The relationship between changes in cardiovascular function and changes in VO₂peak following SIT

By

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Abstract

Background: It is well known that sprint interval training (SIT), induces significant increases in peak oxygen uptake (VO\textsubscript{2peak}) at the group level. However, there have been only a few studies that have addressed the variability of VO\textsubscript{2peak} response following SIT, and precise mechanism(s) that may explain individual magnitude of response are unknown. Purpose: Therefore, the purpose of this thesis was to: 1) examine the inter-individual variability of the VO\textsubscript{2peak} response following SIT, 2) to inspect the relationship between changes in both central and peripheral measures and changes in VO\textsubscript{2peak}, and 3) to assess if peripheral or central adaptations play a role in whether an individual is a high or low responder with respect to VO\textsubscript{2peak}. Subjects: Twenty-two young, recreationally active males (age: 20.4 ± 1.7 years; weight: 78.4 ± 10.2 kg; VO\textsubscript{2peak}: 3.7 ± 0.62 L/min) Methods: VO\textsubscript{2peak} (L/min), peak cardiac output (Qpeak [L/min]), and peak deoxygenated hemoglobin (HHbpeak [mM]) were measured before and after 16 sessions of SIT (Tabata Protocol) over four weeks. Peak a-vO\textsubscript{2diff} was calculated using a derivation of the Fick equation. Results: Due to a systematic error, HHbpeak could not be used to differentiate between individual responses. There was a large range of VO\textsubscript{2peak} response from pre to post testing (-4.75 to 32.18% change) and there was a significant difference between the Low Response Group (LRG) (n=8) and the High Response Group (HRG) (n=8) [f(1, 14)= 64.27, p<0.001]. Furthermore, there was no correlation between delta (Δ) VO\textsubscript{2peak} and Δ Qpeak (r=-0.18, p=0.46) for all participants, nor was there an interaction effect between the Low and High Response Groups [f(1,11)=0.572, p=0.47]. Lastly, there was a significant correlation between VO\textsubscript{2peak} and peak a-vO\textsubscript{2diff} [r=0.692, p<0.001], and a significant interaction effect with peak a-vO\textsubscript{2diff} [f(1, 14)= 13.27, p<0.004] when comparing the HRG to the LRG. Conclusions: There was inter-individual variability of VO\textsubscript{2peak} response following 4
weeks of SIT, but central adaptations did not influence this variation. This suggests that peripheral adaptations may be responsible for VO$_2$peak adaptation.

**Keywords:** Exercise, Sprint Interval Training, VO$_2$peak, Cardiac Output, De-oxygenated Hemoglobin, Peripheral Adaptation, Central Adaptation, Variability of Response
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List of Abbreviations

2XTE = Two Times Typical Error of Measurement

a-\textit{vO}_2\text{diff} = Arteriovenous Oxygen Difference

ANOVA = Analysis of Variance

CVs = Coefficient of Variation

cm = centimeters

ET = Endurance Training

HBO_2 = Oxygenated Hemoglobin

HHb = De-Oxygenated Hemoglobin

HHbpeak = Peak De-Oxygenated Hemoglobin

HIIT = High Intensity Interval Training

HR = Heart Rate

HRG = High Response Group

Kg = Kilogram

L = Litres

LACEP = Laboratory of Clinical Exercise Physiology

LRG = Low Response Group

NIRS = Near Infrared Spectroscopy

Peak a-\textit{vO}_2\text{diff} = Peak Arteriovenous Oxygen Difference

Q = Cardiac Output

Qpeak = Peak Cardiac Output

RPM = Revolutions per Minute

SD = Standard Deviation
SIT = Sprint Interval Training
SV = Stroke Volume
TE = Typical Error of Measurement
VO₂max = Maximal Oxygen Uptake
VO₂peak = Peak Oxygen Uptake
W = Watts
WRpeak = Peak Work Rate
Chapter 1: Introduction

1.1 Inter-Individual Variability of VO$_2$peak Response Following Sprint Interval Training:

Sprint interval training (SIT), a subclass of high intensity interval training (HIIT), are a group of protocols involving ‘all-out’ efforts at supramaximal intensities (>100% peak oxygen uptake [VO$_2$peak] work rate) (Gillen and Gibala, 2013; Sloth et al., 2013). SIT, when compared to traditional endurance training (ET), induces similar health benefits despite a significantly reduced exercise time. These benefits include increases in aerobic and anaerobic exercise performance, muscle oxidative capacity, mitochondrial content, and capillary density (Burgomaster et al., 2008; Gillen and Gibala, 2013; Scribbans et al., 2014b). Additionally, SIT can elicit improvements in VO$_2$peak (Astorino et al., 2012; Astorino et al., 2014; Bailey et al., 2009; Bayati et al., 2011; Burgomaster et al., 2008; Barnett et al., 2004; Cocks et al., 2012; Foster et al., 2015; Hazell et al., 2010; Ma et al., 2013; Scribbans et al., 2014a; Scribbans et al., 2014b; Tabata et al., 1996; Zelt et al., 2014). For instance, a study conducted by Ma et al. (2013) found a marked increase in VO$_2$peak (19%) following 16 sessions of SIT in 8 recreationally active men. Thus, it is clear that at the group level this type of training improves VO$_2$peak.

However, this group effect appears to be masking the individual level of response in VO$_2$peak, as there appears to be large inter-individual variability following SIT. A study assessing individual variability of response in VO$_2$peak following two weeks of SIT, found a wide range of changes from pre-testing to post testing (0-20%) in 20 habitually-active males (Astorino et al., 2014). Additionally, Gurd et al. (2016) recently demonstrated heterogeneity of response in VO$_2$peak following three to six weeks of SIT. Out of the 63 participants, 14 (~22%) were classified as non-responders (using 2x typical error, a statistically sound cut-off point [Hopkins et al., 2000]), while 15 participants had a high response to SIT (>10% change from
pre). Thus, when examining participants at the individual level, there is evidence to suggest that there is a spectrum of VO₂peak response following SIT. Some individuals may respond highly to this type of training, whilst others may see a low, unchanged or even a negative response.

1.2 Cardiovascular Adaptations Following SIT:

The peak amount of oxygen utilized per unit time under incremental exercise is referred to as VO₂peak and it is considered to be one of the best indicators of maximal aerobic fitness (Astrand and Rodahl, 1986; Bhambhani et al., 2001). Improvements in VO₂peak, in compliance with the Fick Equation, must result from a change in either central (cardiac output [Q]) and/or peripheral (Arteriovenous oxygen difference [a-vO₂diff]) function (Montero et al., 2013, MacPherson et al., 2011). While the literature suggests that improvements to VO₂peak after ET is due to increases in peak cardiac output (Qpeak) (Gollnick et al., 1982; Holloszy et al., 1984; Macpherson et al., 2011), SIT is believed to rely more on increases in a-vO₂diff (Burgomaster et al., 2005; Gibala et al., 2006; Macpherson et al., 2011; Jacobs et al., 2011). For instance, a study by Macpherson et al. (2011), when comparing ET and SIT, suggested that the increase in VO₂peak following 6 weeks of SIT were primarily due to increases in a-vO₂diff (+7.1%), not in Qpeak (-2.2%). This suggests that changes in VO₂peak rely more on increases in oxygen extraction (peripheral adaptations), rather than oxygen delivery (central adaptations) following SIT.

While there are studies that suggest SIT improves VO₂peak via peripheral mechanisms, there have been very limited studies that compare central and peripheral adaptations within a single sample following SIT. Further, the studies that have compared adaptations after SIT (Jacobs et al., 2013; Macpherson et al., 2011), did not address VO₂peak responses at the individual level, nor speak to the mechanisms underlying individual variability. Thus, although
we have a reasonable understanding of how SIT induces adaptations at the group level, no study
to date has examined the mechanisms determining the magnitude of individual change in
VO\textsubscript{2peak} following SIT. We hypothesize that peripheral adaptations, rather than central
adaptations, will be the main contributor to individual variation to VO\textsubscript{2peak} after SIT.

1.3 Potential Applicability:

This study may increase our understanding of how an individual’s VO\textsubscript{2peak} responds to
SIT, and elucidate potential mechanisms that determine individual variability in this response.
This, in turn, may eventually help reduce the incidence of non-responders to exercise by tailoring
individual exercise prescription to SIT for young, healthy recreationally active males.

1.4 Thesis objectives and Experimental Approach:

The objective of this study was to examine the inter-individual variability of the
cardiovascular response to SIT, and the relationship between changes in cardiovascular function
and changes in VO\textsubscript{2peak} following SIT. Additionally, we wanted to assess if peripheral or
central adaptations play a role in whether an individual is a high or low responder to VO\textsubscript{2peak}
after SIT. To answer this research question, we attempted to record measurements to provide a
comprehensive picture of central and peripheral adaptations. More specifically, central
adaptations were estimated by measuring changes in Q\textsubscript{peak} (via Finapres and Innocor), whereas
peripheral adaptations were obtained by calculating peak a-vO\textsubscript{2diff} and by measuring de-
oxxygenated hemoglobin (HHb\textsubscript{peak}) (measured via near-infrared spectroscopy [NIRS]).

1.5 Thesis Organization:

In Chapter 2, the reader will find a detailed literature review, outlining the relationship
between the cardiovascular response and SIT. First at the group level, followed by at the
variability of response at the individual level. Additionally, Chapter 2 will review the role that
both $Q_{peak}$ and $HHb_{peak}$ play in adaptations to $VO_2_{peak}$ following SIT. Chapter 3 provides a detailed overview of the methodology carried out in this study. Chapter 4 contains the corresponding results for the thesis. Chapter 5 consists of a discussion of the key findings of the thesis as well as strengths, limitations, and future directions. Lastly, a detailed appendix is attached to provide complete details of the items discussed within the thesis.
1.6 References:


Run sprint interval training improves aerobic performance but not maximal cardiac output.


Chapter 2: Literature Review

2.1 General Overview:

This literature review will begin by exploring the relationship between SIT and VO$_{2peak}$. This will be followed by a discussion of the variability of individual response to VO$_{2peak}$ after SIT and will finish with an investigation of the potential mechanisms underlying this variability.

2.2 Sprint Interval Training and VO$_{2peak}$:

2.2.0 Overview:

SIT, a subclass of high intensity interval training (HIIT), requires participants to complete brief maximal efforts separated by periods of rest (Gillen and Gibala, 2013; Sloth et al., 2013). SIT is considered a time-efficient training protocol as it induces similar improvements in numerous health related factors as endurance training (ET), despite significantly less exercise time (Burgomaster et al., 2008; Gillen and Gibala, 2013; Scribbans et al., 2014b). For instance, Gibala et al. (2006) found that six sessions of SIT elicited comparable increases in aerobic exercise capacity and muscle oxidative potential to ET with approximately 90% lower training volume (2.5 hours with SIT versus 10.5 hours with ET). This is an important finding as one of the major complaints cited by members of the general population for failing to exercise regularly is a lack of time (Godin et al., 1994; Trost et al., 2002). In contrast, some researchers argue that SIT may be inappropriate, as the nature of the supra-maximal intensities could decrease enjoyment, intrinsic motivation, and exercise adherence (Ekkekakis et al., 2011; Hardcastle et al., 2014). These ideas, however, are directed at sedentary populations and thus cannot be applied to the general population. With respect to recreationally active individuals, Bartlett et al.
(2011) found that SIT may be more enjoyable than ET and thus may help increase exercise adherence in that population.

A recent meta-analysis, looking at the effects of SIT on aerobic capacity across 16 studies, found an overall increase in VO$_2$peak of 8% (Gist et al., 2014). Similar results were found in a meta-analysis conducted by Sloth et al. (2013) who, when examining 12 studies, found a group increase in VO$_2$peak ranging from 4 to 13.5%. The next section will explore different protocols of SIT and their group level effect on VO$_2$peak response.

2.2.1 Training Protocols:

There are many different protocols for SIT, the most commonly used being the traditional and modified Wingate, which consist of four to six 30s ‘all-out’ sprints performed on a cycle ergometer separated by three to five-minute recovery periods (Gibala et al., 2012; Gist et al., 2013; Sloth et al., 2013). These protocols have been shown to consistently improve VO$_2$peak (Astorino et al., 2012; Astorino et al., 2014; Bailey et al., 2009; Barnett et al., 2004; Bayati et al., 2011; Burgomaster et al., 2008; Hazell et al., 2010; Laurson et al., 2002; Macdougall et al., 1998; Metcalf et al., 2011; Whyte et al., 2010; see Table 1 below). Adaptations in VO$_2$peak have been shown in a short amount of time. For instance, 20 recreationally active men and women were found to demonstrate meaningful elevations in VO$_2$peak (7.3% increase), following 6 sessions of SIT training (Burgomaster et al., 2008). Correspondingly, another study conducted by Astorino et al. (2012) found that over 6 sessions, relative VO$_2$peak increased by an average of 2.4 ml/kg/min (5.2%) in 20 recreationally active men and women.

Although the Wingate protocol of SIT elicits improvements in VO$_2$peak, questions about its time efficiency remain (Gillen et al., 2014; Hardcastle et al., 2014). Specifically, when accounting for the length of the entire protocol, including warm-up, exercise intervals, recovery
intervals and cool down, this protocol takes up to 30 minutes to complete. This may deter some individuals from partaking in the Wingate protocol because it often adds up to the same amount of time as endurance training. There have been a few studies that have examined if diminishing intervals would still elicit the same cardiovascular health benefits as the traditional Wingate SIT (Hazell et al., 2010; Metcalf et al., 2012; Zelt et al., 2014). All three of these studies demonstrated that reducing the interval duration of SIT does not diminish VO$_2$peak adaptive response (refer to Table 1).

Additionally, Tabata et al. (1996) developed an even shorter protocol (7-8 intervals of 20s at 170% WR$_{peak}$ with only 10s recovery periods) that also induces increases in VO$_2$peak. When implementing this Tabata protocol 4 days a week for 4 weeks in 7 young, healthy active males, VO$_2$peak improved by over 14% from baseline. This finding has since been reproduced in the Queen’s Muscle Physiology Lab, where the same protocol improved VO$_2$peak in recreationally active males by 6-19% (Ma et al, 2013; Scribbans et al., 2014a; Scribbans et al., 2014b). For instance, Ma et al (2013), found the largest overall increase in VO$_2$peak after four weeks of 19% (39.7 ± 3.0 to 47.2 ± 2.9 mL/kg/min) when testing the effects of the Tabata protocol on 10 young, recreationally active males. Therefore, the literature suggests that reducing the duration of intervals and shortening SIT protocols can still elicit meaningful changes in VO$_2$peak in young, healthy individuals compared with the traditional Wingate SIT protocol.

To summarize, it is well established that various SIT protocols induce significant increases in VO$_2$peak at the group level. The next section will explore the inter-individual variability in VO$_2$peak response following SIT.
Table 1: Characteristics and major findings of studies examining the effect of cycle ergometer sprint interval training on VO\textsubscript{2}peak in young, healthy populations. * Indicates significant difference from pre- to post-training.

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Training Frequency and Duration</th>
<th>SIT Protocol</th>
<th>VO\textsubscript{2}peak PRE (mL/kg/min)</th>
<th>VO\textsubscript{2}peak POST (mL/kg/min)</th>
<th>%Change in relVO\textsubscript{2}peak (mL/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astorino et al., 2012</td>
<td>20</td>
<td>3 sessions a week for 2 weeks</td>
<td>30s ‘All-out’ Intervals with 4.5 min</td>
<td>43.6 ± 5.4</td>
<td>46.0 ± 5.2</td>
<td>5.22*</td>
</tr>
<tr>
<td>Astorino et al., 2014</td>
<td>20</td>
<td>3 sessions a week for 2 weeks</td>
<td>30s ‘All-out’ Intervals with 4.5 min</td>
<td>n/a</td>
<td>n/a</td>
<td>6.30*</td>
</tr>
<tr>
<td>Bailey et al., 2009</td>
<td>24</td>
<td>3 sessions a week for 2 weeks</td>
<td>30s ‘All-out’ Intervals with 4 min rest</td>
<td>42 ± 6</td>
<td>45 ± 6</td>
<td>6.67*</td>
</tr>
<tr>
<td>Bayati et al., 2011</td>
<td>16</td>
<td>3 times a week for 4 weeks</td>
<td>30s ‘All-out’ Intervals</td>
<td>n/a</td>
<td>n/a</td>
<td>8.79*</td>
</tr>
<tr>
<td>Burgomaster et al., 2008</td>
<td>20</td>
<td>3 sessions a week for 6 weeks</td>
<td>30s ‘All-out’ Intervals with 4.5 min</td>
<td>41 ± 2</td>
<td>44 ± 2</td>
<td>7.32*</td>
</tr>
<tr>
<td>Barnett et al., 2004</td>
<td>16</td>
<td>3 sessions a week for 8 weeks</td>
<td>30s ‘All-out’ Intervals with 3 min rest</td>
<td>3.78 ± 0.11 L/min</td>
<td>4.09 ± 0.12 L/min</td>
<td>7.58*</td>
</tr>
<tr>
<td>Cocks et al., 2012</td>
<td>16</td>
<td>3 sessions a week for 6 weeks</td>
<td>30s ‘All-out’ Intervals with 4.5 min</td>
<td>41.9 ± 1.8</td>
<td>45.1 ± 2.3</td>
<td>7.64*</td>
</tr>
<tr>
<td>Hazell et al., 2010</td>
<td>13</td>
<td>3 sessions a week for 2 weeks</td>
<td>30s ‘All-out’ Intervals with 4 min rest</td>
<td>n/a</td>
<td>n/a</td>
<td>9.30*</td>
</tr>
<tr>
<td>Zelt et al., 2014</td>
<td>11</td>
<td>3 sessions a week for 4 weeks</td>
<td>30s ‘All-out’ Intervals with 4.5 min</td>
<td>49.8 ± 7.8</td>
<td>51.5 ± 8.1</td>
<td>3.41</td>
</tr>
<tr>
<td>Zelt et al., 2014</td>
<td>12</td>
<td>3 sessions a week for 4 weeks</td>
<td>15s ‘All-out’ Intervals with 4.75 min rest</td>
<td>44.2 ± 8.7</td>
<td>47.1 ± 7.6</td>
<td>6.56*</td>
</tr>
<tr>
<td>Tabata et al., 1996</td>
<td>7</td>
<td>4 sessions a week for 6 weeks</td>
<td>20s intervals at 170% WR\textsubscript{peak} with 10s rest</td>
<td>48.2 ± 5.5</td>
<td>55 ± 6</td>
<td>14.58*</td>
</tr>
<tr>
<td>Ma et al., 2013</td>
<td>10</td>
<td>4 sessions a week for 4 weeks</td>
<td>20s intervals at 170% WR\textsubscript{peak} with 10s rest</td>
<td>39.7 ± 3.0</td>
<td>47.2 ± 2.9</td>
<td>18.89*</td>
</tr>
<tr>
<td>Scribbans et al., 2014a</td>
<td>19</td>
<td>4 sessions a week for 6 weeks</td>
<td>20s intervals at 170% WR\textsubscript{peak} with 10s rest</td>
<td>48.3 ± 6.1</td>
<td>54.9 ± 6.2</td>
<td>13.66*</td>
</tr>
<tr>
<td>Scribbans et al., 2014b</td>
<td>8</td>
<td>3 sessions a week for 4 weeks</td>
<td>20s intervals at 170% WR\textsubscript{peak} with 10s rest</td>
<td>50.4 ± 5.0</td>
<td>53.3 ± 5.4</td>
<td>5.75*</td>
</tr>
<tr>
<td>Foster et al., 2015</td>
<td>21</td>
<td>3 sessions per week for 8 weeks</td>
<td>20s intervals at 170% WR\textsubscript{peak} with 10s rest</td>
<td>34.0 ± 6.5</td>
<td>40.1 ± 6.8</td>
<td>17.94*</td>
</tr>
<tr>
<td>Hazell et al., 2010</td>
<td>11</td>
<td>3 sessions a week for 2 weeks</td>
<td>10s ‘All-out’ intervals with 4 min rest</td>
<td>n/a</td>
<td>n/a</td>
<td>9.2*</td>
</tr>
<tr>
<td>Hazell et al., 2010</td>
<td>12</td>
<td>3 sessions a week for 2 weeks</td>
<td>10s ‘All-out’ with 2 min rest</td>
<td>n/a</td>
<td>n/a</td>
<td>3.8</td>
</tr>
</tbody>
</table>
2.3 Variability of Response to VO$_2$peak after SIT:

2.3.0 Overview:

This section will first introduce variability of response, and then provide a brief overview of papers that address variability in VO$_2$peak response following standardized training. This section will conclude with a summary of the literature that specifically assesses individual VO$_2$peak response following SIT.

2.3.1 Introducing Variability of Response to Exercise:

It is common for exercise science literature to only report their findings at the group level and fail to report responses on the individual level (Bouchard and Rankinen, 2001). The problem with this approach is that group means may be misleading as they can mask individual variability. Although most individuals fall within the normal distribution of responses following exercise training (Cohen et al. 1979), there are individuals who respond very highly (high responders), while others see little or no change (low/non responders) (Mann et al., 2014). Therefore, it is important to fully understand individual level of response to exercise, as doing so may improve exercise prescription strategies.

One of the first studies to specifically examine individual variability of response to exercise training was Lortie et al. (1984) who examined the effects of a 20-week aerobic exercise program on maximal aerobic power and capacity response in 24 young, sedentary individuals. They reported not only the group means for these variables, but also the range of response (5% to 88%). Another seminal study involving individual responses to exercise was the HERITAGE study, an exercise intervention ($N=720$) that reported large heterogeneity in individual responses for numerous factors including maximal oxygen uptake (VO$_2$max), systolic and diastolic blood
pressure, and submaximal heart rate (Bouchard et al., 1998; Bouchard et al., 1999; Bouchard & Rankenin, 2001). These seminal studies prompted further research in this area that since replicated the results and explored variability in training response to various other exercise protocols, including preliminary studies with SIT.

2.3.2 Variability of Response to VO$_2$peak Following SIT:

There is a substantial individual variability in the magnitude of response for peak aerobic capacity (VO$_2$peak) induced by ET, (Bouchard & Rankenin., 2001; Hamel et al., 1986; Hautala et al., 2003; Hautala et al., 2006; Hautala et al., 2012; Karaverta et al., 2011; Kohrt et al., 1991; Mcphee et al., 2010; Scharhag-Rosenberger et al., 2012; Sisson et al., 2009; Vollaard et al., 2009). However, the literature is not as well established with regards to this variation following SIT. Although individual responses in VO$_2$peak have been presented following SIT (Astorino et al., 2012, Boyd et al., 2013; Hazell et al., 2010; Machperson et al., 2011; Zelt et al., 2014), there have been only a few papers that specifically address inter-individual variability in the VO$_2$peak response following SIT (Astorino et al., 2014; Gurd et al., 2016; Raleigh et al., 2016).

Firstly, a study conducted by Astorino et al. (2014) reported a large range of VO$_2$peak response (0-20%), following a retroactive examination of variability in response in VO$_2$peak following 2 weeks of SIT. Secondly, a larger study ($N=63$) assessed inter-individual variation to VO$_2$peak following SIT, and found a similar variability in response (See Figure 1) (Gurd et al., 2016). Both of these studies reported both high responders and low/non-responders to VO$_2$peak following SIT. In order to explore further the reasoning behind the differentiation of response, it is important to properly classify a responder using statistically sound cut-off points.
2.3.3 Using Statistical Cut-off Points to Classify Response to SIT:

An individual who is characterized as a non-responder demonstrates an unchanged VO$_2$peak response following exercise training (Mann et al., 2014; Sisson et al., 2009). In order to accurately distinguish random changes from a real physiological response, it is important to use a statistically sound cut-off point.

In previous studies (Astorino et al., 2014; Scharhag-Rosenberger et al., 2013), responders were classified using a cut point of 1 previously published within-subject co-efficient of variation (CVs) (Katch et al., 1982). The issue with using previously published CVs is that it fails to account for both biological and technical error within the lab conducting the study. Therefore, a more statistically sound cut-off point, typical error of measurement (TE), has been proposed to take into account both of these sources of errors (Bouchard et al., 2012; Hopkins et al., 2000). TE is defined as the standard deviation in each individual’s measurement between tests (Hopkins et al., 2000). Furthermore, multiplying the TE value by 2 can further help classify a responder, as the odds of an individual’s observed response actually being attributed to a
physiological change greater that 2XTE, rather than a random chance, is twelve to one (Hopkins et al., 2000).

One notable study calculated 2XTE for VO₂peak (see Equation 1), by recruiting 8 participants to partake in two identical incremental ramp tests separated by a week (Gurd et al., 2016). When applying this calculation to individual responses following various protocols to SIT, fourteen of the sixty-three individuals were classified as non-responders. Additionally, this cut-off point was repeated within the same lab to assess the role of exercise intensity on incidence of non-responders to VO₂peak on twenty-four recreationally active individuals following three weeks of SIT (Raleigh et al., 2016). This study reported a 12.5% non-response rate (3/24) in the two SIT groups (Mid [115%] and High [150%] VO₂peak work rate).

To conclude, it is essential to use statistically sound cut-off points when examining inter-individual variation of VO₂peak response following exercise as it will help distinguish random chance from a physiological response and therefore incur more accurate and reliable results.

$$2\times\text{TE} = \left(\frac{\text{SD}_{\text{diff}}}{\sqrt{2}}\right)X2$$

**Equation 1:** Standard equation to calculate 2 times typical error of measurement (2XTE). Where SD_{diff} indicates the difference in standard deviation between the 2 tests (Hopkins et al, 2000).

2.3.4 How Participant Characteristics, Training Intensity and Volume Influence Response to Exercise Training:

There are many factors that may contribute to inter-individual variability of response. For instance, participant characteristics (age, sex, race, ethnicity, baseline fitness level, and genetics) and training intensity and/or volume may all influence an individual’s adaptation to training. Regarding participant characteristics, the literature appears to show contradicting results. For instance, Bouchard and Rankenin (2001) examined the contribution of age, sex, baseline fitness,
race, and ethnicity to the variability of VO_{2peak} response following twenty weeks of ET in 720 individuals and found that these characteristics accounted for only a small percentage of individual variation. Conversely, there have been other studies that indicated age (Hautala et al., 2003; Sisson et al., 2009; Parker et al., 2010), sex (Parker et al., 2003), and baseline fitness (Cunningham et al., 1987; Sisson et al., 2009) significantly contribute to the trainability of VO_{2peak} following ET. Race (Bouchard & Rankenin, 2001; Skinner et al., 2001) and ethnicity (Bouchard et al., 2001) appear to not have any effect on variability of response. Moreover, genetic factors could explain up to approximately 47% of the variance in VO_{2peak} response suggesting that trainability of VO_{2peak} following ET may be largely determined by a genetic component (Bouchard et al., 1999). The literature on the effects of participant’s characteristics on the inter-individual variability to VO_{2peak} following SIT is undefined and future research is warranted.

An individual’s VO_{2peak} response following exercise can also be influenced by the intensity and/or volume of the training stimulus and it has been suggested that individuals who are low responders to a particular exercise protocol may see improvements in their adaptive response if the intensity and/or volume of the protocol is increased (Buford et al., 2013). Consistent with this theory, at the group level there appears to be a dose-response relationship following ET and HIIT, indicating that greater volumes of exercise are associated with greater improvements in VO_{2peak} (Ross et al., 2015; Sisson et al., 2009). Sisson et al. (2009) were the first to examine the effect of exercise volume on VO_{2peak} response following 6 months of ET, demonstrating that greater volumes of exercise were associated with a greater chance of becoming a VO_{2peak} responder in post-menopausal women (n=310); randomized into three different exercise volume groups [4, 8 or 12 kcal/kg/week]) who trained at a fixed exercise
intensity (50% VO$_2$peak). Interestingly, Gurd et al. (2016) found that the rate of VO$_2$peak non-response was reduced to zero in studies that trained 4 times per week (Ma et al., 2013; Scribbans et al., 2014a) compared with studies that trained 3 times per week (37% non-response rate) (Scribbans et al., 2014b; Zelt et al., 2014). These results suggest that increasing the volume of SIT may also reduce the rate of non-response in individuals.

Increasing exercise intensity may play a larger role in decreasing the incidence on non-response (Raleigh et al., 2016; Ross et al., 2015). This can be seen in a 24-week exercise training study conducted by Ross et al. (2015), where participants (n=121) were randomized into one of three exercise groups: Low-Amount, Low-Intensity (LALI), High-Amount, Low-Intensity (HALI), and High-Amount, High-Intensity (HAHI). Interestingly, they found that increasing the intensity at a fixed volume of exercise eradicated the VO$_2$peak non-response rate to zero (HAHI) from 17.6% (HALI) after 24 weeks. These results have been supported within our own lab by Raleigh et al. (2016), albeit on a smaller scale. They isolated the effects of exercise intensity on VO$_2$peak by stratifying participants into three volume-matched intensity groups. This study suggests that there may be an optimal dose of exercise intensity to elicit a higher response to HIIT and SIT, but further research on a larger sample size is warranted.

To conclude, the literature suggests that there is a large inter-individual variability in VO$_2$peak response following SIT. The next section will examine what role peripheral or central adaptations play in determining the individual magnitude of response following this type of training.
2.4 Cardiovascular Mechanisms underlying Non-response to VO2peak after SIT:

2.4.0 Overview:

This section will first introduce the determinants of VO2peak (Qpeak, a-vO2diff), and summarize their response to exercise training and increasing exercise intensity. Secondly, it will review the literature’s stance on what role these determinants have on the VO2peak adaptive response following SIT. Lastly, an overview of the validity and reliability of the machines used to measure Qpeak and HHbpeak in this thesis will be provided.

2.4.1 Introducing the Determinants of VO2peak:

During a traditional ramp protocol, the intensity of exercise increases, and in turn, oxygen consumption increases linearly until VO2peak is reached (Laughlen et al., 1999). According to the Fick Principle, the determinants for VO2peak are peak cardiac output (Qpeak) and Peak arteriovenous oxygen difference (a-vO2diff) (Laughlen, 1999; MacPherson et al., 2011; Montero et al., 2013, See Equation 2).

$$\text{VO2peak (L/min)} = \text{Qpeak (L/min)} \times \text{Peak a-vO2diff (mL-O2/100mL)}$$

**Equation 2:** Qpeak can be further broken down into stroke volume (SV) in liters per beat and heart rate (HR) in beats per minute.

Cardiac output (Q) is the amount of blood, in liters, pumped from the heart in one minute. It is a product of heart rate (HR) and stroke volume (SV). HR is how many times the heart beats per min (bpm), while SV is the volume of blood pumped from the left ventricle on each beat (mL/beat) (Jean-Louis Vincent, 2008). Improvements in these central factors following exercise training can improve VO2peak as they increase the amount of oxygen delivered to the active muscles during exercise (Åstrand & Rodahl, 1986).
Arteriovenous oxygen difference (a-VO₂diff [mL·O₂/100mL]) is the difference between the oxygen content of the arterial blood and the mixed venous blood. a-VO₂diff increases with increasing exercise intensity, owing to the fact that there is a decrease in mixed venous oxygen content (Laughlen, 1999). This is due to the redistribution of blood flow from areas that are in less need of oxygen (i.e. kidneys) to active muscle sites (Pool et al., 1992). With training, increases in a-VO₂diff can result in increases in VO₂peak due to the active muscle increasing oxygen extraction (Macpherson et al., 2011). Another variable that can give a representation of oxygen extraction is de-oxygenated hemoglobin (HHb) and it is a proxy-variable to a-VO₂diff. HHb are red blood cells that do not have oxygen bound to them, and increase at the onset of exercise as the oxygen is extracted into the active muscle (Prieur et al, 2013).

2.4.2 Measuring Cardiac Output:

The Inert Gas Re-breathing Method (Innocor, Innovision, Odense, Denmark) is a non-invasive method to measure Q and was developed as a substitute to the invasive direct Fick Method (Cournand et al, 1942). During the rebreathing maneuver (that can be used at rest and during exercise), the participant breaths in both blood-soluble (0.5% nitrous oxide) and blood-insoluble (0.1% sulfur hexafluoride) gases. The rate of the disappearance of nitrous oxide is proportional to pulmonary blood flow and pulmonary blood flow is equivalent to systemic blood flow (Q). Therefore, Innocor is a non-invasive way to obtain an accurate estimate of Q. When comparing Innocor to the direct Fick Method, there was a strong correlation (r=0.95) and measures of Q were not significantly different between methods (Agostoni et al., 2005). Additionally, Innocor was found to have high test-retest reliability for determining Q during graded exercise tests at rest and at submaximal power in 30 young, recreationally active
participants (Fontana et al., 2009). Thus, using Innocor provides a valid and reliable measure of Q in healthy, recreationally active individuals.

Unfortunately, due to measurement limitations, Innocor was unable to be utilized to measure Qpeak in this thesis. This is primarily due to the time it requires to prepare Innocor for the rebreathing maneuver (filling the bag up full of nitrous oxide, sulfur hexafluoride and ambient air) and the researcher’s inability to accurately predict when a participant would reach their maximal exertion. To solve this issue, the Finometer finger cuff (Finometer MIDI, Finapress Medical Systems, The Netherlands), a device used to continuously monitor HR and reconstructed brachial arterial pressure through non-invasive finger arterial pressure measurements (Guelen et al., 2003), was used in combination with Innocor to estimate Qpeak. The finger cuff uses diodes located on the anterior and posterior sides of the finger to detect any changes in artery diameter and subsequently changes the inflation of the cuff (by using an air bladder connected to an air hose and pump) to maintain a set arterial diameter (Bogert et al., 2005; Hodgson et al., 2012). Additionally, this device is capable of calculating Q and SV using the ModelFlow method (Wesseling et al., 1993). Q is then calculated using SV and corresponding HR (Azabji Kenfack et al., 2004; Bogert et al., 2005). Unfortunately, overestimation of Q can result from this method if used independently, and thus cannot be used without a correction factor from another method (Azabji Kenfack et al., 2004). Therefore, both Innocor and Finometer were utilized at submaximal work rates and the relationship between the two was used to adjust/correct the estimation of Q from the Finometer using slope and intercept parameters at the higher work rates when Innocor was not used (see Figure 2).
2.4.3 Measuring Arteriovenous Oxygen Difference and De-Oxygenated Hemoglobin:

Peak systemic a-vO$_{2\text{diff}}$ can be calculated using a modified Fick Principle equation (Peak a-vO$_{2\text{diff}}$ [mL·O$_2$/100mL] = VO$_2$peak [L/min]/Qpeak [L/min]. Using this equation to calculate systemic a-vO$_{2\text{diff}}$ has been used in previous exercise research (De Cort et al., 1991; Montero et al., 2015; Murias et al., 2011). Unfortunately, calculating a-vO$_{2\text{diff}}$ may have limitations: firstly, it is an in-direct method to estimate a-vO$_{2\text{diff}}$ quantified using two other measured variables, and secondly, it does not provide information of oxygen extraction within active muscle, but an estimation of systemic oxygen extraction. HHb can be used as a proxy variable for a-vO$_{2\text{diff}}$, as it provides a continuous and absolute measure of oxygen extraction within active muscles. To measure absolute HHb, multi-distance frequency domain near-infrared spectroscopy (NIRS: Oxyplex, ISS Inc., Champaign, IL) can be utilized by passing near-infrared light through the biological tissue to be absorbed by oxygenated hemoglobin (HbO$_2$) or HHb. This is possible as it is able to detect the differences between HbO$_2$ and HHb’s colour wavelengths (850nm and
760nm respectively) (Bhambhani et al., 2001). Additionally, NIRS is a non-invasive way to measure these variables in the active muscle at rest and during exercise (Bailey et al., 2009; Richardson et al., 1999; Soul et al., 1999). Celie et al. (2011) assessed the consistency of the Oxyplex NIRS and discovered that it has a high test-retest reliability. Thus, using NIRS probe at the vastus lateralis during a graded exercise test to exhaustion can provide reliable absolute values of HHb and an estimate of a-VO$_{2\text{diff}}$ within exercising muscle.

2.4.4 Training Response to Central and Peripheral Measures Following SIT:

The precise mechanisms that are responsible for increased VO$_{2\text{peak}}$ following SIT are still unclear. With typical ET, improvements in VO$_{2\text{peak}}$ are primarily associated with increases in Qpeak (Montero et al., 2015; Murias et al., 2011), with these adaptations predominately due to increases in peak SV, rather than peak HR (Blomqvist, 1983). However, the literature examining central adaptations following SIT have garnered equivocal results (Macpherson et al., 2011; Matsuo et al., 2014; Trilik et al., 2011). For instance, Macpherson et al. (2011), found no change in Qpeak after 6 weeks of SIT in young, recreationally active males and females. Conversely, Matsuo et al. (2011) reported that 8 weeks of SIT increased SV (+5.3±8.3%) and decreased HR (-7.1±11.1%) in 14 sedentary males. Lastly, Trilik et al. (2011) observed that 4 weeks of SIT did not change Q at submaximal work rate (50% VO$_{2\text{peak}}$) in overweight, obese women. The study duration of Matsuo et al. (2014) was 8 weeks, compared with 6 (Macpherson et al., 2011) and 4 weeks (Trilik et al., 2011), suggesting that longer training durations of SIT may be required to induce central adaptations. Further research needs to be conducted on larger samples to assess the effect of SIT on central adaptations and how that may influence VO$_{2\text{peak}}$ response.

SIT’s effect on peripheral adaptations is more clear. Typically, increases in VO$_{2\text{peak}}$ have been found to be associated with increases in a-VO$_{2\text{diff}}$ at the group level following SIT.
(Macpherson et al., 2011). Specifically, this improvement in VO$_2$peak is the result of increased oxygen extraction in active muscle (Burgomaster et al., 2008; Gibala et al., 2006; Macpherson et al., 2011; Prieur et al., 2012). For example, Prieur et al. (2012) found an increase in oxygen extraction into the active muscle site (vastus lateralis) when measuring HHb after 6 weeks of SIT in young, sedentary males. This increase in oxygen extraction may be the result of increased capillary density, mitochondrial content and/or muscle oxidative capacity (Burgomaster et al., 2008; Gillen and Gibala, 2013; Scribbans et al., 2014b). Interestingly, SIT can elicit these peripheral adaptations after only 6 sessions of SIT (Burgomaster et al., 2005; Gibala et al., 2006).

2.4.5 Role of Central and Peripheral Adaptations on Heterogeneity of VO$_2$peak Response following SIT:

Unfortunately, no study to date has examined to what extent central and peripheral adaptations determine the magnitude of individual change in VO$_2$peak following SIT. There has been one study that had presented individual responses to central and peripheral measures graphically, but did not discuss the corresponding variability in these measures nor relate it back to individual VO$_2$peak responses (Macpherson et al., 2011).

2.5 Thesis Purpose:

Therefore, the purpose of this thesis were: 1) to examine the inter-individual variability of VO$_2$peak response following four weeks of SIT; 2) to inspect the relationship between changes in both central and peripheral measures and changes in VO$_2$peak; and, 3) to assess if central or peripheral adaptions determine whether an individual is a high or low responder for VO$_2$peak.

2.6 Thesis Hypothesis:

We hypothesize large inter-individual variability of VO$_2$peak responses following four weeks of SIT, which would correspond with previous literature (Astorino et al., 2014; Gurd et al., 2016; Raleigh et al., 2016). We also hypothesize that there will be a strong positive
correlation (r= 0.60 to 1.0) between peripheral adaptations (HHbpeak and a-vO_{2diff}) and VO_{2peak}, and a weak correlation (r=0.10 to 0.29) between Qpeak and VO_{2peak}. Finally, we hypothesize that peripheral adaptations, and not central adaptations, will be significantly greater in the high responders to VO_{2peak} compared with the low responders.
2.7 References:


training in older and young men. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 66(9), 957–964.


Chapter 3: Methods

3.1 Experimental Approach:

To examine the inter-individual variability of the cardiovascular response to SIT, and the relationship between changes in cardiovascular function and changes in VO\(_2\)peak following SIT, participants underwent two separate incremental ramp tests to measure VO\(_2\)peak, Qpeak and HHbpeak at baseline and after SIT. Each SIT training session consisted of eight 20-second intervals targeting 170% of peak work rate (WRpeak), separated by 10 seconds of rest (for a total of four-minutes). Training was performed four times per week for four weeks, for a total of sixteen sessions of SIT (see Figure 3).

Figure 3: Overview of the study design. Where VO\(_2\)peak is peak oxygen uptake (L/min); WR is work rate (W); RPM is revolutions per minute; SIT is sprint interval training; LACEP is Laboratory of Clinical Exercise Physiology; Qpeak is peak cardiac output; HHbpeak is peak de-oxygenated hemoglobin.
3.2 Participants:

Thirty-one healthy, recreationally active, non-smoking men were recruited to participate in this study, but only 22 completed the protocol in its entirety (see Figure 4). Participant characteristics for the individuals who fully completed the study are presented in the results section (Table 2). All participants were male and between 18-30 years old. They participated in no more than 150 minutes per week of structured aerobic physical activity at enrollment. The Health Sciences Human Research Ethics Board at Queen’s University approved this study protocol. Verbal and Written explanation of the experimental protocol and associated risks was provided to all participants prior to obtaining written informed consent.

Figure 4: Flowchart of the number of participants throughout the duration of this study.
3.3 Baseline Testing:

3.3.1 $VO_2\text{peak}$ Incremental Ramp Test:

Participants arrived for the first laboratory visit at the Queen’s Muscle Physiology Lab in the School of Kinesiology and Health Studies in the morning following an overnight fast (~12hrs). Following arrival, approximately 20 mL of venous blood was taken, followed by a resting vastus lateralis muscle biopsy using the Bergstrom needle biopsy technique as we have done previously (Boyd, Simpson, Jung, & Gurd, 2013; Edgett et al., 2013; Gurd et al., 2006; Scribbans et al., 2014; Scribbans et al., 2014b). Biopsy data were used in another analysis and will not be utilized in this study. Immediately following the muscle biopsy, participants consumed a standardized breakfast (toasted bagel [~190 kcal; 1 g fat, 36 g carbohydrate, 7 g protein] with 15 g of cream cheese [~45 kcal; 4 g fat, 1 g carbohydrate, 1 g protein]), and 250mL of Minute Maid orange juice [50kcal; 0g fat, 13g carbohydrate, 1g protein]). Participant’s anthropometric measures (height [cm], and weight [kg]) were then recorded following ingestion of the standardized breakfast. Thirty minutes following breakfast, participants completed a $VO_2\text{peak}$ incremental ramp test to exhaustion on a Monark Ergomedic 874E stationary ergometer (Vansbro, Sweden). The $VO_2\text{peak}$ ramp protocol, has been described previously (Edgett et al., 2013). Briefly, it consisted of a five-minute load less warm-up with a cadence of 80 revolutions per minute (RPM), followed by a step increase to 80 W for one minute and subsequent increases in work rate 25 W per min until participant reached volitional fatigue (determined as the inability of the participant to maintain a minimum cadence of 70 RPM). Gas exchange and heart rate were measured with a metabolic cart (Moxus AEI Technologies, Pittsburgh, PA), and calibrated before each test using a two-point gas calibration (known gas and atmospheric air) and a 3 Litre (L) syringe for volume calibration. Absolute $VO_2\text{peak}$, relative
VO₂peak, peak heart rate (HRpeak) and WRpeak was determined as the highest value of continuous 30 second averages for each measure during the protocol.

### 3.3.2 Cardiovascular Function Tests:

During the second visit, participants completed a progressive cycling exercise to exhaustion at the Laboratory of Clinical Exercise Physiology (LACEP) located at the Kingston General Hospital. This second visit occurred within a week of the muscle biopsy and incremental ramp test and a minimum of 72 hours prior to the start of training. Participants rested on the bike for five minutes prior to beginning of the modified incremental ramp test. After a four-minute baseline measure, the exercise commenced at 40 W at a self-selected RPM and increased 40 W every 4 minutes until 160 W. Following 160 W, exercise intensity increased by 25 W every minute until volitional exhaustion or failure to maintain RPM within 15 rpm of their self-selected RPM.

### 3.3.3 Peripheral Measures:

Prior to the start of the cardiovascular function test participants were fitted with a Near-infrared Spectroscopy (NIRS; Oxyplex, ISS Inc., Champaign, IL) probe over the vastus lateralis on their right leg. The probe was positioned at the point two-thirds from the anterior superior iliac spine to the lateral side of the patella. A latex-free bandage that was secured with tape was used to ensure the probe did not move during exercise and to reduce probe exposure to external light. Oxygenation status of the muscle was recorded continuously throughout exercise until exhaustion. Unfortunately, the NIRS data was not used due to a systematic error. See discussion for more details.

Peak systemic a-vO₂diff was calculated using a modified Fick Principle equation (Peak a-vO₂diff [mL·O₂/100mL] = VO₂peak [L/min]/Qpeak [L/min]. Using this equation to calculate
systemic a-VO_{2\text{diff}} has been used in previous exercise research (De Cort et al., 1991; Murias et al., 2011; Montero et al., 2015).

3.3.4 Central Measures:

To determine Q, the Inert Gas Re-breathing Method (Innocor, Innovision, GbH) was utilized. Participants breathed a mixture of three gases (99.4% oxygen, 0.5% nitrous oxide, and 0.1% sulfur hexafluoride) from a rebreathing bag. The disappearance of nitrous oxide into the blood allowed for the measurement of pulmonary blood flow and therefore Q. The breathing maneuvers were completed five times during the modified ramp protocol; at the end of baseline, and at the end of each 40 W increment up to and including 160 W.

To obtain continuous estimates of Q, and to estimate Q_{peak}, the Finometer (Finapres Medical Systems, The Netherlands) was used. The finometer was positioned on the middle finger of the left hand to measure mean arterial blood pressure and HR throughout exercise. Both arms were supported by clip on Bontrager aerobrars (Trek, Waterloo, WI) to allow the hand to remain in the same position relative to heart level at all times. ModelFlowTM (Finapres Medical Systems, The Netherlands) was used to provide estimates of SV and, with using HR, could thereby compute Q.

3.3.5 Q_{peak} Estimation:

Due to measurement limitations, Innocor was unable to measure Q_{peak} during the modified VO_{2\text{peak}} ramp test. However, in order to obtain valid Q_{peak} measures, both Innocor measures and Finometer estimates of Q were obtained at each submaximal exercise intensity. The relationship between both of these measures were established using a linear regression equation and estimates of Q_{peak} from the Finometer were adjusted accordingly.
3.4 Post-Training Measures:

Post-training measures were conducted in an identical manner as the baseline measures.

3.5 Statistical Analysis:

Group means of all measured variables (pre- to post-training) were compared using paired t-tests (significance accepted at \( p < 0.05 \); see Table 1). Pearson’s Correlations were performed between individual change scores (change from pre- to post-training) of VO\(_2\)peak (dependent variable), and changes in Qpeak and a-VO\(_2\)diff (independent variables).

For the 22 participants who completed all testing, each participant was awarded a score between 1 and 22, corresponding to their ranking in descending order for the magnitude of change in VO\(_2\)peak following training (i.e. the participants with the lowest magnitude of change in VO\(_2\)peak will be awarded a score of one, while the participant with the highest magnitude of change will be awarded a score of 22). These rankings will then be used to form three groups of absolute VO\(_2\)peak response: Low Response Group (LRG) (1-8), Middle Response Group (MRG) (9-14) and High Response Group (HRG) (15-22). Individual VO\(_2\)peak responses, including groupings are presented in Figure 9. A mixed model analysis of variance (ANOVA) was used to examine whether changes in cardiovascular responses were different between all three groups.

The calculation of 2XTE (Hopkins et al, 2000) for absolute VO\(_2\)peak (0.107L/min) was calculated in our lab previously (Bonafiglia et al, unpublished) by recruiting eight recreationally active participants (age, 21.0 ± 0.75 y; VO\(_2\)peak 2.9 ± 0.52 L/min). They reported to the lab on two separate occasions separated by at least a week. On each visit to the lab participants performed identical incremental ramp tests as described above.

All statistical analyses and figures was made using GraphPad Prism v 7.0 (GraphPad Software Inc., La Jolla, CA, USA). Statistical significance was accepted at \( p < 0.05 \), while the
strength of correlational relationships will be defined as weak, moderate and strong ($r = \pm 0.10$ to $\pm 0.29$, $r = \pm 0.30$ to $\pm 0.59$, $r = \pm 0.60$ to $\pm 1.0$, respectively) (Cohen, 1988). All data was presented as means +/- SD, unless otherwise indicated.
3.6 References:


Chapter 4: Results

4.1 Exercise Compliance:

For all participants ($N=22$) analyzed in this study there was a 100% compliance with our training intervention. Participant characteristics are presented in Table 2 below. A flow diagram of the participant selection process is outlined in Figure 6.

Table 2. Participant characteristics ($N=22$) pre and post four weeks of SIT.

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>20.33 ± 1.79</td>
<td>___</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>182.23 ± 6.54</td>
<td>___</td>
</tr>
<tr>
<td>Body Mass (kg)</td>
<td>79.32 ± 10.55</td>
<td>79.19 ± 10.75</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>23.84 ± 2.44</td>
<td>23.79 ± 2.48</td>
</tr>
<tr>
<td>Absolute VO$_2$peak (L/min)</td>
<td>3.78 ± 0.62</td>
<td>4.15 ± 0.54*</td>
</tr>
<tr>
<td>Relative VO$_2$peak (mL/kg/min)</td>
<td>48.65 ± 6.39</td>
<td>53.39 ± 5.99*</td>
</tr>
<tr>
<td>Peak Aerobic Power (W)</td>
<td>278.30 ± 41.83</td>
<td>307.45 ± 46.05*</td>
</tr>
</tbody>
</table>

Note: Values are means with ± Standard deviation in brackets. y, years; cm, centimeters; kg, kilogram; m, meters; L, litres; min, minute; mL, milliteres, W, watts. *Main effect of training, $p <0.001$.

4.2 Near-Infrared Spectroscopy and a-vO2diff:

Due to a systematic error with the NIRS probe throughout the duration of the study, the data collected were not usable to detect between-subject variation (see discussion). It was still able to be utilized in a within subject capacity to detect differences between pre-and post at the group level. To combat this, a-vO$_2$diff calculation was used as a substitute for oxygen extraction measure.
4.3 Variability in Response to SIT:

Individual responses for VO\textsubscript{2}peak (n=22), Qpeak (n=19) and calculated peak a-vO\textsubscript{2}diff (n=19) for all participants following four weeks of SIT are presented in Figure 5. Three participants were excluded from the Qpeak analysis and subsequently a-vO\textsubscript{2}diff calculation due to measurement error. A large range of VO\textsubscript{2}peak response (-4.75 to 32.18% change) was observed including five non-responders (classified using 2XTE). There was a strong positive correlation between the change in VO\textsubscript{2}peak and the change in peak a-vO\textsubscript{2}diff \[r=0.692, p<0.001\]. A significant relationship between the change in VO\textsubscript{2}peak and the change in Qpeak was not present \[r=-0.18, p=0.46\] (See Figure 6).

4.4 High vs Low Response to VO\textsubscript{2}peak:

When comparing the HRG to the LRG, there was a significant interaction effect with respect to VO\textsubscript{2}peak \[f(1, 14)= 64.27, p<0.001\] and Peak a-vO\textsubscript{2}diff \[f(1, 14)= 13.27, p<0.004\] following SIT. A multiple comparisons using Bonferroni correction revealed that this significant interaction occurred between pre- and post-training for the HRG \(t[7]=14.18, p<0.0001\). (See Figure 7). There was no significant interaction observed for Qpeak \(f(1,11)=0.572, p=0.4655;\) Figure 7]. Additionally, the HRG (3.35 L/min) had a significantly lower baseline VO\textsubscript{2}peak compared with the LRG (3.87 L/min) \(t(7)=2.45, p=0.04\). With respect to the MRG, there was a significant difference between pre- and post-training \(t[4]=5.77, p<0.0001\). There were no differences between groups for all other baseline measures (Table 3).

4.5 Group Response to SIT:

There was a significant difference between absolute VO\textsubscript{2}peak at pre-testing (3.78 ± 0.62) and post-testing (4.15 ± 0.54) at the group level \(t[21]=5.63, p<0.0001\). There was also a
significant difference between a-vO$_2$diff pre-testing (18.06 ± 2.30) and post-testing (19.50 ± 2.31) at the group level (t[18]=2.23, p<0.04; See Table 2 and Figure 8). There was no significant difference between Qpeak pre-testing (21.08 ± 3.50) and post-testing (21.69 ± 4.13) at the group level for (t[18]=1.15, p=0.26; see Figure 8).
Figure 5. Individual participant responses to (A) VO$_{2}$peak (mL/kg/min), (B) Qpeak (L/min), and (C) peak a-vO$_{2}$diff (mL•O$_{2}$/100mL) after four weeks of SIT (Change from pre to post-testing). Dotted line in (A) indicates cut off line for non-response (2x Typical Error [0.107 L/min]). This calculation was computed elsewhere by Bonafiglia et al, (Unpublished). No Data (ND) in (B) and (C) indicates unusable participant data for change in Qpeak and thus unable to compute a-vO$_{2}$diff.
Figure 6: Scatterplots showing the relationship between delta (Δ) VO₂peak (A), Δ peak a-VO₂diff and (B) Δ Qpeak.
Figure 7. Difference between groups (Low Response Group [LRG], Mid Response Group [MRG], and High Response Group [HRG]) and time (pre- and post-testing) for (A) VO\textsubscript{2}\text{peak} (L/min), (B) Qpeak (L/min), and (C) a-\text{VO}_2\text{diff} (mL\textcdot}O_2/100mL) following four weeks of SIT. * indicates significant difference between pre and post-training for the MRG and HRG. ** indicates significant difference between LRG and HRG for baseline VO\textsubscript{2}peak.
Figure 8. Group responses to (A) VO₂peak (L/min), (B) Qpeak (L/min), and (C) Peak a-vO₂diff (mL•O₂/100mL) after four weeks of SIT (change from pre- to post-testing). * indicates a significant change from pre- to post-testing (p<0.05). (D) illustrates the mean response from baseline (0 W) to peak exercise for cardiac output (L/min). The pre-responses are shown as open circles, and the post responses are shown as grey squares.
Table 3. Baseline participant characteristics for the Low Response Group (n=8) and High Response Group (n=8).

<table>
<thead>
<tr>
<th></th>
<th>Low Response Group</th>
<th>High Response Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>20.63 ± 1.60</td>
<td>19.75 ± 1.58</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>180.63 ± 6.95</td>
<td>180.56 ± 6.57</td>
</tr>
<tr>
<td>Body Mass (kg)</td>
<td>76.16 ± 10.33</td>
<td>72.69 ± 7.68</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>23.32 ± 2.31</td>
<td>22.28 ± 1.79</td>
</tr>
<tr>
<td>Absolute VO(_2)peak (L/min)</td>
<td>3.87 ± 0.60</td>
<td>3.35 ± 0.46*</td>
</tr>
<tr>
<td>Peak Cardiac Output (L/min)</td>
<td>20.63 ± 3.96</td>
<td>19.47 ± 3.19</td>
</tr>
<tr>
<td>Peak Arteriovenous Oxygen Difference (mL•O(_2)/100mL)</td>
<td>19.14 ± 1.67</td>
<td>16.96 ± 2.60</td>
</tr>
</tbody>
</table>

Note: Numbers in brackets denotes standard deviation. y, years; cm, centimeters; kg, kilogram; m, meters; L, litres; min, minute; mL, milliters, W, watts. *Significant difference between groups p<0.05.
Chapter 5: Discussion

5.1 Summary of Key Findings:

The objectives of this thesis were: 1) to examine the inter-individual variability of VO$_2$peak response following four weeks of SIT; 2) to inspect the relationship between changes in both central and peripheral measures and changes in VO$_2$peak; and, 3) to assess if central or peripheral adaptions determine whether an individual is a high or low responder for VO$_2$peak. In accordance with these objectives, the major findings were: 1) there was inter-individual variability in the response to VO$_2$peak following SIT; 2) the variability in VO$_2$peak response did not appear to be determined by central adaptations and may be instead driven by peripheral adaptations.

5.2 Variability in VO$_2$peak Response Following SIT:

In our study, there was a main effect of training after SIT at the group level. This coincides with previous studies (See Table 1) that also used the Tabata protocol as the form of SIT training (Ma et al., 2013; Tabata et al., 1999). However, we found that on an individual level, four weeks of SIT resulted in inter-individual variability in the VO$_2$peak response. This variability is indicated by both the range of VO$_2$peak response among individual participants from pre to post testing (-4.75 to 32.18% change) and the significant difference between the LRG (n=8) and the HRG (n=8) (Figure 9). These results are consistent with past studies that addressed inter-individual variability in VO$_2$peak response following SIT (Astorino et al., 2014; Gurd et al., 2016; Raleigh et al., 2016). For instance, Astorino et al. (2014) retroactively examined variability of response to VO$_2$peak in 20 recreationally active men and women following two weeks of SIT and reported a similarly large range of VO$_2$peak response (0 to 20%).

A non-responder is defined as an individual who demonstrates an unchanged response in a
given variable following exercise training (Mann et al., 2014; Sisson et al., 2009). Using a statistically sound cut off point (Two times typical error of measurement [2XTE]; Hopkins et al., 2000) allowed us to differentiate between a random change and a true physiological response with a high degree of confidence. An unchanged response to VO$_2$peak in our study was defined as a change in VO$_2$peak falling within ±0.107 L/min (2XTE; Bonafiglia et al., unpublished). The rate of non-response following SIT, using 2XTE, has been previously addressed in our lab (Gurd et al, 2016; Raleigh et al., 2016). When applying this calculation to individual responses following various protocols to SIT (from five previous studies), 14 out of 63 (~22%) individuals were classified as non-responders. Interestingly, the rate of response was reduced to zero when training frequency was increased to four days a week from three. In contrast to this finding, the current study employed SIT four times per week but resulted in a non-response rate to VO$_2$peak of ~22%. Both previous studies that saw zero non-responders after employing SIT four times per week (Ma et al., 2013; Scribbans et al., 2014b), implemented the same protocol (Tabata) and recruited participants with similar fitness patterns as this study; thus the discrepancy between our results may be due to a larger sample size of 22 participants in the current study, compared with only eight (Ma et al., 2013) and ten (Scribbans et al., 2014b) participants studied previously.

The variability of response seen in our study could also be explained by differences in the distribution of baseline characteristics. The HRG had a significantly lower baseline VO$_2$peak value compared with the LRG (Table 3). Although, baseline VO$_2$peak between groups may contribute to the difference in response rates between the current study and previous SIT studies utilizing a training protocol consisting of four training sessions per week, it still does not give any indication of the physiological mechanisms that may be responsible for said difference in VO$_2$peak between groups.
5.3 Central Adaptation’s Role in VO$_2$peak Response Following SIT:

To our knowledge, this is the first study that addressed Qpeak’s influence on inter-individual variability of response following SIT. Interestingly, we observed no relationship between individual changes in Qpeak and VO$_2$peak, nor was there any difference in the change in Qpeak between the LRG and the HRG (Figure 9) following four weeks of SIT. This suggests that the variability in VO$_2$peak response following four weeks of SIT was not determined by central adaptations. This idea of central adaptations not influencing VO$_2$peak following SIT aligns with previous findings that Qpeak is not increased at the group level following SIT (Jacobs et al., 2013; Macpherson et al., 2011). In a study addressing the effects of SIT in a similar population as ours (young, recreationally active individuals), Macpherson et al. (2011) found that six weeks of SIT did not result in an appreciable change in Qpeak (24.5±1.2 to 24.4±1.2 L/min).

Increases in central adaptations may be more likely to manifest following longer durations of lower intensity interval training (eg. HIIT) (Daussin et al., 2007; Daussin et al., 2008; Matuso et al., 2014; Wisloff et al., 2009). For example, Daussin et al., (2008) found a significant increase in Qpeak (17.5±1.3 to 19.5±1.8 L/min; P < 0.01) following eight weeks of HIIT (90% peak power). Matsuo et al. (2014) also found increases in central adaptations using HIIT over eight weeks, double the length of our study. In the Matuso et al. (2014) investigation, central adaptations were evidenced by increases in LV mass, an indication of SV adaptation. It is important to note, that along with having increased durations (eight weeks vs. four weeks), both of the aforementioned protocols implemented longer submaximal intervals compared with our SIT protocol. Increasing the length of the intervals, and thus the volume of exercise, may be
crucial to effectively stimulate the heart and induce adaptations needed to increase oxygen delivery via increased cardiac output (Blomqvist, 1983).

5.4 Peripheral Adaptation’s Role in VO$_2$peak Response Following SIT:

Adaptations in VO$_2$peak following four weeks of SIT were not due to improvements in central adaptations, suggesting that individual differences in changes in VO$_2$peak are not the result of increases in bulk oxygen delivery to the active muscle. This suggests that increases in oxygen extraction (peripheral adaptations) may be responsible for variability in the VO$_2$peak response. This contention is consistent with our hypothesis that the HRG would have greater peripheral adaptations compared with the LRG.

Unfortunately, there was a large systematic error with the near-infrared spectroscopy (NIRS) probe used throughout the duration of the current study. Specifically, at the completion of data collection, the corresponding NIRS data did not make physiological sense, prompting us to test the validity of the specific NIRS probe from our study. This was done by recruiting three participants to partake in ischemic forearm exercise to exhaustion on two separate occasions. The first visit used the NIRS probe from our study while the second visit used a different NIRS probe that had been previously validated. The results of this test demonstrated that the NIRS probe from our study had largely underestimated HHb and that the underestimation varied from individual to individual due to degree of calibration. We were unable to use the NIRS probe data to differentiate individual response of oxygen extraction into the active muscle following SIT, nor were we able to use this data on a group level, and thus were excluded from analysis.

In response to the NIRS probe not working, a-VO$_2$diff was calculated using a derivation of the Fick equation, as done previously (Duassin et al, 2007; Daussin et al, 2008; Macpherson et al, 2011). Interestingly, there was a significant correlation between the changes in VO$_2$peak and
peak $a$-$vO_{2\text{diff}}$ (Figure 8) and a significant interaction was seen between the HRG and LRG (Figure 9). This corresponds with a previous study (Macpherson et al., 2011) wherein six weeks of SIT induced significant changes in peak $a$-$vO_{2\text{diff}}$ at the group level. Calculating $a$-$vO_{2\text{diff}}$ using the Fick equation has limitations (see strengths and limitations section below), therefore, future studies should implement more direct measures of oxygen extraction at the active muscle site. These results suggest that differences in peripheral adaptation explain why some individuals demonstrate an increase in VO$_2$peak following SIT and others do not. This is consistent with literature demonstrating that peripheral adaptations are primarily responsible for group improvements in VO$_2$peak following SIT (Burgomaster et al., 2008; Gist et al., 2013; Scribbans et al., 2014b). While our findings do not specify what factor is responsible for the increased $a$-$vO_{2\text{diff}}$, it could be due to increases in capillary density (Scribbans et al., 2014b), mitochondrial content and function (Jacobs et al., 2013), and/or oxidative capacity (Burgomaster et al., 2008).

5.5 Study Strengths and Limitations:

One of the main strengths to this thesis was being the first to address potential mechanisms that may explain inter-individual variability of VO$_2$peak response following SIT. An additional strength was using a statistically sound cut off point to classify non-response as using 2XTE accounted for both biological and technical error within our own machine that we used to assess VO$_2$peak (Bonafiglia et al. unpublished; Hopkins et al. 2000). Furthermore, using the submaximal relationship between the Innocor’s gold standard measure of Q and Modelflow’s continuous estimation of Q (Finometer) to provide a reliable and valid measure of Qpeak was also a strength.

The primary limitation with the current work was our inability to explain inter-individual variability of VO$_2$peak response using our central and peripheral measures. This may be due to
the systematic error with the NIRS probe, which inhibited us from differentiating between individual responses. Had the NIRS probe been functioning properly, it would have provided an absolute value of oxygen extraction at the active muscle site during the graded exercise test. To counteract this, we calculated peak a-vO$_{2\text{diff}}$ derived from the Fick equation. However, the Fick equation does not provide the same accuracy as NIRS and there are limiting factors associated with the equation: firstly, it is an indirect method to estimate a-vO$_{2\text{diff}}$ quantified using two other measured variables; and secondly, it does not provide information on oxygen extraction to the active muscle site, but instead provides an estimate of systemic oxygen extraction.

Lastly, we were unable to use an objective measure to account for habitual physical activity (external energy expenditure) throughout the duration of the study intervention. This was due to time constraints and feasibility issues. We obtained baseline habitual physical activity habits using the 7-day Physical Activity Recall (PAR) and 1-year physical activity questionnaire and asked participants to maintain the same physical activity habits throughout the duration of the study. It is possible that changes in external physical activity may have influenced the VO$_{2\text{peak}}$ response across individuals as we did not measure each individual’s external energy expenditure when they were not in our lab.

5.6 Future Directions:

Future studies should not only give an indication of muscle oxygen extraction using reliable and validated methods (NIRS), but to expand the peripheral measures (ie. capillary density, mitochondrial content and oxidative capacity) to try to elucidate how the muscle is utilizing oxygen. In doing so, this may help unravel the precise mechanisms responsible for individual heterogeneity of VO$_{2\text{peak}}$ response following SIT. Additionally, increasing the
sample size could potentially increase the number of non-responders in the LRG and therefore it could be grant a statistically sound comparison between non-responders and high responders.

Furthermore, future studies should increase the duration of the SIT protocol to test the hypothesis that performing SIT for longer durations elicits greater central adaptations. In order to try and pin point when these adaptations will occur, it may be beneficial to measure outcomes at specific intervals throughout the training intervention.

Lastly, studies should examine how participant characteristics (age, sex, race, and ethnicity) and habits (external energy expenditure) influence inter-individual variability of response following SIT. Understanding how these characteristics and habits effect VO$_2$peak response may further help with optimizing exercise prescription.

5.6 Conclusions:

After four weeks of SIT, we found that there was a large inter-individual variability in the response to VO$_2$peak. This variability in VO$_2$peak response did not appear to be determined by central adaptations, but instead may be in response to increases in peripheral adaptations. This coincides with our initial hypotheses, but due to measurement issues, we are unable to precisely explain inter-individual variability of VO$_2$peak response following SIT. Future studies need to incorporate more measures for peripheral oxygen extraction, increase sample size and prolong the study durations. By doing so, the potential mechanisms that explains individual magnitude of response may be further understood. This could allow for better optimization for prescribing exercise to individuals who are classified as non-responders to SIT.
5.7 References:


Chapter 6: Appendices

Appendix A: Ethics Form

QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD

March 22, 2010

Dr. R. Gurd
School of Kinesiology and Health Studies
Queen's University

Dear Dr. Gurd,

Study Title: Effect of exercise training at a variety of intensities on mitochondrial function in young lean and obese adults

The members of the Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board have examined the protocol, questionnaires and the revised consent form for your project (as stated above) and consider it to be ethically acceptable. This approval is valid for one year from the date of the Chair’s signature below. Please attend carefully to the following list of ethics requirements you must fulfill over the course of your study:

- Reporting of Amendments: If there are any changes to your study (e.g. consent, protocol, study procedures, etc.), you must submit an amendment to the Research Ethics Board for approval. (see http://www.queensu.ca/vpr/reb.htm).
- Reporting of Serious Adverse Events: Any unexpected serious adverse event occurring locally must be reported within 2 working days or earlier if required by the study sponsor. All other serious adverse events must be reported within 15 days after becoming aware of the information.
- Reporting of Complaints: Any complaints made by participants or persons acting on behalf of participants must be reported to the Research Ethics Board within 7 days of becoming aware of the complaint. Notice: All documents supplied to participants must have the contact information for the Research Ethics Board.
- Annual Renewal: Prior to the expiration of your approval (which is one year from the date of the Chair’s signature below), you will be reminded to submit your renewal form along with any new changes or amendments you wish to make to your study. If there have been no major changes to your protocol, your approval may be renewed for another year.

Yours sincerely,

[Signature]
Chair, Research Ethics Board

Date: March 22, 2010

Study Code: PHE-100-10

Investigators please note that if your trial is registered by the sponsor, you must take responsibility to ensure that the registration information is accurate and complete.
Appendix B: Subject Recruitment and Information Forms

Sample Recruitment form displayed in bulletin boards and television monitors around Queen’s University Campus. Including the School of Kinesiology and Health Studies, Athletic and Recreation Centre, and John Deutsch University Centre

The MEGA Study

The Muscle Biochemistry Lab at Queen’s is interested in measuring health outcomes after Sprint Interval Training

Are you?
• Recreationally Active (Less than 3hrs of structured physical activity)
• Lean male between the ages of 18-30 (Pant size less than 36)
• No history of cardiovascular and metabolic diseases (stroke, hypertension, type II diabetes)
• Not currently taking prescribed medication
• A non-smoker

$100 compensation and Free personal training to meet your New Years Resolutions!

This study involves four weeks of supervised training, muscle biopsies, and Cardiovascular Fitness Testing.

Email Matthew Giles at 9mdg2@queensu.ca for more information!
Physical Activity Readiness Questionnaire was completed by all subjects prior to subject screening.
Consent to Volunteer for Participation in a Study

TITLE: Effect of central and peripheral adaptations on the variability of response to aerobic capacity following sprint interval training

PRINCIPAL INVESTIGATOR: Brendon J. Gurd, PhD
Queen’s University
School of Kinesiology and Health Studies
Kingston, Ontario, K7L 3N6
613-533-6000 ext. 79023

You are being invited to participate in a study examining the influence of different exercise protocols that vary in intensity (difficulty), duration (length) and mode (type) on mitochondrial function (the ability of your muscle to produce energy) and exercise capacity. This study will also compare the effects of these different exercise protocols in young adults who are either lean or overweight. You have been invited to participate in this study because you are a young adult (20-40 years) who is either lean (waist circumference <86 cm) or overweight (waist circumference >94 cm). The following brief is intended to provide you with the details you should be aware of prior to your consent as a participant in this study. Please read the following information carefully and feel free to ask any question that you may have.

BACKGROUND INFORMATION

Exercise capacity (Fitness) is an important predictor of long term health. More specifically, the ability of your heart and cardiovascular system to deliver oxygen, and your muscle’s mitochondria to produce energy (mitochondrial function) can be
impaired with obesity and is a predictor of both further weight gain and development of type II diabetes. Further, fat cells also contain mitochondria, and decreased mitochondrial function in fat is also associated with weight gain and the development of disease. In healthy active populations interval training (repeated bouts of exercise separated by periods of recovery) is a potent, time effective stimuli for increasing mitochondrial function and exercise capacity. In addition, recreational activity is recommended as part of a healthy lifestyle, however its effects on the heart, the cardiovascular system and mitochondrial function and exercise capacity are unknown. This study will examine the ability of different exercise training protocols and modes (cycling, running, whole body exercise or recreational games [i.e. sport]) to improve heart, cardiovascular system and mitochondrial function and exercise capacity. We will also ask you a series of questions designed to increase our understanding of what type of exercise you would prefer and/or are likely to perform during your normal daily routine.

You will not be able to participate in the study if you have been diagnosed previously with any respiratory, cardiovascular (e.g. High blood pressure, heart conditions), metabolic (e.g. Diabetes), neurological or musculoskeletal disease; or you are currently on medication; or you are a smoker; or you respond to the exercise protocol in an irregular manner (i.e. chest pains, dizziness, shortness of breath, excessive awareness of breathing).

EXPLANATION OF PROCEDURES

Participation
Participation in the study is voluntary. You may refuse to participate or withdraw from the study at any time with no effect on your academic or employment status. Should you choose to participate you will take part in experimental procedures outlines below. These include exercise tests, physiological tests, and one of a selection of exercise training protocols. The investigator will explain to you, in detail how each of these procedures will be conducted in the study in which you have agreed to participate.

The majority of the procedures described below, and all exercise training will take place within the Muscle Physiology Lab at the School of Kinesiology and Health Studies. Measurement of muscle oxygenation and cardiac output will be performed in the Laboratory of Clinical Exercise Physiology located within Kingston General Hospital.
**Exercise tests:**
During each of the exercise tests you will be required to wear a nose-clip (to prevent you from breathing through your nose) and a rubber mouthpiece (similar to breathing through a snorkel or diving mask). This will enable us to measure the volume of air that you breathe in and out, and measure the gas concentration in that air. You may experience some initial discomfort from wearing the nose-clip and mouthpiece. You will also be required to wear a heart rate monitor around your chest during all tests. You will be asked to perform each of these tests on one occasion before and one occasion following exercise training.

**Incremental exercise test:** This test is performed on either a cycle ergometer (a stationary bike) or a treadmill and is designed to measure your fitness level. During this test the intensity of exercise increases gradually until you are physically unable to continue exercising because the intensity is either too high or too uncomfortable. The test will begin with the exercise intensity being very light and easy (very little resistance). After a few minutes the exercise intensity will gradually and continuously increase until you are unable to continue because of fatigue, or until you wish to stop.

**Psychological Questionnaires:**
On the first visit, prior to the VO\textsubscript{2}peak test, you will be required to fill out a series of questionnaires designed to determine the amount of physical activity you regularly perform and to predict whether or not you will enjoy high intensity exercise. It is expected that these questionnaires will take less than 30 minutes to complete.

In addition, during training sessions of this study you will be asked a series of questions designed to evaluate how you are feeling towards the exercise you are performing.

Finally, following the exercise protocol you will be asked to fill out a series of questionnaires designed to determine how much you enjoyed the exercise and how likely you are to part-take in exercise in the future. These final questionnaires should also take less than 30 minutes to complete.

All results from these questionnaires will be kept private and will be recorded in an anonymous fashion (i.e. by subject number rather than by name).

**Physiological tests:**
**Blood sample:** Both before and following training you will be asked to have a small sample of blood taken. You may experience some minor discomfort when this small blood sample is drawn from a vein in your arm. The blood
sampling may be painful and minor bruising is possible following venous blood sampling but generally fades within a few days.

**Muscle Biopsy:** Before and after training you will also be asked to have small amounts of muscle removed from your thigh muscle (quadriceps muscle) by means of a needle biopsy. The muscle biopsies will be taken by a medical doctor or by an individual trained in the technique under the supervision of a medical doctor. While you are resting on a bed, an anesthetic will be applied locally to anesthetize the skin over your thigh muscle at the sites where the biopsies will be taken. A small incision (less than 1 cm each) will be made through your skin and into your muscle at points approximately midway between your hip and knee. Small samples of muscle will be taken from each incision. This procedure is referred to as a biopsy.

There may be some discomfort associated with the biopsy procedure (like someone pressing hard into your muscle) but you should experience no pain. Following the exercise there may be light bruising of the leg muscle but this will generally fade within a couple of days. There is also a slight risk of infection following a biopsy but proper sterilization of equipment and cleaning of the sampled area minimizes this risk. If the site of the muscle biopsy becomes more tender and redness and/or swelling develops in that area over the next five to seven days you should seek medical attention immediately. You should also report this change to the research person supervising your study as soon as possible. Please refer to the Muscle Biopsy Information Sheet for more information regarding this procedure.

**Measurement of Muscle Oxygenation:** Before and after training you will be asked to have the changes in muscle oxygenation measured during an incremental exercise test (described above). Muscle oxygenation, a measure of how much blood is being delivered by your cardiovascular system to your muscle, is measured by a sensor that will be strapped to your leg and that uses infra-red light (near infra-red spectroscopy) measure tissue oxygenation. This process is a non-invasive, optical (light-based) method with no reported side-effects related to its use in humans.

**Cardiac Output Evaluation:** Before and after training you will be asked to have the amount of blood pumped by your heart each beat (cardiac output) measured during an incremental exercise test (described above). To measure cardiac output a mixture of gases (oxygen, hexafluoride, and nitrous oxide) will be given to you through the same mouthpiece used to measure oxygen uptake at pre-selected points during exercise. These gases are harmless and they do not change your blood oxygen levels, cause discomfort, or cause shortness of breath. We will advise you when these gases will be switched on.
and you will breathe them for 5 breaths. You will also know when you are breathing this mixture because a bag in front of you will inflate and deflate as you exhale and inhale. Minimal coaching on breathing rate (“breathe a little faster” or “breathe a little slower”) may be provided during this measurement. There are no reported complications or side effects from completing this procedure.

**Exercise Training Protocols:**
Any exercise carries a slight risk of heart attack or may be uncomfortable if you are unfit or not used to exercise. The risk of a cardiac event (heart attack, dysrhythmias etc.) in a mixed subject population (healthy low risk and unhealthy high risk patients together) is approximately 6:10 000, however this risk decreases in a previously healthy (i.e. young, moderately active) population. There may be some minor discomfort during the exercise testing. You may experience increased awareness of breathing, muscle pain and/or fatigue, increased sweating, or a general feeling of fatigue or nausea, all of which are not unexpected consequences of exercise. You are being asked to participate in one of the following exercise training programs. The investigator will explain to you exactly what is involved in the specific protocol you are being assigned to. Please initial beside the box that is checked.

- [ ] **High-intensity exercise training:** This protocol involves riding a bike at a high-intensity, like an all-out sprint, for 20 seconds at a time (called an interval) followed by 10 seconds of rest. This interval will be repeated 8 times. You will be asked to perform these protocols 4 times a week for a period of 4 weeks.
RISK OF INJURY

All exercise also carries a small risk of personal injury. Should any such injury occur during your participation in this study you will be initially cared for by the study administrators, all of whom are certified in first aid. Should further assistance be required you will be taken to the university health centre/hospital or emergency as required.

POTENTIAL BENEFITS OF PARTICIPATION

You will gain no direct benefit through participation in this study.

CONFIDENTIALITY

During the course of your participation in this study you will not be required to provide any personal information beyond your name and phone number (for study purposes only). All information obtained during the course of this study, including your name and fitness results, is strictly confidential and your anonymity will be protected at all times. Your information will be kept in locked files and will be available only to Dr. Brendon Gurd and those working within his laboratory. Your identity will not be revealed in any description or publication. By signing this consent form, you do not waive your legal rights nor release the investigator(s) and sponsors from their legal and professional responsibilities.
VOLUNTARY CONSENT
I have been given an opportunity to ask any questions concerning the procedures. All of my questions regarding the research project have been satisfactorily answered. I understand that my test results are considered confidential and will never be released in a form that is traceable to me. I do understand that I am free to deny consent if I so desire, and may withdraw from the study at any time without any effect on my academic or employment status. Should I have any questions about the study, I know that I can contact Dr. Brendon Gurd (613 533-6000, ext 79023), Dr. Jean Coté, Head, School of Kinesiology and Health Studies (613 533-6601). If you have any concerns about your rights as a research participant please contact Dr. Albert Clark, Chair for the Queen’s University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board (613 533-6081). A copy of this consent form will be provided me for my records. My signature below means that I freely agreed to participate in this study.

Volunteer’s Signature

Date

STATEMENT OF INVESTIGATOR
I, or one of my colleagues, have carefully explained to the subject the nature of the above research study. I certify that, to the best of my knowledge, the subject understands clearly the nature of the study and demands, benefits, and risks involved to participants in this study.

Principal Investigator’s Signature

Date
7-Day Physical Activity Recall Questionnaire

**Physical Activity Recall** Day this form was completed: Mon - Tues - Wed - Thurs - Fri - Sat - Sun
Date (DD/MM/YY) : __________

1. Were you employed in the last seven days (paid or volunteer)? □ Yes □ No  ➔ Go to Question # 4
2. How many days of the last seven did you work? _____ (round to the nearest day)
3. How many total hours did you work in the last seven days? _____ (hours)
4. What days of the week do you consider to be your weekend or non-work days? For most people, this would be Saturday and Sunday, but it may be different for you.

   - □ Sunday
   - □ Monday
   - □ Tuesday
   - □ Wednesday
   - □ Thursday
   - □ Friday
   - □ Saturday

************ Explain Moderate, Hard, and Very Hard Intensity level ************

At the end of the interview:
5. Compared to your physical activity over the past three months, was last week’s physical activity more, less or about the same?

   - □ More
   - □ Less
   - □ Same

Participant ID: __________________________ Interviewer: __________________________

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Rounding of time: 10-22min = 0.25 hrs  23-37min = 0.5 hrs  38-52min = 0.75 hrs  53-1:07 min = 1 hr  1:02-1:22 = 1.25 hrs

Participant ID: __________________________ Interviewer: __________________________
Appendix C: Sample Finometer Output

Sample output from Finometer and ModelFlowTM (Finapres Medical Systems, The Netherlands)