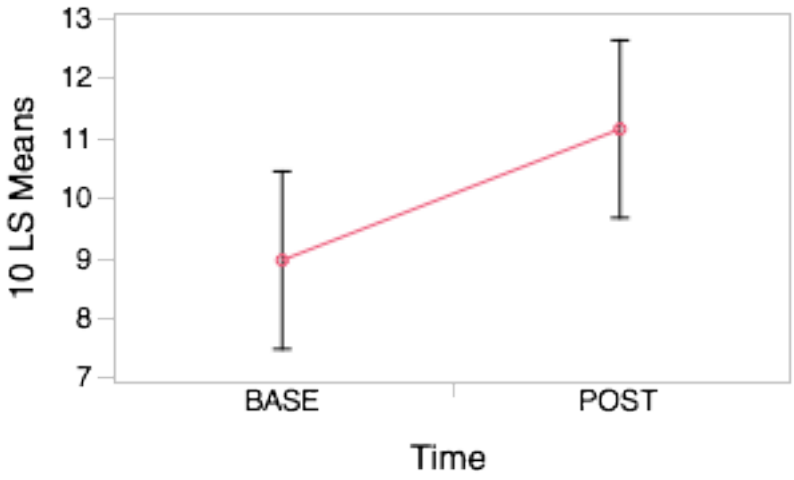


Figure 2. IL-10 at base line and after Tabata training. P = 0.0426

Appendix C: IRB Documentation

VCU RESEARCH PLAN TEMPLATE

Use of this template is required to provide your VCU Research Plan to the IRB. Your responses should be written in terms for the non-scientist to understand. If a detailed research protocol (e.g., sponsor's protocol) exists, you may reference specific sections of that protocol. NOTE: **If that protocol does not address all of the issues outlined in each Section Heading, you must address the remaining issues in this Plan. It is NOT acceptable to reference a research funding proposal**.

ALL Sections of the Human Subjects Instructions must be completed with the exception of the Section entitled "Special Consent Provisions." Complete that Section if applicable. When other Sections are not applicable, list the Section Heading and indicate "N/A."

NOTE: The Research Plan is required with ALL Expedited and Full review submissions and MUST follow the template, and include version number or date, and page numbers.

DO NOT DELETE SECTION HEADINGS OR THE INSTRUCTIONS.

I. TITLE

Comparison of two different work to rest ratios on the acute metabolic and inflammatory effects of a single bout of sprint interval training

II. RESEARCH PERSONNEL

A. PRINCIPAL INVESTIGATOR

List the name of the VCU Principal Investigator

Edmund Acevedo

B. STUDY PERSONNEL

NOTE:

1. **Information pertaining to each project personnel, including their role, responsibilities, and qualifications, is to be submitted utilizing a *VCU IRB Study Personnel Information and Changes Form.* This form is available at http://www.research.vcu.edu/forms/vcuirb.htm.**
2. **A roster containing a list of project personnel is to be maintained as a separate study document which is retained with the Research Plan, and is to be updated as applicable. The roster is to include all VCU project personnel (including the principal investigator) who are *engaged* in this research protocol, as well as non-VCU personnel who are also *engaged* but do not have local IRB approval for this protocol from their own institution,. This template document, entitled *VCU IRB Study Personnel Roster*, is available at http://www.research.vcu.edu/forms/vcuirb.htm.**

C. Describe the process that you will use to ensure that all persons assisting with the research are adequately informed about the protocol and their research-related duties and functions.

All study personnel have completed VCU CITI research training. Personnel will take part in all research planning meetings and be trained and practice all study related duties prior to data collection. Personnel will all be familiarized with lab safety procedures and basic CPR.

III. CONFLICT OF INTEREST

Describe how the principal investigator and sub/co-investigators might benefit from the subject's participation in this

project or completion of the project in general. Do not describe (1) academic recognition such as publications or (2) grant or contract based support of VCU salary commensurate with the professional effort required for the conduct of the project

Chris Harnish will be completing this research as part of his doctoral training, while Dr. Acevedo, the PI and advisor; will complete his role as Mr. Harnish's advisor. The basic questions answered by this research will further the understanding of the role that specific exercise modes, shaping more expansive research in the future.

IV. RESOURCES

Briefly describe the resources committed to this project including: (1) time available to conduct and complete the research, (2) facilities where you will conduct the research, (3) availability of medical or psychological resources that participants might require as a consequence of the research (if applicable), and (4) financial support.

The majority of data collection will take place in the morning hours. Chris Harnish will manage all data collection, and has weekday mornings allotted specifically for research. The duration of the study is partially dependent upon subject recruitment success. However, we believe all subjects can be identified, enrolled and completed between 2 and 6 months after beginning the study. Mr. Harnish has submitted grant proposals to the National Strength and Conditioning Association and Foundation for Aging and Exercise Science for support of this project. Nonetheless, the Dept. of Health and Human performance has pledge to support this project to its completion. The Virginia Commonwealth University's (VCU) Exercise Physiology lab is well equipped with the tools needed to complete this research, including a Parvo OneMax VO_2 system, YSI blood lactate analyzer and polar heart rate monitors, as well as all body composition analysis equipment. Oral glucose tolerance tests (OGTT) will be conducted at the VCU Center for Clinical and Translational Research (CCTR). OGTT's will be administered by the principal investigator with the aid of a trained research nurse. Blood samples will be prepared and transferred to the Clinical Research Service (CRS) lab for analysis.

The principle investigator of this study has extensive experience conducting research studies, and is familiar with all of the techniques and equipment used in this study. Statistical design and analysis consultation will be provided by Dr. Roy Sabo from the VCU Dept. of Biostatistics. Dr. Sabo has extensive experience in biomedical statistical analysis and was intimately involved in our prior arm crank sprint study in spinal cord injured persons.

V. HYPOTHESIS

Briefly state the problem, background, importance of the research, and goals of the proposed project.

Exercise intensity is a critical stimulus for endurance training adaptations and metabolic regulation. Several contemporary lines of research have shown that a variety of low volume, sprint interval training (SIT) programs are effective at eliciting significant metabolic changes, including increased mitochondrial function and insulin sensitivity (Si). However, little is known on how work to rest ratio (W:R) interacts with these protocols; it is well-known that short rest periods during high-intensity training elicits a larger neuro-endocrine response than similar volumes of moderate intensity training. In addition, recent research has suggested that muscle-derived inflammatory cytokines, termed myokines, are intimately involved in fuel regulation during and after exercise. It is believed that activation of large muscle groups leads to rapid increases of circulating IL-6, which positively influences IL-10 following exercise; both of these cytokines are seen as key players in the management of blood sugar. Research has been inconclusive on the acute impact of high-intensity interval or sprint interval training on this myokine/cytokine release. Likewise, little is known on the impact of manipulating W:R on their release, as well. Therefore the purposes of this research are to compare the acute (i.e., 1, 24 hr post) inflammatory and metabolic responses to SIT of different W:R. *Twelve to sixteen males and twelve to sixteen females* ages 18-35 will be recruited to completed a cross-over comparison of two SIT interventions; either the more recently tested Wingate protocol (five 30 sec sprints with ~4 min recovery), or a Tabata protocol (ten 20 sec sprints with 10 sec recovery). Subjects will complete oral glucose tolerance tests to assess Si and blood tests to determine IL-6, TNF-a, and IL-10 levels at baseline, prior to each training session and ~24 hr after exercise. Following SIT, we hypothesize that Si will improve 24 hr after Tabata but not Wingate training, and will be proportional to increases in both IL-6 and IL-10.

VI. SPECIFIC AIMS

It is widely accepted that acute and chronic endurance and high-intensity interval training enhance Si. In comparison, it appears that chronic, but not a single bout of SIT will improve Si. It is unclear whether a single bout of SIT using a low W:R, like that proposed by Tabata et al. (1996), could improve Si; many of the mechanisms for such a response remain undefined. Exercise is generally anti-inflammatory (Brandt and Pedersen 2010) in the sense that on balance, anti-inflammatory myokines like IL-6 and IL-10 exceed inflammatory cytokines like TNF-a (Ropelle et al. 2010), and that the release of IL-6 is proportional to the intensity and muscle mass utilized during training. Further, IL-10 has been proposed as a major influence on Si at rest (Staczkowski et al. 2005), and Steensberg et al. (2003) have shown that IL-6 infusion enhances IL-10 release. However, the relationship between Si, IL-6 and IL-10 following SIT are unclear, but should follow trends similar to those published by Meckel et al. (2009; 2011) following sprint running. We hypothesize that SIT utilizing brief rest periods, but similar total work will elicit a greater myokine response, and that this larger myokine release will positively influence the acute improvement in Si. Based on the current literature and our own pilot work, we hypothesize that:

1. SIT with a higher W:R (i.e., Tabata) will improve Si, whereas SIT using a lower W:R (i.e., Wingate) will not.
2. Either SIT protocols will increase IL-6 release, however, Tabata training will elicit a greater response immediately post-exercise, and at 1 hr post.
3. IL-10 increases following training will be proportional to IL-6 increases, but Tabata training will elicit a larger IL-10 release, which may further positively influence Si.

VII. BACKGROUND AND SIGNIFICANCE

Include information regarding pre-clinical and early human studies. Attach appropriate citations.

Exercise can be effective in reducing body fat (Sigal et al. 2004; Volek et al. 2005; Thorogood et al. 2011), however, it is far more effective at improving many of the components of metabolic syndrome, including insulin sensitivity (Sigal et al. 2004; Earnest 2008; Colberg and Grieco 2009). Insulin sensitivity (Si) and glucose effectiveness, or the ability to uptake glucose into the cell, are driven by a number of factors that include translocation of glucose transporter 4 (GLUT4) inside the cell, and capacity and density of the mitochondria (Bournat and Brown 2010). The link between improved mitochondrial function and GLUT4 expression led Earnest (2008) to hypothesize that high-intensity interval training provides a more powerful stimulus to improve Si than moderate aerobic exercise, directly impacting aerobic metabolic processes. Several researchers (Gibala 2011; Babraj et al. 2009; Burgomaster et al. 2008) have demonstrated that brief bouts of sprint interval training (SIT) can elicit improvements in oxidative capacity, metabolic function and Si that are analogous to moderate intensity endurance training.

Babraj et al. (2009) showed that six sessions of SIT improved insulin sensitivity by 37%, while other groups have reported similar findings among obese men (Whyte et al. 2010) and obese women (Trilk et al 2011). In contrast, a single

relationships is lacking. Exercise professionals and coaches understand that W:R can drastically impact metabolic stress, cardiovascular demand, and even potentiate the endocrine response during training (Gray et al. 1993), but little is known about how W:R would impact cytokine release during SIT.

In light of the current interest in sprint interval training, but the dearth of data on the acute (i.e., 1 – 24 hr post) response to sprint interval training of different W:R, it would be prudent to compare two sprint protocols of similar total work (kJ) but distinctly different W:R. Further, it is important to elucidate the inflammatory response pathways that are activated following these activities. In particular, it is believed that both IL-6 and IL-10 play important roles in carbohydrate regulation, but it is unclear how either relates to Si following sprint interval training. Therefore, the purpose of this study would be to compare the *Wingate* SIT protocol with a modified *Tabata* protocol (Tabata et al. 1996), where subjects complete 20 sec maximal sprints with 10 sec recovery for a total of 5 min. Recent pilot work (n=5 males, 5 min *Tabata*) indicated that both IL-6 and IL-10 will increase within 1 hr of exercise.

VIII. Preliminary Progress/Data Report

If available.

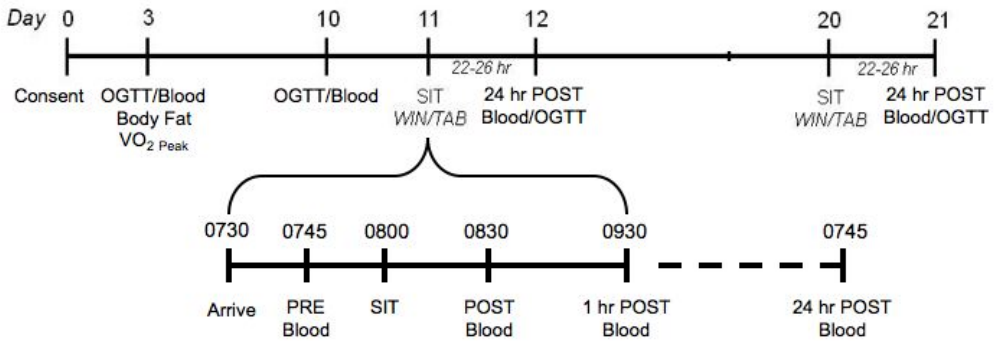
N/A

IX. Research Method and Design

Include a brief description of the project design including the setting in which the research will be conducted and procedures. If applicable, include a description of procedures being performed already for diagnostic or treatment purposes.

The experimental protocol (Figure 1) will be similar to previous SIT studies, and will consist of a one-week intra-subject control period, with baseline (B) and pre-training (PRE) oral glucose tolerance tests (OGTT) and plasma myokine analyses. Subjects will then perform two different acute SIT protocols – *Tabata* and *Wingate*, utilizing a cross-over trial design, with each training bout separated by no less than one week. Half the subjects will perform the *Tabata* first, while the other half will perform the *Wingate* first. All exercise will take place using a mechanically braked Monark Peak Bike (Monark Exercise AB, Sweden). Blood samples (~10 ml) will be taken immediately following, and 1 hr after each training session, as well as prior to the 24 hr post-exercise OGTT (Febbraio and Pedersen 2002). Each exercise session will last 30 minutes or less.

Figure 1. Graphic summary of the experimental design for the study. Note: OGTT=oral glucose tolerance test, SIT = sprint interval training, TAB = Tabata – 10X 20 sec sprints/10 sec rest, WIN = Wingate – 5X 30 sec sprints/240 sec rest.



X. Plan for Control of Investigational Drugs, Biologics, and Devices.

<u>Investigational drugs and biologics</u>: IF Investigational Drug Pharmacy Service (IDS) is not being used, attach the IDS confirmation of receipt of the management plan.

Investigational and humanitarian use devices (HUDs): Describe your plans for the control of investigational devices and HUDs including:
(1) how you will maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s);
(2) plan for storing the investigational product(s)/ HUD as specified by the sponsor (if any) and in accordance with applicable regulatory requirements;
(3) plan for ensuring that the investigational product(s)/HUDs are used only in accordance with the approved protocol; and
(4) how you will ensure that each subject understands the correct use of the investigational product(s)/HUDs (if applicable) and check that each subject is following the instructions properly (on an ongoing basis).

N/A

XI. DATA ANALYSIS PLAN

For investigator–initiated studies.

All data will be presented as means ± SE. The Cederholm index, which represents peripheral insulin sensitivity, will be calculated using the formula:

$$ISI_{Cederholm} = 75000 + (G_0 - G_{120}) \times 1.15 \times 180 \times 0.19 \times BW/120 \times G_{mean} \times log\ (I_{mean})$$

BW = body weight, G_0 and G_{120} are plasma glucose concentration at 0 and 120 min ($mmol \cdot l^{-1}$), and I_{mean} and G_{mean} are the mean insulin ($mU \cdot l^{-1}$) and glucose ($mmol \cdot l^{-1}$) concentrations during the OGTT.

All training responses will be analyzed using repeated measures ANOVA with post hoc Tukey tests as follows:
1. A 2 X 4 model used to assess the effect of SIT on IL-6, IL-10, TNF- α, and cortisol.
2. A 2 X 2 model used to assess PRE to POST exercise response to the OGTT, including Si.
3. Dependant t-tests comparing IL-6, IL-10, TNF- α, and cortisol for both SIT sessions.
4. Dependant t-tests comparing change in Si following SIT sessions at baseline and 24 hr.
5. Pearson's correlation coefficients will be calculated to examine the relationships between Si and changes in myokine response.

XII. DATA AND SAFETY MONITORING

- **If the research involves greater than minimal risk and there is no provision made for data and safety monitoring by any sponsor, include a data and safety-monitoring plan that is suitable for the level of risk to be faced by subjects and the nature of the research involved.**
- **If the research involves greater than minimal risk, and there is a provision made for data and safety monitoring by any sponsor, describe the sponsor's plan.**
- **If you are serving as a Sponsor-Investigator, identify the Contract Research Organization (CRO) that you will be using and describe the provisions made for data and safety monitoring by the CRO. Guidance on additional requirements for Sponsor-Investigators is available at http://www.research.vcu.edu/irb/wpp/flash/X-2.htm**

Exclusion criteria will be any person classified as *Moderate* or *High* risk for cardiovascular disease according to current ACSM Guidelines for Exercise Testing and Prescription (ACSM, 8th ed, 2009), as well as those with a body fat above 25% for men, and 32% for women, orthopedic limitations preventing full participation in the study, pre-diabetes or diabetes mellitus (fasting glucose > 126), self-reported hypothyroidism, renal disease. In addition, women who are pregnant or those suffering from premature menopause will also be excluded. Self-reported health history will also be reviewed, and each potential subject will be asked to indicate whether he has used any prescription stimulant drugs in the past in the past 6 months. Furthermore, individuals will be asked to review the list of illegal drugs on the Health History Questionnaire (Appendix C) and answer YES to having used any of the drugs listed or NO to never having used any of the drugs listed. We will not ask them to indicate any specific drug use, nor will we record such use. A simple YES or NO will determine eligibility for participation in this study.

All personnel are certified in CPR/BLS, and subjects will have heart rate, blood pressure measurements taken before and

after exercise sessions, as well as rating of perceived exertion during exercise. Should an exercise session result in or indicate an adverse outcome, the session will be terminated. Further, all sprints sessions will be conducted at the CRS. Should any adverse event occur the safety protocols for the CRS will be followed. AED and ALS are available in the CRS. We will defer specific protocols to those endorsed by the CRS to Lou Usry, RN, CCRP, CNML Senior manager (804-828-9229). Should an adverse event occur, the test session will be terminated and the subject care will be managed by CRS staff. All data collection will be tracked via our study event tracking form (Appendix E), including adverse events. All adverse events will be reported to the IRB within 14 days of the occurrence. Finally, only listed study personnel will have access to data. Both Dr. Acevedo and Mr. Harnish will have direct access to all forms of subject data, and only Mr. Harnish will be involved in the consent process. In the event of medical questions for concerns, Dr. Richard Kunz (VCU PM&R), a licensed physician, will assume the medical consulting role left vacated by Dr. Ericksen. Dr. Kunz has been familiarized with the study protocol and can be reached at North 2, 804.828.0861.

Special Note: The Health History Questionnaires for those individuals who are excluded from the study following a review of the inclusion and exclusion criteria will be immediately destroyed (shredded), while consent forms will be stored in a separate secure "screen failure" for future reference.

XIII. MULTI-CENTER STUDIES

If VCU is the lead site in a multi-center project or the VCU PI is the lead investigator in a multi-center project, describe the plan for management of information that may be relevant to the protection of subjects, such as reporting of unexpected problems, project modifications, and interim results.

N/A

XIV. INVOLVEMENT OF NON-VCU INSTITUTIONS/SITES (DOMESTIC AND FOREIGN)

1. **Provide the following information for each non-VCU institution/site (domestic and foreign) that has agreed to participate (all non-VCU institutions/sites are to be listed, including those who obtain local IRB approval from their own institution and those who request deferral to the VCU IRB):**
   - **Name of institution/site**
   - **Contact information for institution/site**
   - **Engaged in Research or not (if YES AND the research involves a DIRECT FEDERAL AWARD made to VCU, include FWA #). See OHRP's guidance on "Engagement of Institutions in Research" at http://www.hhs.gov/ohrp/policy/engage08.html.**
   - **Request for the VCU IRB to review on behalf of the Non-VCU institution?** Submit either the template Authorization Agreement or Individual Investigator Agreement with this application. See additional requirements found at http://www.research.vcu.edu/irb/wpp/flash/XVII-6.htm.
   - See VCU WPPs:
     http://www.research.vcu.edu/irb/wpp/flash/XVII-6.htm and
     http://www.research.vcu.edu/irb/wpp/flash/XVII-11.htm.

Name of Institution	Contact Information for Site	Engaged (Y/N) and FWA # if applicable	Request for VCU IRB to review on behalf of the non-VCU institution (Y/N)*

*NOTE: If a Non-VCU site is engaged in the research, the site is obligated to obtain IRB review or request that the VCU IRB review on its behalf.

2. **Provide a description of each institution's role (whether engaged or not) in the research, adequacy of the facility**

(in order to ensure participant safety in the case of an unanticipated emergency), responsibilities of its agents/employees, and oversight that you will be providing in order to ensure adequate and ongoing protection of the human subjects. You should only identify institutions that have agreed to participate. If additional institutions agree to participate at a later time, they must be added by amendment to the protocol.

N/A

XV. HUMAN SUBJECTS INSTRUCTIONS

ALL sections of the Human Subjects Instructions must be completed with the exception of the section entitled "Special Consent Provisions." Complete that section if applicable.

A. DESCRIPTION

Provide a detailed description of the proposed involvement of human subjects or their private identifiable data.

Prior to enrollment, subjects will complete a risk factor assessment and basic health history based on ACSM guidelines and will ask about illegal drug use; the screening will allow us to identify any *High* risk individuals, or those otherwise unfit to take part in the study. The history and screening (Appendices C and D, respectively) will be conducted by Mr. Harnish in the form of a question and answer session; Mr. Harnish is a certified ACSM Health Fitness Specialist, while Dr. Acevedo is a certified Clinical Exercise Specialist. No other health details will be taken or stored. *Inclusion* criteria will include men between the ages of 18-35 years old who do not engage in regular physical activity more than two days per week, but have a body fat of $\leq$ 25%. Exclusion criteria will be any person classified as Moderate or High risk for cardiovascular disease according to current ACSM clinical guidelines, as well as those with a body fat above 25% for men, and 32% for women, orthopedic limitations preventing full participation in the study, pre-diabetes or diabetes mellitus (fasting glucose > 126), self-reported hypothyroidism, renal disease. In addition, women who are pregnant or those suffering from premature menopause will also be excluded. Chris Harnish will be responsible for determining eligibility of each subject. Once consent forms are signed, they will be kept under lock and key, with risk assessments, in Mr. Harnish's office in 500 AC. Each consent form will be given a unique number. All further data collection will only use that number.

Each participant will be out-patient perform a series of blood samples (totaling approximately 160 ml, or 3/4 cup of blood) and exercise sessions over 3 weeks. FOUR 2 hr oral glucose tolerance tests (OGTT) will be performed (five 5 ml samples per test), plus blood sampling (~10 ml each) will be taken prior to, immediately following and 1 hr after exercise sessions; cortisol will be measure during each PRE test sample (four for OGTT and two for sprints). Sprint sessions will include two different acute sprint protocols – a *Tabata* – 10X 20 sec sprints/10 sec rest, or *Wingate* – 5X 30 sec sprints/240 sec rest, with each training bout separated by no less than one week. Each exercise visit will last approximately 30 minutes. Additional testing will include a maximal graded exercise test (see below), a body fat test, and each will be asked to complete a 3 day diet recall. Body fat testing will use bioelectrical impedance (BIA), which is simple, fast and poses no risk to the participant.

Following the first OGTT, subjects will perform a bicycle $VO_{2\ peak}$ test conducted on an electronically braked bicycle ergometer (VIA Sprint 150P, Viasys Healthcare, Yorba Linda, CA). VO_2 and HR will be measured continuously using a Parvo OneMax system (Parvo Medics, Salt Lake City, UT) and Polar HR monitor (Polar Electro Inc., New Success, NY), respectively. Subjects will be instructed to pedal at their preferred cadence throughout testing. The initial workload will be set at 100 W, increasing by 20 W every 2 min until volitional exhaustion is reached. Blood pressure will be measured with a clinical mercury manometer in the final 30 sec of each stage. For all testing and exercise sessions, activity will be terminated if HR should exceed 220 beats/min or BP exceeds 250 systolic and/or 115 mmHg diastolic blood pressure. Other indications for test termination include a drop in systolic BP of > 10 mmHg, angina, dizziness, nausea or volitional exhaustion (ACSM Guidelines for Exercise Testing and Prescription, 2008).

Table 1. Comparison of Tabata vs. Wingate protocols.

	Workload (% BM)	# of Sprints	Sprint Time (Sec)	Recovery Time (Sec)	Total Sprint Time (Sec)
Tabata	5	10	20	10	200
Wingate	7	5	30	240	150

B. SUBJECT POPULATION

Describe the subject population in terms of sex, race, ethnicity, age, etc., and your access to the population that will allow recruitment of the necessary number of participants. Identify the criteria for inclusion or exclusion of all targeted populations and include a justification for any exclusions. Explain the rationale for the involvement of special cases of subjects, such as children, pregnant women, human fetuses, neonates, prisoners or others who are likely to be vulnerable. If you plan to allow for the enrollment of Wards of the State (or any other agency, institution, or entity), you must specifically request their inclusion and follow guidance in VCU IRB WPP XV-3: Wards and Emancipated Minors available at http://www.research.vcu.edu/irb/wpp/flash/XV-3.htm.

One important note, however, is that extensive review of the literature revealed that power analyses from all but the two listed studies yielded unverifiable estimates on pre and post differences, making calculations unreliable at best. Therefore, drawing about our recent pilot study, we were able to measure cytokine response to a single Tabata session. These data indicate an increase of at least 6 pg.mL-1 for IL-6 and IL-10, which indicates that a sample size of at least 24 total subjects, or 12 per SIT group, would yield a power of at least 80%.

Participants

Up to 16 men and 16 women will be actively recruited from the VCU Monroe and MCV campuses using word of mouth, flyers and emails (see appendix A). As outlined above, this sample size will yield a power of 90% or greater for all dependent measures. All subjects will be evaluated for safe exercise participation using an ACSM risk factor assessment (see appendix B-ACSM Guidelines for Exercise Testing and Prescription) and informed of the purposes of the study before signing an informed consent document approved by the Virginia Commonwealth University IRB. Inclusion criteria will include men between the ages of 18-35 years old who do not engage in regular physical activity more than two days per week, but have a body fat of $\leq$ 25%. Exclusion criteria will be any person classified as Moderate or High risk for cardiovascular disease according to current ACSM clinical guidelines, as well as those with a body fat above 25 for men, and 32% for women, orthopedic limitations preventing full participation in the study, pre-diabetes or diabetes mellitus (fasting glucose > 126), self-reported hypothyroidism, renal disease. In addition, women suffering from premature menopause will also be excluded.

We had chosen to study just males due to the reported differences between men and women in both cytokine levels (Ives et al. 2011; O'Brien et al. 2007; Fernandez-Real et al. 2001) and metabolic parameters like insulin sensitivity (Ives et al. 2011; Fernandez-Real et al. 2001; Clausen et al. 1996). However, since beginning recruitment we have had several inquiries from women. We have also garnered additional resources to collect data on women, which will allow us to greatly increase our sample size and directly compare gender differences.

C. RESEARCH MATERIAL

Identify the sources of research material obtained from individually identifiable living human subjects in the form of specimens, records, or data. Indicate whether the material or data will be obtained specifically for research purposes or whether use will be made of existing specimens, records, or data.

We will be collecting height, weight, age, risk factor assessment (as outlined above), exercise capacity and blood specific to our research question.

D. RECRUITMENT PLAN

Describe in detail your plans for the recruitment of subjects including:
(1) how potential subjects will be identified (e.g., school personnel, health care professionals, etc),
(2) how you will get the names and contact information for potential subjects, and
(3) who will make initial contact with these individuals (if relevant) and how that contact will be done.
If you plan to involve special cases of subjects, such as children, pregnant women, human fetuses, neonates, prisoners or others who are likely to be vulnerable, describe any special recruitment procedures for these populations.

We have developed a number of strategies relevant to all populations that mitigate these potential recruitment problems. Potential subjects will be actively recruited via flyers (see Appendix A) on VCU campuses and around Richmond, *scripted*

class announcements (Appendix A), and word of mouth. We have also applied for two grant awards, which if awarded, will provide funds to compensate subjects. All subjects will also be provided with any health and fitness information collected, and advised on exercise changes they may make following the study.

E. PRIVACY OF PARTICIPANTS

NOTE: Privacy refers to individuals and their interests in controlling access to their identities, their physical person, and how and what kind of information is obtained about them. Privacy also encompasses the interests of defined communities (e.g. those with a certain diagnosis or social circumstance) in controlling access to the group identity and information about the group or individuals as part of the group.

Describe how the privacy interests of subjects (and communities, if appropriate) will be protected including:
(1) in the research setting (e.g., in the identification, recruitment, and intervention settings) and
(2) with the information being sought and the way it is sought. For example, providing drapes or barriers, interviewing in a private room, and collecting only the amount of sensitive information needed for identification, recruitment, or the conduct of the study.

Individual participants need only complete a health history assessment and provide their name and date of birth at consent. These identifiers will not be needed after the consent process and will remain locked at all times during and after the study. Subjects will have a private space to complete all consent forms. Subjects will participate in testing and exercise in a private lab with minimal access and suitable, private changing areas. Data collection will include age, body fat, exercise capacities, and blood exercise response.

Participants will be given a unique numerical identifier written at the top of each consent. Once consent forms are collected and processed, they will then be locked in a cabinet within Mr. Harnish's office. All subsequent data collection will only use the unique identifier.

F. CONFIDENTIALITY OF DATA

NOTE: Confidentiality refers to the way private, identifiable information about a subject or defined community is maintained and shared.

Check all of the following precautions that will be used to maintain the confidentiality of identifiable information:

☒ Paper-based records will be kept in secure location and only accessed by authorized study personnel
☒ Electronic records will be made available only to those personnel in the study through the use of access controls and encryption
☒ Identifiers will be removed from study-related data (data is coded with a key stored in a separate secure location)
☐ For research involving web-based surveys, data is secured via passwords and encryption
☐ Audio or video recordings of subjects will be transcribed and then destroyed to prevent audio or visual identification. Note the date of destruction (e.g., 3 months from close of study; after transcription is determined to be error free).
☐ Obtaining a Certificate of Confidentiality
☒ Other precautions: **Subjects will have private space to complete all consent forms.**

G. POTENTIAL RISKS

Describe potential risks (physical, psychological, social, legal, or other) and assess their likelihood and seriousness. Where appropriate, describe alternative treatments and procedures that might be advantageous to the subjects.

What may present a risk?	Possible Risk/Side Effect	How often has it occurred?

Venous catheter insertion and Blood draws Samples from the earlobe	1. Localized swelling, soreness, bruising, and chance of infection, bleeding, pain, lightheadedness or possible fainting. 2.Soreness, bruising, infection, and scarring. A total of one large drop of blood will be taken each time	1. It occasionally occurs 2. It occasionally occurs
Exercise Testing/Sessions	1. Light-headedness, shortness of breath and altered heart rate & blood pressure. Muscle soreness at your neck, upper back, shoulders, arms & hands 2. Fainting, heart attacks or death 3. Muscle soreness	1. It is fairly common 2. It is very rare 3. It is fairly common
Oral Glucose Tolerance Test	1. Nausea from drinking a lot of glucose (sugar)	1. Occasionally occurs

H. Risk Reduction

Describe procedures for protecting against or minimizing potential risk. Where appropriate, discuss provisions for ensuring necessary medical or professional intervention in the event of adverse events to the subjects. Describe the provisions for monitoring the data collected to ensure the safety of subjects, if any.

To minimize the risk of adverse events, only apparently healthy LOW RISK individuals fit for exercise will participate in this study; no matter how thorough the screening process, it is impossible to define anyone as "healthy", therefore the ACSM uses the term apparently, or outwardly healthy, with no specific signs of disease. It is not necessary to have a physician present during exercise testing with Low Risk individuals. A self-report Health History Questionnaire will be reviewed, and each potential subject will be asked to indicate whether they have used any prescription stimulant drugs in the past in the past 6 months. Furthermore, individuals will be asked to review the list of illegal drugs on the Health History Questionnaire (Appendix C) and simply answer YES to having used any of the drugs listed or NO to never having used any of the drugs listed. All subjects will be advised of the risk for arrhythmias and death after using strong stimulants like amphetamines and cocaine.

Heart rate and effort level will be monitored throughout all exercise sessions. Individuals exhibiting abnormally high heart rates or blood pressures, or symptoms of nausea or syncope, will be stopped from further exercise and asked to lie down for further monitoring. In the event of emergencies, emergency help will be contacted based on CRS standard operating procedures. All research staff are trained in CPR/BLS or ALS and safety procedures will be reviewed prior to beginning the study. An AED will be available should the need arise and emergency numbers will be available to all personnel.

I. Additional Safeguards for Vulnerable Participants

Describe any additional safeguards to protect the rights and welfare of participants if you plan to involve special cases of subjects such as children, pregnant women, human fetuses, neonates, prisoners or others who are likely to be vulnerable.

Safeguards to protect the rights and welfare of participants might relate to Inclusion/Exclusion Criteria: ("Adults with moderate to severe cognitive impairment will be excluded." "Children must have diabetes. No normal controls who are children will be used.") Consent: ("Participants must have an adult care giver who agrees to the participant taking part in the research and will make sure the participant complies with research procedures." "Adults must be able to assent. Any dissent by the participant will end the research procedures.") Benefit: ("Individuals who have not shown benefit to this type of drug in the past will be excluded.").

N/A

J. RISK/BENEFIT

Discuss why the risks to participants are reasonable in relation to the anticipated benefits to subjects and in relation to the importance of the knowledge that may reasonably be expected to result. If a test article (investigational new drug, device, or biologic) is involved, name the test article and supply the FDA approval letter.

None of the study procedures performed in this study exceed what would occur in routine medical testing. Blood sampling will involve small samples, and subjects will be performing exercise sessions at an intensity level that are not uncommon for individuals in this range during general recreation on the weekends (e.g., football, basketball pick up games, or general "play"). While individual benefits will be unlikely, this research will provide greater insight into the underlying mechanisms for why sprint exercise improves metabolic function, as has been shown in many different populations. Further, understanding the cytokine/myokine response to brief exercise may allow us to develop more optimal training programs to treat metabolic diseases, like diabetes, with exercise.

K. COMPENSATION PLAN

Compensation for participants (if applicable) should be described, including possible total compensation, pro-rating, any proposed bonus, and any proposed reductions or penalties for not completing the project.

No compensation will be provided for completing this study. However, participants will receive a summary of their health screening, fitness test results and consultation on starting an exercise program.

L. CONSENT ISSUES

1. CONSENT PROCESS

Indicate who will be asked to provide consent/assent, who will obtain consent/assent, what language (e.g., English, Spanish) will be used by those obtaining consent/assent, where and when will consent/assent be obtained, what steps will be taken to minimize the possibility of coercion or undue influence, and how much time will subjects be afforded to make a decision to participate.

All health screening and consents will be conducted in English by Chris Harnish at the HHP lab in Franklin Street Gym room 332. All subjects informed of the purposes of the study verbally before signing an informed consent document approved by the Virginia Commonwealth University IRB. Once consent has been obtained, we will complete a full health history (as outlined above) and risk factor assessments will use a checklist (Appendix C). Interested participants may take the consent home to read and will be afforded as much as is feasible to conduct the study.

2. SPECIAL CONSENT PROVISIONS

If some or all subjects will be cognitively impaired, or have language/hearing difficulties, describe how capacity for consent will be determined. Consider using the VCU Informed Consent Evaluation Instrument available at http://www.research.vcu.edu/irb/guidance.htm. If you anticipate the need to obtain informed consent from legally authorized representatives (LARs), please describe how you will identify an appropriate representative and ensure that their consent is obtained. Guidance on LAR is available at http://www.research.vcu.edu/irb/wpp/flash/XI-3.htm.

N/A

3. ASSENT PROCESS

If applicable, explain the Assent Process for children or decisionally impaired subjects. Describe the procedures, if any, for re-consenting children upon attainment of adulthood. Describe procedures, if any, for consenting subjects who are no longer decisionally impaired. Guidance is available at http://www.research.vcu.edu/irb/wpp/flash/XV-2.htm and http://www.research.vcu.edu/irb/wpp/flash/XVII-7.htm.

N/A

4. REQUESTS FOR WAIVERS OF CONSENT (COMPLETE IF REQUESTING ANY TYPE OF WAIVER OF CONSENT OR ASSENT)

4-A. REQUEST TO WAIVE SOME OR ALL ELEMENTS OF INFORMED CONSENT FROM SUBJECTS OR PERMISSION FROM PARENTS: A waiver of informed consent means that the IRB is not requiring the investigator to obtain informed consent OR the IRB approves a consent form that does not include or alters some/all of the required elements of consent. **Guidance is available at http://www.research.vcu.edu/irb/wpp/flash/XI-1.htm. NOTE: Waiver is not allowed for FDA-regulated research unless it meets FDA requirements for Waiver of Consent for Emergency Research (see below).**

4-A.1. Explain why a waiver or alteration of informed consent is being requested.
☐

4-A.2. Describe how this study meets ALL FOUR of the following conditions for a waiver or alteration:

- The research involves no more than minimal risk to the participants. → Explain how your study meets this criteria: ☐
- The waiver or alteration will not adversely affect the rights and welfare of participants. → Explain how your study meets this criteria: ☐
- The research could not practicably be carried out without the waiver or alteration. → Explain how your study meets this criteria: ☐
- Will participants be provided with additional pertinent information after participation?
  ☐ Yes
  ☐ No → Explain why not: ☐

4-B. REQUEST TO WAIVE DOCUMENTATION OF CONSENT: A waiver of documentation occurs when the consent process occurs but participants are not required to sign the consent form. Guidance is available at http://www.research.vcu.edu/irb/wpp/flash/XI-2.htm **. One of the following two conditions must be met to allow for consenting without signed documentation. Choose which condition is applicable and explain why (explanation required)**:

☐ The only record linking the participant and the research would be the informed consent form. The principal risk to the participant is the potential harm resulting from a breach of confidentiality. Each participant will be asked whether he/she wants documentation linking the participant with the research and the participants wishes will govern. → Explain how your study fits into the category: ☐

☐ The research presents no more than minimal risk of harm to participants & involves no procedures for which signed consent is normally required outside of the research context. → Explain how your study fits into the category: ☐

4-C. REQUEST TO WAIVE SOME OR ALL ELEMENTS OF ASSENT FROM CHILDREN ≥ AGE 7 OR FROM DECISIONALLY IMPAIRED INDIVIDUALS: A waiver of assent means that the IRB is not requiring the investigator to obtain assent OR

the IRB approves an assent form that does not include some/all of the required elements. Guidance is available at http://www.research.vcu.edu/irb/wpp/flash/XV-2.htm.

4-C.1. Explain why a waiver or alteration of informed consent is being requested.
☐

In order for the IRB to approve a request for waiver of assent, the conditions for 4-C.2, 4-C.3, OR 4-C.4 must be met. Check which ONE applies and explain all required justifications.

4-C.2. ☐ **Some or all of the individuals age 7 or higher will not be capable of providing assent based on their developmental status or impact of illness**. → Explain how your study meets this criteria: ☐

4-C.3. ☐ **The research holds out a prospect of direct benefit not available outside of the research**. → Explain how your study meets this criteria: ☐

4-C.4. ☐ **Describe how this study meets ALL FOUR of the following conditions**:

- The research involves no more than minimal risk to the participants. → Explain how your study meets this criteria: ☐
- The waiver or alteration will not adversely affect the rights and welfare of participants. → Explain how your study meets this criteria: ☐
- The research could not practicably be carried out without the waiver or alteration. → Explain how your study meets this criteria: ☐
- Will participants be provided with additional pertinent information after participation?
  - ☐ Yes
  - ☐ No → Explain why not: ☐

4-D. REQUEST TO WAIVE CONSENT FOR EMERGENCY RESEARCH: Describe how the study meets the criteria for emergency research and the process for obtaining LAR consent is appropriate. See guidance at http://www.research.vcu.edu/irb/wpp/flash/XVII-16.htm.

N/A

5. GENETIC TESTING
If applicable, address the following issues related to Genetic Testing.

5-A. FUTURE CONTACT CONCERNING FURTHER GENETIC TESTING RESEARCH
Describe the circumstances under which the subject might be contacted in the future concerning further participation in this or related genetic testing research.

N/A

5-B. FUTURE CONTACT CONCERNING GENETIC TESTING RESULTS
If planned or possible future genetic testing results are unlikely to have clinical implications, then a statement that the results will not be made available to subjects may be appropriate. If results might be of clinical significance, then describe the circumstances and procedures by which subjects would receive results. Describe how subjects might access genetic counseling for assistance in understanding the implications of genetic testing results, and whether this might involve costs to subjects. Investigators should be aware that federal regulations, in general, require that testing

results used in clinical management must have been obtained in a CLIA-certified laboratory.

N/A

5-C. WITHDRAWAL OF GENETIC TESTING CONSENT
Describe whether and how subjects might, in the future, request to have test results and/or samples withdrawn in order to prevent further analysis, reporting, and/or testing.

N/A

5-D. GENETIC TESTING INVOLVING CHILDREN OR DECISIONALLY IMPAIRED PARTICIPANTS
Describe procedures, if any, for consenting children upon the attainment of adulthood. Describe procedures, if any, for consenting participants who are no longer decisionally impaired.

N/A

5-E. CONFIDENTIALITY OF GENETIC INFORMATION
Describe the extent to which genetic testing results will remain confidential and special precautions, if any, to protect confidentiality.

N/A

Summary of Progress for IRB # 14990

The study titled, *Comparison of two different work to rest ratios on the acute metabolic and inflammatory effects of a single bout of sprint interval training*, has been progressing well since September of 2013. **To date we have enrolled 17 subjects, with a total of 15 completing testing as February 19th; our final subject completed testing on the 19th, with no further enrollees. The data collection for the study is complete.** The following is a summary of subject data:

Consent:	17
Completed:	**15 (13 males, 2 females)**
Currently enrolled:	**0 (all collection completed)**
Withdrawals:	2 (1 male, 1 female)*
Unanticipated events:	7 (Nausea)**
Adverse events:	0

* *Withdrawals:* One male subject developed bronchitis following the first baseline OGTT and withdrew. One female withdrew prior to any study appointments due to lack of time.

** *See below*.

At the end of August, Jeffrey Erickson, medically responsible consultant, left VCU for a new position. Dr. Elizabeth Ripley temporarily filled in as our medical consultant for a brief period before Dr. Richard Kunz assumed the role August 16th, 2013.

In October we received approval to begin enrolling women (see amendment below) into the study and have presently completed a total of 2. We also have 2 males currently enrolled in the study, and expect to complete their appointments by mid-January. All but one subject have been recruited from the VCU Monroe or MCV campus and have generally tolerated the research well. **We have completed all testing at this time. No further subjects have been enrolled since testing ended in February.**

Summary of Progress for IRB # 14990

Amendments:

Only one amendment was added to the study, the request to enroll women. Approval received 10/23/13.

Unanticipated Events:

While we have advised subjects on the potential for dizziness and nausea during sprint training, we did not anticipate the prevalence (7 of 15; 6 males, 1 female) of nausea during our Wingate sprint sessions. This is not uncommon, but generally not seen as often in either research or classroom settings. We surmise the greater prevalence is due to subjects exercising in a fasted state. However, no adverse outcomes have occurred, and all subjects have reported recovering quickly after or even during exercise. It has not had a significant impact on data collection.

Additional Funding:

In order to fund the additional analysis of cytokines for this study we established a crowd funding project page through *Experiment.com,* the leading research crowd funding platform. The page provides an abridged layperson summary of the study purposes and methodology, and adheres to the submitted IRB research plan (6.3.14). Individual donors are known to the public, and those with potential conflicts of interest, like research subjects, can be declined (no persons with COI's donated). Expenditures for study expenses are documented and must conform with the outline of the study on the website. Crowd funding goals must be met for any funds to be made available. Our project successfully met our goal and we will be rerunning some blood samples to complete all our analyses.

June 2nd, 2014

Version 2; 7/31/13

Would you like to test your fitness level?

Do you want to learn more about your Health?

If you answered yes to any of these questions, are between the ages of 18 and 35 years, and do not participate in strenuous exercise training, you may be invited to participate in a 3 week study examining the effect of sprint exercise and health improvement. During this time you will only participate in TWO sprint sessions lasting ~30 minutes and a few other non-exercise test sessions on the VCU campus, including blood draws. As part of your participation you will receive:

- A FREE cardiovascular fitness test
- A FREE dietary assessment
- A FREE Body Fat test
- Detailed information on your cardiovascular fitness and advice on exercise training

Research will involve a series of tests over a 3 week period of time at no cost to you. If you would like more information, please contact Chris Harnish, M.S. in the Dept of Health and Human Performance at VCU.

Sprint Study
harnishc@vcu.edu
804.828.1948

Sprint Study harnishc@vcu.edu 804.828.1948

EMAIL ANNOUNCEMENT

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Please contact Chris Harnish @ harnishc@vcu.edu

CLASS ANNOUNCEMENTS

We are conducting a three week trial comparing two different sprint interval sessions. We want to understand the effect of sprint exercise on health improvements. During the study you will only participate in TWO sprint sessions lasting ~30 minutes and a few other non-exercise test sessions on the VCU campus including blood draws. As part of your participation you will receive:

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- Detailed information on your cardiovascular fitness and advice on exercise training

Research will involve a series of tests over a 3 week period of time at no cost to you. If you would like more information, please contact Chris Harnish, M.S. in the Dept of Health and Human Performance at VCU.

Contact information can be obtained from myself or your instructor.

RESEARCH PARTICIPANT INFORMATION AND CONSENT FORM

TITLE: Comparison of two different work to rest ratios on the acute metabolic and inflammatory effects of a single bout of sprint interval training

VCU IRB PROTOCOL NUMBER: HM14990

INVESTIGATOR: Edmund Acevedo

If any information contained in this consent form is not clear, please ask the study doctor or the study staff to explain any information that you do not fully understand. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

PURPOSE OF THE STUDY

The purpose of this research study is to compare the health benefits of using two different types of sprint exercise with long and short rest periods. You are being asked to take part in this study because you have the age and body characteristics that are representative of common research subjects.

DESCRIPTION OF THE STUDY

Sprint exercise involves pedaling a bicycle as fast as possible for 30 sec or less using a resistance setting based on your body weight. You will be required to perform an exercise fitness test and a series of blood tests over a one week period of time followed by two individual sprint sessions, one with short rest and one with long rests, along with some blood tests after each sprint session. Each session will be separated by at least one week and your total time commitment for the study will be three weeks. Women who are pregnant or experiencing premature menopause will not be included in this study.

Significant new findings developed during the course of the research like improvement in how you process sugar and improvement in blood chemicals that block sugar processing may allow us to better use exercise to control diseases like diabetes. Approximately 16 men and 16 women will participate in this study.

PROCEDURES

If you decide to be in this research study, you will be asked to sign this consent form after you have had all your questions answered. Remaining procedures will take place on the MCV campus' Clinical Research Service in the North Hospital.

At your first study visit (Day 1) of about 1 hour, your medical history will be taken and your risk for heart related disease will be assessed to ensure it is safe for you to participate in this study. Other measurements will include your height and weight, pulse,

and blood pressure. You will also be given a 3 day dietary recall packet for you to record what you eat prior to the next visit.

On your second visit (~about 3 days later) you will perform an oral glucose tolerance test, or OGTT, after an overnight fast between 7 and 8 am; an overnight fast means that you may not eat any food or drink any beverage, other than water, after 8 pm the night prior to any exercise session and/or blood testing. It is also important that you do not take any stimulant products containing caffeine, guarine (guarana), taurine, or nicotine, as well as pain relievers, like aspirin, acetaminophen, naproxen sodium, or ibuprofen, during this fasting period. Any of these products could adversely affect your response to sprint exercise. An OGTT examines your sugar tolerance and how your body uses insulin. A nurse will insert a catheter for blood sampling ease, and a blood sample (about 1-2 tablespoons each) will be taken to measure the amount of glucose and insulin, as well as specific blood chemicals and hormones that affect glucose and insulin. You will then drink a half cup of a sugar drink. Additional blood samples will be taken just prior to drinking the sugar water and then 30, 60, 90 and 120 minutes after drinking. This test will be performed four times during the study. During this OGTT we will estimate the amount of body fat you have using bio-electrical impedance (BIA); the BIA sends a miniscule electrical current that estimates body fat from the amount of water you have in your body.

Following this OGTT, you will perform an exercise test on a bike. A plastic nose plug will be placed on your nose and you will breathe into a rubber mouthpiece so that your breathing can be measured. You will be asked to pedal at a set speed throughout the test session, while workload increases every 2 minutes. You will continue to exercise until you can no longer maintain the speed set, you wish to stop due to volitional exhaustion (you feel you cannot continue), you feel ill, like nausea, or if you experience chest pain. At the end of the test a tiny drop of blood will be collected from your earlobe with a small lancet (the same device a person with diabetes uses to prick the end of their finger to test blood sugar) to measure your lactic acid levels. You might experience some earlobe soreness after testing. Measuring lactic acid helps determine how hard you worked and how much sugar you burn. During the last part of the exercise test, you will be verbally encouraged to continue as long as possible. You will complete this test once during the study.

On your third visit (~day 10) you will complete another OGTT after an overnight fast at the same time of morning as your second visit. This will allow us to be sure there are no changes in your blood tests when you are not exercising; in other words, we should not see a change without sprint exercise. These two visits will last about 2 hours each.

Your fourth visit will take place the following morning (day 11) after an overnight fast at the same time as your first OGTT. We will take one initial blood sample prior to your exercise session measure blood chemicals and hormones, then you will complete an easy 10 min warm-up of light bicycling before completing one of the following sprint exercise sessions (the order you complete these will be determined using a simple coin toss prior to your starting the study):

Sprint session with short rest:

Sprint as fast as possible for 20 sec, then resting for 10 sec. You will repeat this TEN total times (5 min total time), or until you can no longer sprint due to fatigue.

Sprint session with long rest

Sprint as fast as possible for 30 sec, then rest for 4 minutes. You will repeat this for five total times, which will take less than 30 min total.

Following each sprint session we will immediately take a blood sample for chemicals/hormones and a blood lactic acid measurement from the ear. You will then sit quietly for 1 hour after your training session before a final blood sample is taken that day. You are asked to refrain from any strenuous activity throughout the entire study period. Each sprint session will last about 2 hours.

You will return to the lab the following morning, at the same prescribed time, for your fifth visit (day 12). You will complete another OGTT after an overnight fast at the same time of morning as your second visit. This will allow us to determine if the sprint exercise changed your sugar processing ability or blood chemical levels. This visit will take about 2 hours.

You will be given at least one full week of rest after this first sprint session.

Your sixth visit will then take place on day 20 after an overnight fast at the same time as your first OGTT. We will take one initial blood sample prior to your final exercise session to measure blood chemicals and hormones, you will then complete an easy 10 min warm-up of light bicycling before completing the other sprint exercise session. You will again sit quietly for 1 hour after your training session before a final blood sample is taken that day.

On your seventh and final visit (day 21), you will complete a final OGTT after an overnight fast at the same time of morning as your second visit. This will allow us to determine if the sprint exercise changed your sugar processing ability or blood chemical levels and compare it to the other sprint exercise values.

Summary of Testing

Time	Test Procedures that will be done	Time to Finish
Day 0	**Consent forms signed and Health screening**	**~1 hr**
Day 3 – 8 am	**OGTT 1, Body Fat Test, Bike fitness test**	**~2 ½ hrs**
Day 10 – 8 am	**OGTT 2**	**~2 hrs**
Day 11 – 8 am	**Sprint Session 1**	**~1 ½ hrs**
Day 12 – 8 am	**OGTT 3**	**~2 hrs**
Day 20 – 8 am	**Sprint Session 2**	**~1 ½ hrs**
Day 21 – 8 am	**OGTT 4**	**~2 hrs**

RISKS AND DISCOMFORTS

What may present a risk?	Possible Risk/Side Effect	How often has it occurred?
Venous catheter insertion and Blood draws	**1. Localized swelling, soreness, bruising, and chance of infection, bleeding, pain, lightheadedness or possible fainting.**	**1. It occasionally occurs**
Samples from the earlobe	**2.Soreness, bruising, infection, and scarring. A total of one large drop of blood will be taken each time**	**2. It occasionally occurs**
Exercise Testing/Sessions	**1. Light-headedness, shortness of breath and altered heart rate & blood pressure. Muscle soreness at your neck, upper back, shoulders, arms & hands** **2. Fainting, heart attacks or death** **3. Muscle soreness**	**1. It is fairly common** **2. It is very rare** **3. It is fairly uncommon**
Oral Glucose Tolerance Test	**1. Nausea from drinking a lot of glucose (sugar)**	**1. Occasionally occurs**

BENEFITS TO YOU AND OTHERS

There is no guarantee that you will receive any medical benefits from being in this study. The information gained from this research study may lead to a better use of exercise in management of diseases like diabetes and heart disease.

COSTS

There is no cost for the study visits.

PAYMENT FOR PARTICIPATION

Your participation is voluntary and you will not be paid to participate. However, you will receive a summary of your health screening, fitness test results and consultation on starting an exercise program.

ALTERNATIVE TREATMENT

Your alternative is not to participate in this study.

CONFIDENTIALITY

You should know that research data about you may be reviewed or copied by the sponsor of the research or by Virginia Commonwealth University. Personal information about you might be shared with or copied by authorized officials of the Department of Health and Human Services. Potentially identifiable information about you will consist of physical fitness, body fat, and overall health risk factors, as well as blood samples. Data is being collected only for research purposes. Once your consent form is completed you will receive a unique number ID for all study documents. Identification will then be

stored in a secure location. Your name or other personal information will not appear in any data collection or study documents. All personal identifying information will be kept in password protected files and these files will be deleted within 3 years of completion. *Deidentified* data will be kept indefinitely. Access to all data will be limited to study personnel. A data and safety monitoring plan is established.

Although results of this research may be presented at meetings or in publications, identifiable personal information pertaining to participants will not be disclosed.

COMPENSATION FOR INJURY or ILLNESS

If you are injured by, or become ill, from participating in this study, please contact your study doctor immediately. Medical treatment is available at the Virginia Commonwealth University Health System (VCU Health System). Your study doctor will arrange for short-term emergency care at the VCU Health System or for a referral if it is needed.

Fees for such treatment may be billed to you or to appropriate third party insurance. Your health insurance company may or may not pay for treatment of injuries or illness as a result of your participation in this study.

To help avoid research-related injury or illness it is very important to follow all study directions.

VOLUNTARY PARTICIPATION AND WITHDRAWAL

Your participation in this study is voluntary. You may decide to not participate in this study. Your decision not to take part will involve no penalty or loss of benefits to which you are otherwise entitled. If you do participate, you may freely withdraw from the study at any time. Your decision to withdraw will involve no penalty or loss of benefits to which you are otherwise entitled.

Your participation in this study may be stopped at any time by the medical staff or investigator without your consent. The reasons might include:

- the study doctor thinks it necessary for your health or safety;
- you have not followed study instructions; or
- administrative reasons require your withdrawal.

It is important to the study team if you are considering stopping so any risks can be evaluated by the study personnel. If you leave the study before the final regularly scheduled visit we ask you please contact us via telephone, email or in person.

QUESTIONS

If you have any questions, complaints, or concerns about your participation in this research, contact:

Edmund Acevedo, Principal Investigator
P.O. Box 842020
Dept of Health and Human Performance
Virginia Commonwealth University
Richmond, VA 23284
(804) 828-1948
eoacevedo@vcu.edu
and/or
Chris Harnish, student investigator
(804) 592-0512
harnishc@vcu.edu

The researcher/study staff named above is the best person(s) to call for questions about your participation in this study.

If you have general questions about your rights as a participant in this or any other research, you may contact:

Office of Research
Virginia Commonwealth University
800 East Leigh Street, Suite 3000
P.O. Box 980568
Richmond, VA 23298
Telephone: (804) 827-2157

Contact this number for general questions, concerns, or complaints about research. You may also call this number if you cannot reach the research team or if you wish to talk to someone else. General information about participation in research studies can also be found at http://www.research.vcu.edu/irb/volunteers.htm.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

CONSENT
I have been provided with an opportunity to read this consent form carefully. All of the questions that I wish to raise concerning this study have been answered.

By signing this consent form, I have not waived any of the legal rights or benefits, to which I otherwise would be entitled. My signature indicates that I freely consent to participate in this research study. I will receive a copy of the consent form once I have agreed to participate.

_____
Participant Name, printed

_____ _____
Participant Signature Date

_____
Name of Person Conducting Informed Consent Discussion / Witness [3]
(Printed)

_____ _____
Signature of Person Conducting Informed Consent Discussion / Witness Date

_____ _____
Principal Investigator Signature (if different from above) Date [4]

VITA

Chris Harnish was born on May 12, 1974, in Amsterdam, New York, and is an American citizen. Growing up in the central leather stocking region and later the key manufacturing site for Cabbage Patch Kids, he graduated from Amsterdam High School in 1992. He went on to receive a Bachelor of Science in Clinical Exercise Science from Ithaca College, in Ithaca, New York in 1996, and then attended the University of South Carolina, receiving a Masters of Science in Exercise Physiology in 1999. He then spent three years teaching at Ithaca College before moving to Cape Cod to work as a professional cycling coach and event promoter. He enrolled in the PhD program at Virginia Commonwealth University in 2008.