Do Clinical Exercise Tests Permit Exercise Threshold Identification in Patients Referred to Cardiac Rehabilitation?

Randi R. Keltz, The University of Western Ontario

Supervisor: Keir, Daniel A., School of Kinesiology, University of Western Ontario, London, Ontario, Canada; Lawson Health Research Institute, London, Ontario, Canada; Toronto General Research Institute, Toronto General Hospital, Toronto, Ontario, Canada.

A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Kinesiology

© Randi R. Keltz 2023

Follow this and additional works at: https://ir.lib.uwo.ca/etd

Part of the Cardiovascular Diseases Commons

Recommended Citation
https://ir.lib.uwo.ca/etd/9393

This Dissertation/Thesis is brought to you for free and open access by Scholarship@Western. It has been accepted for inclusion in Electronic Thesis and Dissertation Repository by an authorized administrator of Scholarship@Western. For more information, please contact wlswadmin@uwo.ca.
Abstract

The purpose of this thesis was to quantify the proportion of patients whose clinical cardiopulmonary exercise test (CPET) permitted identification of estimated lactate threshold ($\theta_{LT}$) and respiratory compensation point (RCP) and to characterize the variability at which these thresholds occur to evaluate the feasibility of “threshold-based” aerobic exercise prescription. We retrospectively analyzed CPET data of 1102 patients (65±12 yrs; 306 females) referred to cardiac rehabilitation. $\theta_{LT}$ and RCP were identified and reported as oxygen uptake ($\dot{V}O_2$), heart rate (HR), $\%\dot{V}O_{2\text{peak}}$, and $\%HR_{\text{peak}}$. Patients were grouped by threshold identification: group 0) neither $\theta_{LT}$ nor RCP (n=556; 50%); 1) $\theta_{LT}$ only (n=196; 18%); 2) both $\theta_{LT}$ and RCP (n=350; 32%). Compared to group 1, $\theta_{LT}$ in group 2 occurred at a higher $\dot{V}O_2$ and HR, but lower $\%\dot{V}O_{2\text{peak}}$ and $\%HR_{\text{peak}}$ (p<0.05). Only 32% of CPETs exhibited both thresholds. Therefore, contemporary CPET protocols may not be optimal to employ “threshold-based” aerobic exercise prescription.

Keywords

Cardiopulmonary exercise test, estimated lactate threshold, respiratory compensation point, oxygen consumption, exercise intensity domains, aerobic exercise prescription, exercise training, cardiac rehabilitation
Summary for Lay Audience

Exercise is an important part of managing diseases that affect the heart. When people are diagnosed with heart disease, they are often referred to a cardiac rehabilitation program to perform supervised aerobic (“cardio”) exercise training. At the start of these programs, patients perform an exercise test. These tests are used to assess how good a patient’s aerobic fitness is, and to determine how hard they will work (or “intensity”) on a treadmill or stationary bike during their exercise training program. Current guidelines recommend that patients exercise at a fraction of maximal effort achieved during their first exercise test (e.g., training intensity = 50% of maximal effort). This approach assumes that exercising at the same fraction of maximal effort will feel the same in all patients. A recent statement from European, American, and Canadian cardiac rehab groups suggested that a better way to set exercise training intensity is to separate it into three “domains” (moderate, heavy, and severe) based on two “thresholds” that are seen during exercise. In this thesis, we reviewed over 1000 exercise tests performed by patients referred to cardiac rehab to see how many of these tests showed one threshold, both thresholds, or neither of them. We also compared the fraction of maximal effort where these thresholds occurred between patients. We found that half (50%) of the tests we looked at showed at least one threshold, but only about one-third (32%) of the tests showed both thresholds. This may mean that the exercise tests used in modern cardiac rehab settings may not be designed well enough to allow clinical staff to identify both thresholds. Additionally, we found that in the group of patients showing both thresholds, the fraction of maximal effort where these thresholds occurred was very different between patients. This means that we cannot assume that exercise performed at the same fraction of maximal effort will feel the same in all patients referred to cardiac rehab.
Co-Authorship Statement

This dissertation was completed by Randi Keltz, under the supervision of Dr. Daniel Keir. Dr. Glen Belfry and Dr. Marc Mitchell were members of the thesis advisory committee. Data were collected at the St. Joseph’s Health Care Cardiac Rehabilitation and Secondary Prevention Program by Tim Hartley and Dr. Neville Suskin, and exported by Tim Hartley, Rojin Gharaezibaei, and Randi Keltz. Data analysis and manuscript writing were completed by Randi Keltz and Dr. Daniel Keir.

The manuscript in Chapter 2, titled “Do clinical cardiopulmonary exercise tests permit exercise threshold identification in patients referred to cardiac rehabilitation?”, was co-authored by Tim Hartley, Dr. Ashlay Huitema, Dr. Robert McKelvie, Dr. Neville Suskin, and Dr. Daniel Keir.
Acknowledgments

First and foremost, I would like to thank my supervisor Dr. Daniel Keir for his mentorship and copious support over the past two years. Without his guidance and endless feedback, this dissertation and my academic abilities would not be what they now are. I would also like to thank Tim Hartley for his boundless generosity to share in his expertise and knowledge.

To the other members of DAKei lab – Robin Faricier, Nasimi Guluzade, Joshua Huggard, and Lorenzo Micheli – I am grateful for your collaboration, support, and our time together. Thank you to Nasimi, especially, for his statistical wisdom and willingness to share in his skill.

Lastly, I would like to say a special thank you to everyone at St. Joseph’s Cardiac Rehabilitation and Secondary Prevention program. I have greatly appreciated the opportunity to collaborate with and learn from many talented individuals on the care team, namely, Dr. Neville Suskin and Dr. Robert McKelvie.
# Table of Contents

Abstract .......................................................................................................................... ii

Summary for Lay Audience .......................................................................................... iii

Co-Authorship Statement ............................................................................................... iv

Acknowledgments ........................................................................................................... v

Table of Contents .......................................................................................................... vi

List of Tables .................................................................................................................. viii

List of Figures ................................................................................................................ ix

List of Abbreviations ...................................................................................................... x

List of Appendices ......................................................................................................... xii

Chapter 1 ........................................................................................................................... 1

1 Literature Review ........................................................................................................... 1

  1.1 Heart Disease in Canada .......................................................................................... 1

  1.2 Exercise, Aerobic Fitness, and Heart Disease .......................................................... 1

  1.3 Cardiac Rehabilitation Programs in Canada ........................................................... 3

      1.3.1 “Responsiveness” to Exercise-Based Cardiac Rehabilitation ......................... 4

  1.4 Exercise Prescription Based on “Maximal” Variables ............................................. 5

  1.5 Exercise Thresholds: A Submaximal Alternative? .................................................. 6

  1.6 Purpose ................................................................................................................... 9

  1.7 References ............................................................................................................. 10

Chapter 2 .......................................................................................................................... 15

2 Do clinical exercise tests permit exercise threshold identification in patients referred to cardiac rehabilitation? ................................................................. 15

  2.1 Introduction ............................................................................................................. 15

  2.2 Methods ................................................................................................................ 17

      2.2.1 Study Design ................................................................................................. 17
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.2.2 Participants</td>
<td>17</td>
</tr>
<tr>
<td>2.2.3 CPET</td>
<td>18</td>
</tr>
<tr>
<td>2.2.4 Data Analysis</td>
<td>18</td>
</tr>
<tr>
<td>2.2.5 Statistical Analysis</td>
<td>20</td>
</tr>
<tr>
<td>2.3 Results</td>
<td>20</td>
</tr>
<tr>
<td>2.4 References</td>
<td>28</td>
</tr>
<tr>
<td>Chapter 3</td>
<td>31</td>
</tr>
<tr>
<td>3 Discussion</td>
<td>31</td>
</tr>
<tr>
<td>3.1 Limitations</td>
<td>35</td>
</tr>
<tr>
<td>3.2 Conclusions</td>
<td>35</td>
</tr>
<tr>
<td>3.3 Future Directions</td>
<td>36</td>
</tr>
<tr>
<td>3.4 References</td>
<td>37</td>
</tr>
<tr>
<td>Appendix</td>
<td>39</td>
</tr>
<tr>
<td>Curriculum Vitae</td>
<td>40</td>
</tr>
</tbody>
</table>
List of Tables

Table 2.1: Patient characteristics and CPET data for each of the three groups. ..................... 22
List of Figures

Figure 1.1: Breath-by-breath ventilatory and gas exchange cardiopulmonary exercise test (CPET) data of a representative participant. Green area signifies the moderate intensity domain (i.e., exercise below estimated lactate threshold [θ_LT]), blue area signifies the heavy intensity domain (i.e., exercise between θ_LT and respiratory compensation point [RCP]), and red area signifies the severe intensity domain (i.e., exercise above RCP). .......................... 8

Figure 2.1: Frequency distributions of peak oxygen uptake ([VO_2peak], A: mL·min^{-1}; B: mL·kg^{-1}·min^{-1}; C: %predicted) and peak heart rate ([HR_{peak}], D) in the total sample (n = 1102). .......................................................... 21

Figure 2.2: Frequency distributions of estimated lactate threshold (θ_LT) in group 1 (i.e., patients in which only θ_LT, and not respiratory compensation point [RCP], was identified) (A: %VO_2peak; C: %HR_{peak}), and θ_LT and RCP in group 2 (i.e., patients in which both θ_LT and RCP were identified) (B: %VO_2peak; D: %HR_{peak}). .......................................................... 24

Figure 2.3: Frequency distributions of estimated lactate threshold (θ_LT) (A: mL·min^{-1}; B: %VO_2peak; C: %HR_{peak}) in group 1 (θ_LT-G1, i.e., patients in which only θ_LT, and not respiratory compensation point [RCP], was identified) and group 2 (θ_LT-G2, i.e., patients in which both θ_LT and RCP were identified). * indicates a difference (p < 0.05) in θ_LT between groups.... 25

Figure 2.4: Distribution of patients (group 2; n = 350) within the moderate (yellow), heavy (orange), and severe (red) exercise intensity domains at a given %̇VO_2peak (A) and %HR_{peak} (B). Blue borders represent international guideline-recommended aerobic exercise training intensities for cardiac rehabilitation patients. .......................................................... 26

Figure 2.5: Distribution of patients (group 2; n = 350) within the moderate (yellow), heavy (orange), and severe (red) exercise intensity domains, within each of the four “training zones” outlined for exercise intensity prescription in the current European Society of Cardiology guidelines that are based on %̇VO_2peak (A) and %HR_{peak} (B) 8. ................................................. 27
List of Abbreviations

θLT – Estimated lactate threshold

BF – Breathing frequency

BFpeak – Peak breathing frequency

BMI – Body mass index

CAD – Coronary artery disease

CHF – Chronic heart failure

CPET – Cardiopulmonary exercise testing

CR – Cardiac rehabilitation

CV – Coefficient of variation

ESC – European Society of Cardiology

HF – Heart failure

HF-ACTION – Heart Failure: A Controlled Trial Investigating Outcomes of exercise training

HR – Heart rate

HRpeak – Peak heart rate

METS – Metabolic equivalents

PETCO2 – End-tidal partial pressure of CO2

PETO2 – End-tidal partial pressure of O2

RCP – Respiratory compensation point

RER – Respiratory exchange ratio
RER<sub>peak</sub> – Peak respiratory exchange ratio

SAINTEX-CAD – Study on Aerobic INTerval Exercise training in Coronary Artery Disease

SMARTEX-HF – Study of MyocArdial Recovery afTer EXercise training in Heart Failure

\( \dot{V}CO_2 \) – Rate of carbon dioxide exhalation

\( \dot{V}E \) – Rate of ventilation

\( \dot{V}E_{\text{peak}} \) – Peak rate of ventilation

\( VHD \) – Valvular heart disease

\( \dot{VO}_2 \) – Rate of oxygen uptake

\( \dot{VO}_{2\text{max}} \) – Maximal rate of oxygen uptake

\( \dot{VO}_{2\text{peak}} \) – Peak rate of oxygen uptake
List of Appendices

Appendix A: Ethics Approval Letter ................................................................. 39
Chapter 1

1 Literature Review

1.1 Heart Disease in Canada

There are currently 2.6 million Canadians living with heart disease\(^1\). Heart disease is a broad term encompassing conditions that result in damage to or malfunctioning of the heart tissue and its vasculature\(^2\). The most common form of heart disease is coronary artery disease (CAD), but other prevalent heart disease conditions amongst Canadians include heart failure, rhythm disorders, and valvular heart disease\(^3\). In recent years, heart disease has consistently been the second leading cause of death\(^4\) and accounts for two of the five primary causes of hospitalization (namely, heart failure and cardiac arrest)\(^5\). As a result, there is a sizable economic burden of heart disease in Canada, where health-care costs associated with CAD and heart failure total more than $3.4 billion each year\(^6\). Considering the high national prevalence and cost of heart disease, it is of critical importance to evaluate the effectiveness of traditional heart disease management strategies designed to improve patient outcomes.

1.2 Exercise, Aerobic Fitness, and Heart Disease

A common characteristic of individuals living with heart disease is reduced aerobic fitness, and therefore, exercise intolerance\(^7\). Aerobic fitness, generally expressed as maximal ($\dot{V}O_{2}\text{max}$) or peak ($\dot{V}O_{2}\text{peak}$) oxygen uptake obtained from a graded cardiopulmonary exercise test (CPET), represents the ceiling of an individual’s physiologic ability to take up, transport, and utilize oxygen during exercise. $\dot{V}O_{2}\text{peak}$ is defined as the highest rate of oxygen uptake ($\dot{V}O_2$) achieved during a CPET, whereas $\dot{V}O_{2}\text{max}$ represents an individual’s true maximal aerobic fitness, differentiated from $\dot{V}O_{2}\text{peak}$ when $\dot{V}O_2$ values remain stable despite an increase in work rate. Within patient populations, $\dot{V}O_{2}\text{peak}$ is considered the ‘gold-standard’ variable by which to quantify aerobic fitness.

It is well-documented that patients with a low $\dot{V}O_{2}\text{peak}$ have worsened prognoses, health outcomes, and overall quality of life\(^8-11\). More specifically, a low $\dot{V}O_{2}\text{peak}$ obtained from a
symptom-limited CPET strongly and independently predicts the risk of future hospitalization, all-cause and cardiovascular-specific mortality within this population. For example, in 6213 males who were followed over a 6-year period, low VO\textsubscript{2peak} was associated with the highest predictive strength for increased mortality risk, more so than any other risk factor examined (e.g., history of heart disease, smoking, comorbidities, etc.). Additional findings from Kavanagh et al. indicated that, in heart disease patients, a VO\textsubscript{2peak} of < 15 mL·kg\textsuperscript{-1}·min\textsuperscript{-1} obtained during an incremental CPET was associated with a ~50% higher risk of cardiac death over an average follow-up period of 8 years, compared to those who obtained a VO\textsubscript{2peak} of ≥ 15 mL·kg\textsuperscript{-1}·min\textsuperscript{-1}. Keteyian et al. corroborated these findings, demonstrating a large risk reduction over time (~7 years) occurring in heart disease patients achieving a VO\textsubscript{2peak} ≥ 15 mL·kg\textsuperscript{-1}·min\textsuperscript{-1} during a clinical CPET.

Given that a reduced aerobic fitness in individuals living with heart disease results in a poorer prognosis, it is therefore unsurprising that improving aerobic fitness through exercise training has been shown to reduce the severity of heart disease symptoms and improve prognosis. In fact, an improvement in VO\textsubscript{2peak} through routine exercise training exhibits the greatest association to an improved prognosis compared to other correlates such as age, gender, comorbidities, and participation in resistance training, among others. For instance, Vanhees et al. reported that for every 1% increase in VO\textsubscript{2peak} after an exercise training program, risk of cardiovascular mortality was reduced by 2% in male patients with CAD. Furthermore, in a similar study including both male and female patients with heart disease, a 1 mL·kg\textsuperscript{-1}·min\textsuperscript{-1} increase in VO\textsubscript{2peak} following 4.5 months of exercise training was associated with a 10% reduction of premature mortality. An analysis by Swank et al. of the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of exercise trainingNing) trial found that following a 3-month exercise program, every 6% increase in VO\textsubscript{2peak} from pre-training values was related to a 5% lower risk of all-cause mortality or hospitalization, a 4% lower risk of cardiovascular mortality or hospitalization, and an 8% lower risk of hospitalization for heart failure symptoms. Additionally, chronic heart failure patients that completed a 10-year exercise training program demonstrated a 32% relative risk reduction in cardiac mortality compared to those with chronic heart failure that did not participate in an exercise program. It is based on
these compelling data that the Canadian Cardiovascular Society and the Canadian Association of Cardiac Rehabilitation, as well as other leading American and European cardiology societies, recommend participation in exercise training-based programs as the standard of care in the management of heart disease. \(^{19-22}\)

1.3 Cardiac Rehabilitation Programs in Canada

Nationally and internationally, cardiac rehabilitation (CR) programs are the main channel by which patients are referred to and can access exercise training. In Canada, CR is a government-funded program composed of five main elements: patient education, nutrition counselling, psychosocial counselling, risk factor counselling/management, and exercise. \(^{19}\) Of these elements, the exercise component is designed specifically to improve aerobic fitness through supervised endurance exercise training. In many programs throughout Canada referral to CR is closely followed by an incremental stress test, whereby workload on a treadmill or cycle ergometer is increased progressively until volitional exhaustion (or symptom limitation), during which respiratory gas exchange and ventilatory measures are acquired (i.e., CPET). CPETs in CR are used to characterize and diagnose the pathophysiology of exercise limitation, inform prognosis, to establish the ceiling of aerobic fitness through identification of \(\dot{V}O_2\text{peak}\) or peak heart rate (HR\(_\text{peak}\)), and to prescribe aerobic endurance training intensity through calculation of a percentage of these maximal variables, or their reserves (i.e., percentage of [max minus rest] plus rest) \(^{23-26}\). Exercise prescription for both healthy and clinical populations typically follows the FITT principle, comprised of four components: frequency, intensity, time (or duration), and type of exercise. Guidelines from the Canadian Association of Cardiac Rehabilitation recommend a frequency of 3–5 exercise training sessions/week for a minimum of 12 weeks at an intensity of 40–85% of HR or \(\dot{V}O_2\) reserve, for 20–40 minutes/session using both aerobic and resistance exercise. \(^{19}\) Most programs in Canada target two supervised sessions per week and recommend additional home-based exercise sessions. At St. Joseph’s CR and Secondary Prevention program (London, Ontario, Canada), exercise training is performed off-site at a YMCA facility (30–60 mins/session) supervised by an exercise specialist. Ultimately, the goal of exercise training-based CR is to increase weekly volume of exercise through an individually prescribed manipulation of intensity, frequency, and/or duration.
over a 6-month period\textsuperscript{19,27}, targeting a minimal improvement in aerobic fitness of 0.5 METS (1.75 mL·kg\textsuperscript{-1}·min\textsuperscript{-1})\textsuperscript{28,29}.

### 1.3.1 “Responsiveness” to Exercise-Based Cardiac Rehabilitation

Although the benefits of improving aerobic fitness through supervised endurance training in heart disease patients are clear, recent data indicate that ~50% of patients who undergo exercise training in traditional CR settings exhibit only minor increases or even decreases in $\dot{V}O_2\text{peak}$.\textsuperscript{10,16,17,30} For instance, De Schutter et al.\textsuperscript{16} found that after 4.5 months of exercise training, $\dot{V}O_2\text{peak}$ decreased in 23% and marginally increased in 30% of patients enrolled in CR that attended 100% of the scheduled training sessions (~2 sessions/week). Similarly, Savage et al.\textsuperscript{17} found that $\dot{V}O_2\text{peak}$ decreased in 21% and marginally increased in 25% of patients who underwent 3 months of exercise training-based CR. Interestingly, there was no difference in the number of exercise sessions attended between “improvers” (i.e., $\Delta\dot{V}O_2\text{peak} > 0$ mL·kg\textsuperscript{-1}·min\textsuperscript{-1}; 23.8 ± 8.9 sessions attended) and “non-improvers” (i.e., $\Delta\dot{V}O_2\text{peak} \leq 0$ mL·kg\textsuperscript{-1}·min\textsuperscript{-1}; 24.5 ± 10.0 sessions attended). Moreover, a recent analysis by Karlsen et al.\textsuperscript{31} of data collected from the SMARTEX-HF (Study of MyocArdial Recover afTer EXercise training in Heart Failure) demonstrated that ~60% of subjects assigned to a 3-month supervised program of either interval or continuous aerobic exercise training did not demonstrate a meaningful change in aerobic fitness. Finally, results from a recent preliminary investigation of the effectiveness of a Canadian CR program to improve aerobic fitness indicate that (using a pragmatic minimal detectable change in $\dot{V}O_2\text{peak}$ of ± 100 mL·min\textsuperscript{-1}) 34% of patients were classified as “non-responders”, and 15% as “negative responders”\textsuperscript{30}. Collectively, these data reveal an inequality in the effectiveness of exercise training-based CR where a large percentage of patients do not obtain the aerobic fitness improvements required to achieve a better quality of life and a risk reduction in hospitalization and premature mortality. To emphasize this point, a recent meta-analysis by Powell et al.\textsuperscript{32} concluded that exercise-based CR has no benefit on hospitalization, all-cause or cardiovascular-specific mortality rates compared to a no-exercise control. Providing patients with an exercise prescription that will optimize fitness during CR is of high importance, as longitudinal studies have reported a strong inverse correlation between aerobic fitness improvements during CR and 10-year mortality\textsuperscript{16,29}. 
1.4 Exercise Prescription Based on “Maximal” Variables

It remains unclear why a considerable proportion of heart disease patients “respond” to exercise training, while others exhibit a neutral, or even negative, exercise training response. One explanation that has yet to be explored is the insufficiency of $\dot{V}O_{2\text{peak}}$ to characterize true aerobic fitness in heart disease patients. As mentioned, in clinical settings, aerobic fitness (and its improvement) is assessed near exclusively based on $\dot{V}O_{2\text{peak}}$ obtained during a “maximal” CPET. In the case of most individuals who are accustomed to exhaustive exercise and provide a symptom-free maximal effort, their measured $\dot{V}O_{2\text{peak}}$ provides a reasonable estimate of $\dot{V}O_{2\text{max}}$ and the ceiling of their aerobic fitness. However, in clinical settings, heart disease patients are rarely accustomed to exhaustive exercise and CPET protocols are commonly symptom-limited due to breathlessness and fatigue. In such situations, the $\dot{V}O_{2\text{peak}}$ achieved may be submaximal, as maximal efforts are challenging to obtain (and confirm) in this population.

In clinical situations, various verification criteria, such as an end-exercise peak respiratory exchange ratio (RER$_{\text{peak}}$) greater than 1.00-1.15 or an end-exercise HR (i.e., HR$_{\text{peak}}$) within 10 bpm of age-predicted maximum, are often used to confirm maximum effort and corroborate that the $\dot{V}O_{2\text{peak}}$ reflects $\dot{V}O_{2\text{max}}$; however, these criteria are limited and may even lead to the invalid acceptance of $\dot{V}O_{2\text{peak}}$ as $\dot{V}O_{2\text{max}}$, underestimating $\dot{V}O_{2\text{max}}$ by as much as 27%. For example, in a group of 24 heart failure patients who obtained an RER$_{\text{peak}}$ above 1.10 on a ramp-incremental exercise test, 7 participants were able to increase their $\dot{V}O_{2\text{peak}}$ by more than 10% in a subsequent constant-work rate verification trial at 95% peak power output. Thus, even in those patients who satisfy the RER- and HR$_{\text{peak}}$-based criterion for a “maximal” effort, $\dot{V}O_{2\text{peak}}$ may be an underestimate of their true aerobic fitness.

Such underestimations are of major consequence to the contemporary “range-based” prescriptive method which relies on the assumption that measured $\dot{V}O_{2\text{peak}}$ represents the ceiling of aerobic fitness. Current exercise prescription guidelines endorsed by leading cardiology and CR organizations worldwide recommend that aerobic exercise training intensity is prescribed between ~40–85% of $\dot{V}O_{2\text{peak}}$, ~65–90% of HR$_{\text{peak}}$, or 40–85% of HR or $\dot{V}O_{2}$ reserve. These various submaximal intensity ranges that are prescribed
to patients for endurance training are all based on “maximal” variables, often obtained from symptom-limited CPETs. For example, consider an instance in which a patient terminated their CPET (or had their CPET terminated) prematurely at 70% VO$_2$max (i.e., VO$_2$peak is 70% of maximum) and was prescribed an exercise training intensity of 50% VO$_2$peak – the dose of exercise would be equivalent to 35% of their true maximum. In this example, the exercise stimulus would be largely underestimated, the patient would be undertrained, and thus, may not achieve the evidence-based threshold of VO$_2$ improvement during CR that is associated with reduced mortality$^{16}$, thereby exposing the first shortcoming of the range-based approach to exercise prescription.

### 1.5 Exercise Thresholds: A Submaximal Alternative?

Recognizing that VO$_2$peak and HR$_{peak}$ (and their reserves) can vary widely between patients, the range-based prescriptive approach assumes that the cardiorespiratory and metabolic responses to exercise of all individuals are similar when exercising at a common %VO$_2$peak. However, this framework ignores the existence of exercise thresholds that demarcate alterations in the physiological stress imposed by exercise$^{39-41}$ and occur at widely variable fractions of VO$_2$peak (and HR$_{peak}$) in populations of health$^{42,43}$ and cardiovascular disease$^{44}$.

During an ideal exhaustive bout of incremental exercise, two submaximal metabolic boundaries are crossed as VO$_2$ rises to its maximum. The crossing of these boundaries elicit reproducible changes in the ventilatory and gas exchange profiles that manifest as exercise thresholds$^{45,46}$. The first threshold signifies the onset of blood lactate elevation above resting concentrations, termed the estimated lactate threshold ($\theta_{LT}$; often referred to as gas exchange threshold, anaerobic threshold, or first ventilatory threshold), and the boundary between “comfortably sustainable” versus “uncomfortably sustainable” exercise (i.e., moderate- versus heavy-intensity domains; see Figure 1.1). The second identifies the onset of worsening metabolic acidosis and the compensatory hyperventilatory response, termed the respiratory compensation point (RCP; often referred to as second ventilatory threshold), and the boundary between “uncomfortably sustainable” and “uncomfortably unsustainable” exercise (i.e., heavy- versus severe-intensity domains; see Figure 1.1). Unlike VO$_2$peak, identification of the $\theta_{LT}$ and RCP from a CPET is more reproducible and less reliant on a maximal effort$^{47}$. Additionally, these thresholds are more reflective of the
metabolic requirements of daily living, as most activities completed in daily life rarely reach metabolic rates near $\dot{V}O_2^{peak}$. Therefore, the $\theta_LT$ and RCP may be equally or more informative than $\dot{V}O_2^{peak}$ to evaluate changes in aerobic fitness in CR-eligible populations.
**Figure 1.1**: Breath-by-breath ventilatory and gas exchange cardiopulmonary exercise test (CPET) data of a representative participant. Green area signifies the moderate intensity domain (i.e., exercise below estimated lactate threshold [$\theta_{LT}$]), blue area signifies the heavy intensity domain (i.e., exercise between $\theta_{LT}$ and respiratory compensation point [RCP]), and red area signifies the severe intensity domain (i.e., exercise above RCP).

In 2012, a joint statement from the Canadian, American, and European associations for CR presented rationale for the adoption of a “threshold-based” exercise prescription model, rather than the traditional “range-based” approach, to individualize aerobic exercise intensity prescription and improve outcomes of exercise training-based CR. However, since publication of the position statement over a decade ago, the “range-based” exercise prescription continues to inform exercise prescription guidelines and clinical practice in modern rehabilitative exercise settings.

A potential barrier to the uptake of the proposed “threshold-based” approach could be that $\theta_{LT}$ and RCP are difficult to discern from traditional CPET protocols. Contemporary CPET protocols are designed to ensure time efficiency and standardization between patients and care centres such that results are easily interpretable and intuitive for prognostication, risk assessment, and clinical decision making. The requirement for standardization has resulted in the routine employment of a small collection of CPET protocols – most often the Bruce treadmill test or its modified version. The Bruce protocol is a standardized stepwise treadmill test consisting of 3-min stages, beginning at a speed of 1.7 mph and a 10% grade, with ~0.5–0.9 mph and 2% grade increments at every stage; the modified Bruce protocol consists of a similar progression, with two extra preliminary stages at 1.7 mph and a 0% and 5% grade, respectively. These protocols may not be ideal for $\theta_{LT}$ and RCP identification in CR patients due to the long step durations, potentially aggressive step increments, and intense baseline work rates. In those who are deconditioned, have a low functional capacity, and are unaccustomed to exhaustive exercise, such features may lead to premature CPET termination due to physical or psychological limitation rather than true $\dot{V}O_2_{\text{max}}$ attainment and, in doing so, reduce the probability of crossing the metabolic boundaries that lead to $\theta_{LT}$ and RCP expression. Collectively, these findings suggest that contemporary CPET protocols may not apply external loads in a manner that is conducive
to express the $\theta_{LT}$ and RCP thresholds that are necessary to employ the threshold-based model of aerobic exercise prescription in CR populations.

1.6 Purpose

Before the recommended “threshold-based” prescriptive approach can be employed, whether contemporary CPET protocols performed in a CR setting permit sufficient data to identify $\theta_{LT}$ and RCP must first be explored. Therefore, the purpose of this thesis was to quantify the proportion of patients referred to CR whose clinical CPET data allowed for exercise threshold identification. We retrospectively analyzed CPET data of 1102 patients referred to CR to characterize the frequency in which $\theta_{LT}$ only, both $\theta_{LT}$ and RCP, or neither $\theta_{LT}$ and RCP could be identified, and to explore factors that might influence the identification of these thresholds. Additionally, in patients in whom both thresholds were evident, we characterized the inter-patient variability of the $\% \dot{V}O_{2\text{peak}}$ and $\% \dot{HR}_{\text{peak}}$ at which $\theta_{LT}$ and RCP occur.
1.7 References


33. Murias JM, Pogliaghi S, Paterson DH. Measurement of a true $\dot{V}O_2$max during a ramp incremental test is not confirmed by a verification phase. Front Physiol 2018;9:1–8.
34. Iannetta D, Azevedo R de A, Ingram CP, Keir DA, Murias JM. Evaluating the suitability of supra-PO$_{\text{peak}}$ verification trials after ramp-incremental exercise to confirm


Chapter 2

2 Do clinical exercise tests permit exercise threshold identification in patients referred to cardiac rehabilitation?

Randi R. Keltz\textsuperscript{a,b}, Tim Hartley\textsuperscript{b,c}, Ashlay A. Huitema\textsuperscript{c,d}, Robert S. McKelvie\textsuperscript{c,d}, Neville G. Suskin\textsuperscript{b,c,d} & Daniel A. Keir\textsuperscript{a,b,e}

\textbf{Author Affiliations:} \textsuperscript{a}School of Kinesiology, University of Western Ontario, London, Ontario, Canada; \textsuperscript{b}Lawson Health Research Institute, London, Ontario, Canada; \textsuperscript{c}Cardiac Rehabilitation and Secondary Prevention Program, St. Joseph’s Health Care, London, Ontario, Canada; \textsuperscript{d}Schulich School of Medicine, University of Western Ontario, London, Ontario, Canada; \textsuperscript{e}Toronto General Research Institute, Toronto General Hospital, Toronto, Ontario, Canada.

2.1 Introduction

Cardiopulmonary exercise testing (CPET) combines incremental exercise with respiratory gas exchange and ventilatory measures to assess how the cardiorespiratory system responds to increasing muscle metabolic requirements. In cardiac rehabilitation (CR), CPETs are routinely performed to characterize and diagnose the pathophysiology of exercise limitation, inform prognosis, to establish the ceiling of aerobic fitness through identification of peak oxygen uptake (\(\dot{V}\text{O}_2\text{peak}\)) or heart rate (\(HR\text{peak}\)), and to prescribe aerobic endurance training intensity using these variables\textsuperscript{1–4}. Providing patients with an exercise prescription that will optimize fitness during CR is of high importance because longitudinal studies have reported a strong inverse correlation between aerobic fitness improvements during CR and 10-year mortality\textsuperscript{5,6}.

Current exercise prescription guidelines endorsed by leading cardiology and CR organizations worldwide recommend that aerobic exercise training intensity is prescribed between \(\sim 40–85\%\) of \(\dot{V}\text{O}_2\text{peak}\) or \(\sim 65–90\%\) of \(HR\text{peak}\)\textsuperscript{7–10}. Recognizing that \(\dot{V}\text{O}_2\text{peak}\) (and \(HR\text{peak}\)) can vary widely between patients, this approach assumes that the cardiorespiratory and metabolic responses to exercise of all individuals are similar when exercising at a
common $\% \dot{V}O_2\text{peak}$. However, this framework ignores the existence of exercise thresholds that demarcate alterations in the physiological stress imposed by exercise$^{11-13}$ and occur at widely variable fractions of $\dot{V}O_2\text{peak}$ (and $HR_{\text{peak}}$) in healthy$^{14,15}$ and cardiovascular disease populations$^{16}$.

During an ideal exhaustive bout of incremental exercise, two metabolic boundaries are crossed as $\dot{V}O_2$ approaches its maximum. The crossing of these boundaries elicit reproducible changes in the ventilatory and gas exchange profiles that manifest as exercise thresholds$^{17,18}$. The first threshold signifies the onset of blood lactate elevation above resting concentrations, termed the estimated lactate threshold ($\theta_{LT}$; often referred to as gas exchange threshold, anaerobic threshold, or first ventilatory threshold), and the boundary between “comfortably sustainable” versus “uncomfortably sustainable” exercise (i.e., moderate- versus heavy-intensity domains). The second identifies the onset of worsening metabolic acidosis and the compensatory hyperventilatory response, termed the respiratory compensation point (RCP; often referred to as second ventilatory threshold), and the boundary between “uncomfortably sustainable” and “uncomfortably unsustainable” exercise (i.e., heavy- versus severe-intensity domains). In 2012, a joint statement from the Canadian, American, and European associations for CR presented a rationale for the adoption of a “threshold-based” exercise prescription model, rather than the traditional “range-based” approach, to individualize aerobic exercise intensity prescription and improve outcomes of exercise training-based CR$^{19}$. However, since publication of the position statement over a decade ago, the “range-based” exercise prescription continues to inform exercise prescription guidelines$^{7,8,10}$ and clinical practice in modern rehabilitative exercise settings.

A potential barrier to the uptake of the “threshold-based” approach could be that $\theta_{LT}$ and RCP are difficult to discern from commonly used CPET protocols. The CPET protocols currently employed in CR settings are designed to ensure time efficiency and standardization between patients and care centres such that results are easily interpretable and intuitive for prognostication, risk assessment, and clinical decision making$^7$. The requirement for standardization has resulted in the routine employment of a small collection of CPET protocols – most often the Bruce treadmill test or its modified version$^7$. 
These protocols may not be ideal for $\theta_{LT}$ and RCP identification in CR patients due to the long stage durations, potentially aggressive step increments, and intense baseline work rates. In those who are deconditioned, have a low functional capacity, and are unaccustomed to exhaustive exercise such features may lead to premature CPET termination due to physical or psychological limitation rather than $\dot{V}O_{2\text{max}}$ attainment$^{7,20}$ and, in doing so, reduce the probability of crossing the metabolic boundaries that lead to $\theta_{LT}$ and RCP expression.

The objective of this study was to assess whether commonly used CPET protocols performed in a clinical setting permit sufficient data to identify $\theta_{LT}$ and RCP. We retrospectively assembled a dataset of 1102 patients who completed a CPET after referral to CR to: i) characterize the frequency with which $\theta_{LT}$ and RCP can be identified; ii) explore factors that might influence whether or not $\theta_{LT}$ and RCP are identified; and iii) characterize the inter-patient variability of the absolute and relative $\dot{V}O_2$ and HR at which $\theta_{LT}$ and RCP occur.

2.2 Methods

2.2.1 Study Design

This was a retrospective analysis of patients referred to St. Joseph’s Cardiac Rehabilitation and Secondary Prevention program in London, Ontario, Canada. De-identified retrospective data were used, and therefore, patient consent was not required. The protocol for this study was approved by the University of Western Ontario’s Health Sciences Research Ethics Board (WREM: 119962).

2.2.2 Participants

This analysis included 1102 adults aged 24–94 years (796 males; 306 females) who were referred to St. Joseph’s Cardiac Rehabilitation and Secondary Prevention program between January 2017 and September 2019 for coronary artery disease (CAD; acute coronary syndrome event, percutaneous coronary intervention, coronary artery bypass graft), chronic heart failure (CHF), atrial fibrillation, or repaired valvular heart disease (VHD).
Patients were included in the analysis if they completed at least one CPET within this time range.

2.2.3 CPET

CPETs were conducted as usual standard of care for intake to and discharge from CR. Briefly, testing complied with recommendations from the American Heart Association (AHA) and the American Thoracic Society (ATS)\textsuperscript{21–23}. Patients were instrumented with a 12-lead ECG (GE CASE, GE HealthCare, Chicago, USA), automated blood pressure (Tango M2, SunTech Medical, Morrisville, USA) and breath-by-breath ventilatory and gas exchange monitor (Medisoft Ergocard, MediSoft Group, Sorinnes, Belgium). All tests for this analysis were performed on a treadmill (T2100, GE HealthCare, Chicago, USA [98%]) or cycle ergometer (Ergoselect 200, Ergoline, Windhagen, Germany [2%]). After review of patient disposition and medical history, patients performed a symptom-limited, maximal, incremental exercise test in a clinical stress laboratory under the supervision of a cardiologist. The CPET protocol was selected at the discretion of the physician based upon initial review of patients’ prior medical history. Data collection was initiated for up to 2 minutes of seated rest at which point the exercise protocol began. The majority of treadmill tests increased work rate according to the Bruce (55%) or modified Bruce (27%) protocols. The Naughton (3%), Balke (0.4%), and custom (11%) protocols (2 min at 2 mph and 0% grade, followed by 1-min stages at 3 mph with grade increases of 1.7% per min) were also used. For all cycle ergometer tests, a step-incremental protocol was used.

2.2.4 Data Analysis

A modified version of a free online application designed to assess gas exchange and ventilatory responses to incremental exercise (exercisethresholds.com) was used to identify peak variables and the $\dot{V}O_2$ and HR associated with $\theta_L$ and RCP\textsuperscript{17}.

Prior to analysis, $\dot{V}O_2$ data were edited on an individual basis by removing aberrant data that lay outside the 95% confidence prediction band of a cubic spline fit to the $\dot{V}O_2$ versus time data series (excluding baseline). Next, peak values corresponding to $\dot{V}O_2$, RER, ventilation ($\dot{V}_E$), and breathing frequency (BF) were calculated as the highest 20-second rolling average. The $\dot{V}O_2$peak was expressed in absolute (mL·min$^{-1}$) and relative (mL·kg$^{-1}$·min$^{-1}$).
1·min⁻¹) terms, and as a percent of the age, sex, body mass, height, and modality-specific predicted units (%predicted) using equations incorporating a 1.11 correction factor for treadmill-cycling comparisons. This equation has been recommended for use in cardiac rehabilitation populations. HRpeak was identified as the highest recorded HR value.

After removing data from the baseline period, first minute of exercise, and recovery period, the profiles of VE, gas exchange (VO₂ and VCO₂), their combination (VE/VCO₂, VE/VO₂), RER, and end-tidal partial pressures of O₂ and CO₂ (PETO₂ and PETCO₂) were plotted against VO₂ and visually inspected to identify the VO₂ at θLT and RCP. A plot of VE vs VCO₂ was also displayed. After ruling out potential confounding effects of CO₂ storage on θLT detection by confirming the absence of an early change-point in the RER versus VO₂ relationship, the θLT was determined as the VO₂ at which VCO₂ and VE began to increase disproportionately in relation to VO₂, with a systematic rise in VE/VO₂ and PETO₂, whereas PETCO₂ and VE/VCO₂ were stable. RCP was determined as the VO₂ at which PETCO₂ began to fall after a period of isocapnia, corroborated by the second and first breakpoints in the VE- and VE/VCO₂-VO₂ relationships, respectively.

Patients were placed into one of three groups depending on the presence or absence of θLT and RCP. Group 0 included those in whom neither θLT nor RCP were identifiable. Both θLT and RCP were deemed not identifiable in situations where: i) only baseline data, and no incremental portion of the exercise test, were available; ii) RER began and remained above 1.0 for the entirety of the exercise test; iii) data were too noisy for confident threshold detection; or iv) neither θLT nor RCP were evident in the data. Group 1 included patients in whom θLT but not RCP was observed, and group 2 included those who exhibited both θLT and RCP. There were no instances in which RCP was identified but θLT was not.

Using the cohort of patients exhibiting both θLT and RCP (i.e., group 2), distributions were created to illustrate the frequency of patients positioned within each exercise intensity domain (i.e., moderate [exercise below θLT], heavy [exercise between θLT and RCP], and severe [exercise above RCP]) at 5% increments of %VO₂peak and %HRpeak. Additionally, similar domain-specific distributions were created for each of the four
%\(\dot{V}O_2\)peak- and %HRpeak-based “training zones” outlined for aerobic exercise intensity prescription in the current European Society of Cardiology (ESC) guidelines\(^8\).

### 2.2.5 Statistical Analysis

Frequency of participants within each group, and the deviation from expectation in group distribution, was assessed using a chi-square test. Group differences in patient demographics and CPET data were compared using a one-way independent group ANOVA and Tukey’s post-hoc analysis (continuous variables), or a chi-square test (categorical variables). The coefficient of variation (CV) was used to assess the within-group variability of \(\theta_{LT}\) and RCP in groups 1 and 2. \(\dot{V}O_2\) (expressed in %\(\dot{V}O_2\)peak, mL·min\(^{-1}\), and mL·kg\(^{-1}\)·min\(^{-1}\)) and HR (expressed in %HRpeak, and bpm) where \(\theta_{LT}\) occurs were compared between groups 1 and 2 via two-tailed independent t-test. Data are presented as means ± SD. For all statistical analyses (performed using RStudio Version 1.4.1717) significance was accepted at an \(\alpha = 0.05\).

### 2.3 Results

The total sample consisted of 1102 CR-referred patients (306 females; 796 males) aged 65 ± 12 years (range: 24–94 years), with an average height, body mass, and body mass index (BMI) of 1.70 ± 0.10 m (range: 1.38–2.01 m), 84 ± 18 kg (range: 36–160 kg), and 29 ± 5 kg·m\(^{-2}\) (range: 14–57 kg·m\(^{-2}\)), respectively (Table 2.1). The majority of the sample was referred due to CAD diagnosis (71%) – other reasons for referral included VHD (11%), CHF (7%), and atrial fibrillation (5%). Overall group mean \(\dot{V}O_2\)peak was 1523 ± 627 mL·min\(^{-1}\) (range: 315–3789 mL·min\(^{-1}\)), 18.0 ± 6.5 mL·kg\(^{-1}\)·min\(^{-1}\) (range: 5.2–46.5 mL·kg\(^{-1}\)·min\(^{-1}\)), and 80 ± 44% predicted (range: 10–332%). HRpeak averaged 123 ± 24 bpm (range: 52–207 bpm). Histograms including HRpeak and absolute, relative, and %predicted \(\dot{V}O_2\)peak for all 1102 patients are provided in Figure 2.1. Group mean RERpeak, \(\dot{V}_E\)peak, and BFpeak were 1.20 ± 0.13 (range: 0.86–2.17), 65.9 ± 26.0 L·min\(^{-1}\) (range: 15.5–177.0 L·min\(^{-1}\)), and 41.7 ± 9.2 breaths·min\(^{-1}\) (range: 19.2–93.8 breaths·min\(^{-1}\)), respectively.
Figure 2.1: Frequency distributions of peak oxygen uptake ([\(\dot{V}O_{2peak}\), A: mL\(\cdot\)min\(^{-1}\); B: mL\(\cdot\)kg\(^{-1}\)\(\cdot\)min\(^{-1}\); C: %predicted) and peak heart rate ([HR\(_{peak}\), D) in the total sample (n = 1102).
Table 2.1: Patient characteristics and CPET data for each of the three groups.

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Group 0 (no thresholds)</th>
<th>Group 1 (only θ_LT)</th>
<th>Group 2 (θ_LT and RCP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (Females)</td>
<td>556 (212)</td>
<td>196 (51)</td>
<td>350 (43)</td>
</tr>
<tr>
<td>Group size (%total [%F])</td>
<td>50 (38)</td>
<td>18 (26)</td>
<td>32 (12)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>68 ± 11†^</td>
<td>63 ± 11**</td>
<td>61 ± 11†^</td>
</tr>
<tr>
<td>Mass (kg)</td>
<td>82 ± 19†^</td>
<td>87 ± 19*</td>
<td>86 ± 16*</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.68 ± 0.10†^</td>
<td>1.72 ± 0.09*</td>
<td>1.73 ± 0.08*</td>
</tr>
<tr>
<td>BMI (kg·m⁻²)</td>
<td>29 ± 6</td>
<td>30 ± 6</td>
<td>29 ± 4</td>
</tr>
<tr>
<td>Reason for Referral (n [%])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>359 (65)</td>
<td>147 (75)</td>
<td>274 (78)</td>
</tr>
<tr>
<td>CHF</td>
<td>55 (10)</td>
<td>13 (7)</td>
<td>14 (4)</td>
</tr>
<tr>
<td>AF</td>
<td>25 (4)</td>
<td>9 (5)</td>
<td>18 (5)</td>
</tr>
<tr>
<td>VHD</td>
<td>75 (13)</td>
<td>17 (9)</td>
<td>28 (8)</td>
</tr>
<tr>
<td>Other</td>
<td>42 (8)</td>
<td>10 (5)</td>
<td>16 (5)</td>
</tr>
<tr>
<td>Medications (n [%])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARBs</td>
<td>115 (21)</td>
<td>46 (23)</td>
<td>65 (19)</td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td>323 (58)</td>
<td>121 (62)</td>
<td>245 (70)</td>
</tr>
<tr>
<td>β-blockers</td>
<td>463 (83)</td>
<td>153 (78)</td>
<td>306 (87)</td>
</tr>
<tr>
<td>Cholesterol Absorption Inhibitors</td>
<td>65 (12)</td>
<td>25 (13)</td>
<td>44 (13)</td>
</tr>
<tr>
<td>Statins</td>
<td>472 (85)</td>
<td>174 (89)</td>
<td>313 (89)</td>
</tr>
<tr>
<td>PAIs</td>
<td>262 (47)</td>
<td>101 (52)</td>
<td>222 (63)</td>
</tr>
<tr>
<td>ASA</td>
<td>461 (83)</td>
<td>175 (89)</td>
<td>309 (88)</td>
</tr>
<tr>
<td>Factor Xa Inhibitors</td>
<td>73 (13)</td>
<td>11 (6)</td>
<td>23 (7)</td>
</tr>
<tr>
<td>CPET Information</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>θ_LT (mL·min⁻¹)</td>
<td>N/A</td>
<td>1240 ± 410^</td>
<td>1390 ± 360†</td>
</tr>
<tr>
<td>θ_LT (mL·kg⁻¹·min⁻¹)</td>
<td>N/A</td>
<td>14.2 ± 4.0†</td>
<td>16.0 ± 3.2†</td>
</tr>
<tr>
<td>θ_LT (%V̇O₂peak)</td>
<td>N/A</td>
<td>75 ± 8^</td>
<td>70 ± 8†</td>
</tr>
<tr>
<td>θ_LT (bpm)</td>
<td>N/A</td>
<td>103 ± 15^</td>
<td>107 ± 15†</td>
</tr>
<tr>
<td>θ_LT (%HR peak)</td>
<td>N/A</td>
<td>84 ± 6^</td>
<td>78 ± 7†</td>
</tr>
<tr>
<td>RCP (mL·min⁻¹)</td>
<td>N/A</td>
<td>N/A</td>
<td>1680 ± 440</td>
</tr>
<tr>
<td>RCP (mL·kg⁻¹·min⁻¹)</td>
<td>N/A</td>
<td>N/A</td>
<td>19.4 ± 4.0</td>
</tr>
<tr>
<td>RCP (%V̇O₂peak)</td>
<td>N/A</td>
<td>N/A</td>
<td>84 ± 7</td>
</tr>
<tr>
<td>RCP (bpm)</td>
<td>N/A</td>
<td>N/A</td>
<td>118 ± 17</td>
</tr>
<tr>
<td>RCP (%HR peak)</td>
<td>N/A</td>
<td>N/A</td>
<td>87 ± 6</td>
</tr>
<tr>
<td>V̇O₂peak (mL·min⁻¹)</td>
<td>1174 ± 450†^</td>
<td>1659 ± 561**</td>
<td>2002 ± 556†</td>
</tr>
<tr>
<td>V̇O₂peak (mL·kg⁻¹·min⁻¹)</td>
<td>14.4 ± 4.7†^</td>
<td>19.1 ± 5.7**</td>
<td>23.2 ± 5.5†</td>
</tr>
<tr>
<td>V̇O₂peak (%predicted)</td>
<td>63 ± 35†^</td>
<td>85 ± 39**</td>
<td>106 ± 47†</td>
</tr>
<tr>
<td>HR peak (bpm)</td>
<td>115 ± 23†</td>
<td>123 ± 20**</td>
<td>137 ± 22†</td>
</tr>
<tr>
<td>RER peak</td>
<td>1.19 ± 0.15^</td>
<td>1.17 ± 0.09^</td>
<td>1.25 ± 0.09†</td>
</tr>
<tr>
<td>V̇E peak (L·min⁻¹)</td>
<td>53.5 ± 20.2†^</td>
<td>63.7 ± 19.3**</td>
<td>86.9 ± 24.2†</td>
</tr>
</tbody>
</table>
Table 2.1 provides the patient characteristics and mean CPET variable data for each group.

Note: BMI, body mass index; CAD, coronary artery disease; CHF, chronic heart failure; AF, atrial fibrillation; VHD, valvular heart disease; ARBs, angiotensin receptor blockers; ACE, angiotensin-converting enzyme; PAIs, plasminogen activator inhibitors; ASA, acetylsalicylic acid; θLT, estimated lactate threshold; RCP, respiratory compensation point; N/A, not applicable; VO2peak, peak oxygen uptake; HRpeak, peak heart rate; RERpeak, peak respiratory exchange ratio; V̇Epeak, peak ventilation; BFpeak, peak breathing frequency; VTpeak, peak tidal volume; CPET, cardiopulmonary exercise test. Data presented as mean ± SD. Continuous variables: * indicates a significant difference (p < 0.05) from group 0, † indicates a significant difference (p < 0.05) from group 1, and ‡ indicates a significant difference (p < 0.05) from group 2. Categorical variables: † indicates a significant positive deviation (p < 0.05) from expectation, and ‡ indicates a significant negative deviation (p < 0.05) from expectation.

Of the 1102 patients, neither θLT nor RCP were identifiable in 556 patients (50% of total sample; 212 females [group 0]). Of those 556 patients, 396 (71%) had only baseline data available, 93 (17%) had an RER that began and remained above 1.0 for the entirety of the test, 60 (11%) had data that were too noisy to permit confident threshold detection, and 7 (1%) had data where neither θLT nor RCP were evident despite absence of all previously listed criteria. Only θLT, and not RCP, was identified in 196 patients (18% of total sample; 51 females [group 1]) and both θLT and RCP were identified in 350 patients (32% of total sample; 43 females [group 2]).
Figure 2.2: Frequency distributions of estimated lactate threshold (\(\theta_{LT}\)) in group 1 (i.e., patients in which only \(\theta_{LT}\), and not respiratory compensation point [RCP], was identified) (A: %\(\bar{V}O_2\)peak; C: %HR\(_{peak}\)), and \(\theta_{LT}\) and RCP in group 2 (i.e., patients in which both \(\theta_{LT}\) and RCP were identified) (B: %\(\bar{V}O_2\)peak; D: %HR\(_{peak}\)).

For group 1, average \(\theta_{LT}\) was identified at 1240 ± 410 mL·min\(^{-1}\) (range: 580–2560 mL·min\(^{-1}\); CV = 33%) which equated to approximately 75 ± 8%\(\bar{V}O_2\)peak (range: 52–92%\(\bar{V}O_2\)peak; CV = 11%; see Figure 2.2A). In group 2, average \(\theta_{LT}\) was identified at 1390 ± 360 mL·min\(^{-1}\) (range: 640–2430 mL·min\(^{-1}\); CV = 26%) or 70 ± 8%\(\bar{V}O_2\)peak (range: 41–88%\(\bar{V}O_2\)peak; CV = 11%; see Figure 2.2B), and average RCP was identified at 1680 ± 440 mL·min\(^{-1}\) (range: 730–3090 mL·min\(^{-1}\); CV = 26%), or 84 ± 7%\(\bar{V}O_2\)peak (range: 54–99%\(\bar{V}O_2\)peak; CV = 8%; see Figure 2.2B). Average HR at \(\theta_{LT}\) in group 1 was 103 ± 15 bpm (range: 71–146 bpm; CV = 15%) which equated to approximately 84 ± 6%HR\(_{peak}\) (range: 64–96%HR\(_{peak}\); CV = 7%; see Figure 2.2C). In group 2, average HR at \(\theta_{LT}\) was 107 ± 15 bpm (range: 65–155
bpm; CV = 14%) or 78 ± 7%HR\text{peak} (range: 52–96%HR\text{peak}; CV = 10%; see Figure 2.2D), and average HR at RCP was 118 ± 17 bpm (range: 67–167 bpm; CV = 15%) or 87 ± 6%HR\text{peak} (range: 59–99%HR\text{peak}; CV = 7%; see Figure 2.2D). Average θ_{LT} was higher (p < 0.05) in group 2 than 1 when expressed in mL·min\(^{-1}\) (Figure 2.3A) but was lower (p < 0.05) than group 1 when expressed as %\text{VO}_2\text{peak} (Figure 2.3B). Similarly, average HR in bpm at θ_{LT} was higher (p < 0.05) in group 2 than 1, but average %HR\text{peak} at θ_{LT} was lower (p < 0.05) in group 2 than 1 (Figure 2.3C).

**Figure 2.3**: Frequency distributions of estimated lactate threshold (θ\text{LT}) (A: mL·min\(^{-1}\); B: %\text{VO}_2\text{peak}; C: %HR\text{peak}) in group 1 (θ\text{LT-G1}, i.e., patients in which only θ\text{LT}, and not respiratory compensation point [RCP], was identified) and group 2 (θ\text{LT-G2}, i.e., patients in which both θ\text{LT} and RCP were identified). * indicates a difference (p < 0.05) in θ\text{LT} between groups.

Figure 2.4 illustrates the distribution of patients in group 2 within the moderate, heavy, and severe exercise intensity domains at 5% intervals of %\text{VO}_2\text{peak} (Figure 2.4A) and %HR\text{peak} (Figure 2.4B). Similar, domain-specific distributions for %\text{VO}_2\text{peak} and %HR\text{peak} within each of the four ESC guideline-defined “training intensity zones” for exercise prescription are also presented (Figure 2.5).
Figure 2.4: Distribution of patients (group 2; n = 350) within the moderate (yellow), heavy (orange), and severe (red) exercise intensity domains at a given %VO₂peak (A) and %HR_peak (B). Blue borders represent international guideline-recommended aerobic exercise training intensities for cardiac rehabilitation patients.

### A

<table>
<thead>
<tr>
<th>Intensity</th>
<th>VO₂peak Range (%)</th>
<th>%VO₂peak Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>&lt;40</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>40–69</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>70–85</td>
<td></td>
</tr>
<tr>
<td>Very High</td>
<td>&gt;85</td>
<td></td>
</tr>
</tbody>
</table>

### B

<table>
<thead>
<tr>
<th>Intensity</th>
<th>HR_peak Range (%)</th>
<th>%HR_peak Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>&lt;55</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>55–74</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>75–90</td>
<td></td>
</tr>
<tr>
<td>Very High</td>
<td>&gt;90</td>
<td></td>
</tr>
</tbody>
</table>
**Figure 2.5:** Distribution of patients (group 2; n = 350) within the moderate (yellow), heavy (orange), and severe (red) exercise intensity domains, within each of the four “training zones” outlined for exercise intensity prescription in the current European Society of Cardiology guidelines that are based on %$\dot{V}O_{2}\text{peak}$ (A) and %$\dot{H}R_{\text{peak}}$ (B)\(^8\).

On average, from groups 0 to 2, patients were younger ($p < 0.05$), and had progressively higher ($p < 0.05$) $HR_{\text{peak}}$, $RER_{\text{peak}}$, $\dot{V}E_{\text{peak}}$, and $\dot{V}O_{2}\text{peak}$ (see Table 2.1). Group 0 was comprised of more ($p < 0.05$) CHF and VHD patients, and less ($p < 0.05$) CAD patients, whereas group 2 was comprised of more ($p < 0.05$) CAD patients, and less ($p < 0.05$) CHF and VHD patients (Table 2.1). In group 0, the Naughton and custom protocols were used more often ($p < 0.05$), and the Bruce protocol was used less often ($p < 0.05$). For group 1, more ($p < 0.05$) patients underwent the modified Bruce protocol, and less ($p < 0.05$) completed the Naughton protocol. Group 2 had more ($p < 0.05$) patients who completed the Bruce protocol, and less ($p < 0.05$) that completed the modified Bruce, Naughton, and custom protocols (see Table 2.1).
2.4 References


Chapter 3

3 Discussion

This study quantified the proportion of CR-referred patients whose clinical CPET data permitted identification of $\theta_{LT}$ and RCP and characterized the variability at which these thresholds occur. There were four main findings of the study. First, only 32% of clinical CPETs exhibited both $\theta_{LT}$ and RCP (group 2) and neither were evident in 50% (group 0). Second, from groups 0 to 2, patients were younger and had progressively higher HR$_{peak}$ and $\dot{V}O_2$$_{peak}$ values (i.e., group 2 > group 1 > group 0). Third, the $\%\dot{V}O_2$$_{peak}$ and $\%$HR$_{peak}$ at which $\theta_{LT}$ and RCP occurred were widely variable between patients ($\theta_{LT}$ ranges: 41–92$\%\dot{V}O_2$$_{peak}$, 52–96$\%$HR$_{peak}$; RCP ranges: 54–99$\%\dot{V}O_2$$_{peak}$, 59–99$\%$HR$_{peak}$). Fourth, compared to group 2, the $\%\dot{V}O_2$$_{peak}$ and $\%$HR$_{peak}$ at which $\theta_{LT}$ occurred was higher in those who did not exhibit an RCP (i.e., group 1). Findings indicate that the CPET protocols currently used in CR settings may not apply external loads in a manner that is conducive to express the $\theta_{LT}$ and RCP thresholds that are necessary to employ the threshold-based model of aerobic exercise prescription in CR populations. In those in whom both thresholds were evident, the wide variability at which $\%\dot{V}O_2$$_{peak}$ and $\%$HR$_{peak}$ occur demonstrate that guideline-recommended “range-based” exercise prescription approaches are ineffective at homogenizing exercise intensity.

In comparison to recent literature, the proportion of patients in which neither $\theta_{LT}$ nor RCP could be identified was high (50%). For example, Carriere et al.$^1$ observed neither threshold in only 15% of 1995 individuals with heart failure (HF) whereas Hansen et al.$^2$ reported absence of both thresholds in zero of 272 patients with established cardiovascular disease. The discrepancy in proportions may be due to the differences in CPET protocols employed. Whereas these studies utilized individualized ramp CPET protocols on a cycle ergometer tailored to exhaust patients in 8–12 minutes, the majority of patients in the current study completed a standardized stepwise treadmill-based CPET protocol (i.e., Bruce, modified Bruce). Rather than applying external load gradually in a way that is difficult to perceive, these 3-min stage, step-based protocols may have been less than ideal for the patient to exercise long enough to exhibit $\theta_{LT}$ and RCP. Indeed, 71% of patients in group 0 had only baseline data available and 17% had an RER that began and remained above 1.0 for the
entirety of the test, indicating that the baseline intensity was likely above $\theta_{LT}$ and RCP. Of the remaining 12% in group 0, 11% of patient CPET data exhibited insufficient signal-to-noise profiles for confident threshold identification. Such data may be associated with equipment issues which could be rectified provided sufficient time is available for troubleshooting. Notably, only seven patients ($< 1\%$) completed a CPET in which sufficient data were provided but thresholds were simply not evident.

Interestingly, in group 0, a greater proportion of patients were assigned Naughton and custom protocols. These protocols are typically selected because both apply external load less aggressively compared to the Bruce protocol. Despite this, both $\theta_{LT}$ and RCP were not expressed suggesting that even the less intense protocol options are too challenging for patients to begin below $\theta_{LT}$ and cross both metabolic boundaries en route to maximum. Although the reason for test termination data were not available in all 556 patients in group 0, of the 464 with test termination data, 46% requested to stop, 40% developed symptoms to which exercise continuation was contraindicated, 11% developed musculoskeletal pain, and 3% were terminated due to equipment issues. It is anticipated that alternative protocol selection and execution would significantly increase the proportion of patients exhibiting at least one identifiable threshold – particularly in the group that requested to stop. This could be accomplished by designing and using protocols with lower starting intensities, shorter stage durations, and smaller step increments (e.g., individualized ramp protocols). In such protocols, the small, near-instantaneous changes in external work rate are hardly detectable by the participant, increasing the likelihood that task disengagement is due to physiological rather than physical or psychological limitation. An additional benefit is that $\dot{V}O_2$ rises smoothly with external load which increases clarity of the gas exchange and ventilatory profiles necessary to identify $\theta_{LT}$ and RCP and prescribe exercise\(^3\). Collectively, these findings indicate that commonly used clinical CPET protocols are not always ideal to yield and identify exercise thresholds in CR-referred patients.

Patients in group 2 were younger, and had higher $HR_{peak}$, $\dot{V}O_2_{peak}$, and $RER_{peak}$ values than those in groups 1 and 0 (Table 2.1). Additionally, $HR_{peak}$ and $\dot{V}O_2_{peak}$ values were higher, and patients were younger in group 1 than group 0. The observed trends of $HR_{peak}$, $\dot{V}O_2_{peak}$, and $RER_{peak}$ between groups (i.e., a progressive increase along with an increase in
identified thresholds) and age between groups (i.e., a progressive decrease along with an increase in identified thresholds) are similar to recent findings reported in HF patients. These results might suggest that individuals with either one or no identifiable thresholds were simply older and less fit than those with both $\theta_{LT}$ and RCP identified. Although $HR_{peak}$ and $VO_{2peak}$ reduce with age, the age-adjusted predicted $VO_{2peak}$ fell from 106% in group 2, to 85% and 63% in groups 1 and 0, respectively. This indicates that something other than age (and sex, body mass, and height) is responsible for the differences. Alternatively, or perhaps additionally, patients exhibiting no thresholds or only $\theta_{LT}$ may have had their tests terminated at a submaximal intensity that was at or below $\theta_{LT}$ (group 0) or RCP (group 1). Indeed, 46% of these tests were terminated volitionally and 40% due to symptoms. In such cases, the $VO_{2peak}$ from the CPET would underestimate the true ceiling of aerobic fitness (i.e., $VO_{2max}$).

Group 1 versus 2 comparisons provide evidence of a mismatch between $VO_{2peak}$ and $VO_{2max}$. Compared to group 2, patients in group 1 exhibited a $\theta_{LT}$ at a higher $%VO_{2peak}$ and $%HR_{peak}$ (i.e., 75 vs. 70$%VO_{2peak}$ and 84 vs. 78$%HR_{peak}$, for group 1 vs. 2, respectively) and their distribution curves in Figures 2.3B and 2.3C also appear shifted upwards despite a similar shape as group 2. Assuming that the $%VO_{2max}$ and $%HR_{max}$ at which $\theta_{LT}$ occurs is independent of age, sex, and fitness status, the greater $%VO_{2peak}$ in group 1 may be explained by a systematic underestimation of $VO_{2max}$ by $VO_{2peak}$ in this group.

In most individuals who provide a symptom-free and maximal effort, the $VO_{2peak}$ achieved provides a reasonable estimate of their $VO_{2max}$ and the ceiling of aerobic fitness. However, in those unaccustomed to exhaustive exercise, such an effort is challenging to obtain (and confirm); in such situations, the $VO_{2peak}$ achieved may be submaximal. Such underestimations are of major consequence to the “range-based” prescriptive method which relies on the assumption that measured $VO_{2peak}$ represents the ceiling of aerobic fitness. For example, assuming a patient in group 0 terminated their CPET (or had their CPET terminated) prematurely at 70$%VO_{2max}$ (i.e., $VO_{2peak}$ is 70% of maximum) and was prescribed an exercise training intensity of 50$%VO_{2peak}$, the dose of exercise would be equivalent to 35% of their true maximum! In this example, the exercise “stimulus” would be largely underestimated, the patient would be undertrained and thus may not achieve the
evidence-based threshold of $\dot{V}O_2$ improvement during CR that is associated with reduced mortality\textsuperscript{9}.

Within the cohort of patients expressing both $\theta_{LT}$ and RCP (i.e., group 2), there was large variability of where $\theta_{LT}$ and RCP occurred when expressed as $\%\dot{V}O_2$peak and $\%HR_{peak}$; $\theta_{LT}$ occurrence ranged from 41–88$\%\dot{V}O_2$peak or 52–96$\%HR_{peak}$, and RCP from 54–99$\%\dot{V}O_2$peak or 59–99$\%HR_{peak}$ (see Figures 2.2B and 2.2D). Interestingly, ranges for both $\theta_{LT}$ and RCP in terms of $\%HR_{peak}$ and $\%\dot{V}O_2$peak were wider than what has been previously observed in healthy cohorts\textsuperscript{10,11}. The increased variability in the relative position of both thresholds is likely due to submaximal $\dot{V}O_2$peak values and the diversity in medication usage among patients (see Table 2.1). According to current international CR guidelines, exercise training should be performed between $\sim$40–85$\%\dot{V}O_2$peak or $\sim$65–90$\%HR_{peak}$\textsuperscript{12–15}. However, these guidelines do not account for the relative position of $\theta_{LT}$ and RCP and the three exercise intensity domains they create (i.e., moderate [exercise below $\theta_{LT}$], heavy [exercise between $\theta_{LT}$ and RCP], and severe [exercise above RCP])\textsuperscript{3,16}. Importantly, these three intensity “domains” provide personalized ranges of work rate that engender common physiological (and perceptual) stress characteristics, predictable exercise tolerability\textsuperscript{17,18}, and, presumably, responsiveness to exercise training. Figure 2.4 illustrates the distribution of patients in group 2 who would be positioned within each exercise intensity domain at 5% increments of $\%\dot{V}O_2$peak (Figure 2.4A) and $\%HR_{peak}$ (Figure 2.4B). The inner blue box highlights the range of international guideline-recommended exercise training intensities (i.e., 40–85$\%\dot{V}O_2$peak or 65–90$\%HR_{peak}$). Figure 2.5 conveys similar information except domain-specific distributions are depicted for $\%\dot{V}O_2$peak (Figure 2.5A) and $\%HR_{peak}$ (Figure 2.5B) for each of the 4 intensity zones (i.e., “low”, “moderate”, “high”, and “very high”) defined by the current ESC guidelines\textsuperscript{13}. Notably, all three exercise intensity domains are possible within the “moderate” and “high” intensity zones. Collectively, data reveal that within the group 2 cohort, there is not a single guideline-recommended $\%\dot{V}O_2$peak or $\%HR_{peak}$ that can guarantee a domain-specific exercise prescription and thus a common metabolic and physiological response profile.

If one considers the mid-range of guideline recommended intensity (i.e., 65$\%\dot{V}O_2$peak), data indicate that 53% of patients would be below their $\theta_{LT}$, 43% between $\theta_{LT}$ and RCP, and 3%
above their RCP (Figure 2.4A). Similarly, even at the minimal end of guideline-recommended prescription based on %HR_{peak} (i.e., 65%HR_{peak}), 11% and 1% of patients would be exercising in the heavy- and severe-intensity domains, respectively (Figure 2.4B). Interestingly, the training intensity for the moderate continuous training groups in SAINTEX-CAD and SMARTEX-HF were very close to the aforementioned values and may explain why high intensity interval training conferred no extra benefit on aerobic fitness after 3 months of exercise training^{19-21}. The variability in the relative position of θ_{LT} and RCP exhibited by group 2 demonstrates that a common domain and thus uniform physiological stress profile cannot be ensured, exposing another shortcoming of the range-based prescriptive approach.

3.1 Limitations

Several aspects of the data warrant consideration. Comorbidities were not recorded. It is unknown whether pathology-specific limitations along the O₂ transport chain played a significant role in threshold attainment. In addition, the reason for test termination was unavailable in 20% of participants. Thus, we do not know whether the onset of symptoms that are contraindicated for exercise continuation were more or less frequent between the three cohorts. Lastly, only physical limitations were recorded for reason for test termination, therefore, psychological limitations were not accounted for or explored.

3.2 Conclusions

This study demonstrated that 50% of patients’ CPET data permitted identification of θ_{LT}, however, only 32% permitted the identification of both θ_{LT} and RCP. Importantly, these thresholds occurred across a wide range of %\dot{V}O₂_{peak} and %HR_{peak}. Thus, the boundaries of the exercise intensity domains that should be used to guide training intensity are not fixed but occur at variable fractions of \dot{V}O₂_{peak} and HR_{peak} that differ between patients. “Threshold-based” training is the best means by which to control exercise intensity. Although two-thirds of CPET data did not reveal both thresholds, data indicate that modifications to conventional CPET protocols could rectify this issue in most cases. CPET protocols must be chosen and designed judiciously to ensure that intensity begins within
the lower regions of the moderate domain and rises at a rate that provides sufficient time and data for participants to cross both metabolic boundaries (i.e., $\theta_{LT}$ and RCP).

### 3.3 Future Directions

This thesis evaluated the proportion of patients referred to CR whose clinical CPET data permitted identification of $\theta_{LT}$ and RCP. Future research should explore the effectiveness of current (“range-based”) exercise training guidelines to improve aerobic fitness, by evaluating the proportion of patients that demonstrate a minimal meaningful change in $\theta_{LT}$, RCP, and $\dot{V}O_{2\text{peak}}$ post-CR. Additionally, the feasibility of employing a “threshold-based” prescriptive approach using individualized ramp CPET protocols to identify thresholds in this population should be explored. It is hypothesized that the employment of a “threshold-based” exercise prescription model in CR settings will allow for a higher proportion of patients to achieve meaningful changes in aerobic fitness, and enhance the overall effectiveness of exercise training-based CR to improve heart disease prognosis and premature mortality risk.
3.4 References


7. Murias JM, Pogliaghi S, Paterson DH. Measurement of a true $\dot{V}O_2_{max}$ during a ramp incremental test is not confirmed by a verification phase. Front Physiol 2018;9:1–8.


Appendix

Appendix A: Ethics Approval Letter

Date: 1 November 2021

To:

Project ID: 119962

Study Title: An Evaluation of the Effectiveness of Exercise Training-Based Cardiac Rehabilitation to Improve Aerobic Fitness

Application Type: HSREB Initial Application

Review Type: Delegated

Full Board Reporting Date: 16 Nov/2021

Date Approval Issued: 01 Nov/2021

REB Approval Expiry Date: 31 Nov/2022

Dear [Name],

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above mentioned study as described in the WREIM application form, as of the HSREB Initial Approval Date noted above. This research study is to be conducted by the investigator noted above. All other required institutional approvals and mandated training must also be obtained prior to the conduct of the study.

Documents Approved:

<table>
<thead>
<tr>
<th>Document Name</th>
<th>Document Type</th>
<th>Document Date</th>
<th>Document Version</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPET Export Data dictionary</td>
<td>Other Data Collection Instruments</td>
<td>29/Sep/2021</td>
<td>1</td>
</tr>
<tr>
<td>CPET Report Summary</td>
<td>Other Data Collection Instruments</td>
<td>29/Sep/2021</td>
<td>1</td>
</tr>
<tr>
<td>CARDIOLOGICA Data Dictionary</td>
<td>Other Data Collection Instruments</td>
<td>27/Sep/2021</td>
<td>1</td>
</tr>
</tbody>
</table>

No deviations from, or changes to, the protocol or WREIM application should be initiated without prior written approval of an appropriate amendment from Western HSREB, except when necessary to eliminate immediate hazard(s) to study participants or when the change(s) involves only administrative or logistical aspects of the trial.

REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with, and is constituted in accordance with, the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 0000040.

Please do not hesitate to contact us if you have any questions. Sincerely,

[Signature]

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).
Curriculum Vitae

Name: Randi Keltz

Post-secondary Education and Degrees: The University of Western Ontario
London, Ontario, Canada
2017-2021 B.Sc. Honours

The University of Western Ontario
London, Ontario, Canada
2021-2023 M.Sc. Integrative Biosciences

Honours and Awards: Kinesiology Graduate Student Conference Travel Award
2023

Ontario Graduate Scholarship
2022-2023

Western Scholar
2019-2021

Dean’s Honour List
2018-2019, 2020-2021

The Western Scholarship of Excellence
2017

Related Work Experience: Graduate Teaching Assistant
The University of Western Ontario
2021-2023

Publications:


Publications Under Review:

2. Faricier R, Keltz RR, Hartley T, Prior PL, Suskin NG, Keir DA. Quantifying reliable change in \( \dot{V}O_{2\text{peak}} \) and submaximal exercise thresholds in cardiovascular disease. CHEST-D-23-01840 (In Submission)

Publications in Conference Proceedings:


4. Keltz RR, Guluzade NA, Huggard JD, Keir DA. The relationship between central and peripheral chemoreflex sensitivities and \( \dot{V}E-\dot{V}CO_2 \) slope below and above the respiratory compensation point of incremental exercise. FASEB J 2022;36(S1). 10.1096/fasebj.2022.36.S1.L7767
