

## **CLINICAL TRIAL PROTOCOL**

# **COMPARING THE EFFICACY OF CARDIAC REHABILITATION FOR PATIENTS WITH PERIPHERAL ARTERY DISEASE TO PATIENTS WITH CORONARY ARTERY DISEASE**

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### **List of Abbreviations/ Terminology** *(in alphabetical order)*

6MWT	6 Minute Walk Test
CAD	Coronary Artery Disease
CLI	Critical Limb Ischemia
CI	Confidence Interval
ES	Effect Size
IC	Intermittent Claudication
ICC	Intraclass Correlation Coefficient
PAD	Peripheral Artery Disease
SF-36	Short Form-36 Health Survey
QOL	Quality of Life
TRI	Toronto Rehabilitation Institute
VO2peak	Peak Oxygen Consumption
WIQ	Walking Impairment Questionnaire

### **Protocol Summary**

#### **COMPARING THE EFFICACY OF CARDIAC REHABILITATION FOR PATIENTS WITH PERIPHERAL ARTERY DISEASE TO PATIENTS WITH CORONARY ARTERY DISEASE**

*Short Title:* Exercise for PAD

Clinical Phase / Type of Study: Phase IV

#### **Sample Size**

N= 28 x 2 groups (coronary artery disease (CAD) and peripheral artery disease (PAD))

#### **Study Population**

Patients diagnosed with PAD, CAD or concomitant PAD and CAD. Patients with vascular aneurysms, chronic heart failure, cancer, stroke, respiratory disease, chronic kidney disease, foot ulcers/skin breakdowns which may impede ability to exercise and patients who cannot follow instructions in English will be excluded

#### **Accrual Period**

January 2018 – June 2018

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### **Study Design**

This study is a prospective two-arm cohort study with both groups (CAD and PAD) undergoing the same intervention (standard 6 month out-patient cardiac rehabilitation program offered at the Toronto Rehabilitation Institute Rumsey Centre).

### **Study Duration**

January 2018- December 2018

### **Study Agent/ Intervention/ Procedure**

The standard out-patient cardiac rehabilitation program involves weekly 1.5 hour visits at the Toronto Rehabilitation Institute Rumsey Centre for 6 months. Each visit will consist of an exercise component as well as a risk factor education lecture. Prior to the start of the program, participants will attend two assessment sessions with cardiac rehabilitation staff members to review medical history as well as complete a cardiopulmonary exercise test. During the cardiac rehabilitation program, participants will walk at 60-80% of their  $VO_{2peak}$  heart rate based on the results of their exercise test, as per standard care procedures. Adjustments will be made to the patient's exercise prescription as their fitness improves under the discretion of the cardiac rehabilitation supervisor, as per standard care procedures. Patients will also be asked to exercise an additional four times during the week on their own time for a total of five times per week, as per standard care procedures.

### **Primary Objective**

The primary objective of this proposed study is to compare the magnitude of the responses to a 6-month cardiac rehabilitation program for patients with PAD in contrast to patients with CAD. The primary variable of interest will be peak oxygen consumption ( $VO_{2peak}$ ) with a secondary variable of interest being functional capacity, as measured by the 6-minute walk test. Tertiary variables of interest will include walking impairment, as measured by the Walking Impairment Questionnaire, and quality of life, as measured by the Short Form-36 health survey (SF-36).

**Secondary Objective** The second objective of this proposed study is to determine if the magnitude of responses to cardiac rehabilitation for patients with PAD are dependent on biological sex or type of PAD (asymptomatic, post-surgical intervention, or intermittent claudication).

**Exploratory Objectives** Exploratory objectives include comparing acute exercise responses (prescribed exercise training load, actual training load, exercising heart rate and rating of perceived exertion) between PAD and CAD patients.

**Endpoints of the study** This study will allow for the comparison of the efficacy of cardiac rehabilitation for CAD and PAD patients to provide further support of the application of exercise rehabilitation for PAD patients. In addition, this study will inform future studies investigating optimal exercise prescriptions for PAD patients.

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## **1.0 General Information**

### 1.1 Protocol title and date.

Comparing The Efficacy Of Cardiac Rehabilitation For Patients With Peripheral Artery Disease To Patients With Coronary Artery Disease -November 30, 2017

### 1.2 Name and title of the investigators responsible for conducting the trial

**Dr. Paul Oh**, Principal Investigator, Medical Director of the Cardiovascular Prevention and Rehabilitation Program and a Scientist at the Toronto Rehabilitation Institute (TRI)  
**Cindy Nguyen**, Co-investigator, M.Sc student at the University of Toronto  
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## **2.0 Background Information**

### 2.1 A summary of previous literature

Patients and clinicians have expressed an interest in the use of nonpharmacological interventions for health management (Crowe et al., 2015). Exercise is commonly recommended as a treatment for patients who present with any type of peripheral artery disease (PAD) (Hernando & Conejero, 2007; Ouriel 2001). In fact, participation in exercise programs for treatment of intermittent claudication (IC), which is a hallmark symptom of PAD consisting of pain with walking, is considered a gold standard (Thukkani & Kinlay, 2015). There is strong evidence to support the efficacy of exercise training in improving functional capacity and symptoms for patients with asymptomatic and symptomatic PAD (Class of recommendation I, level of evidence A) (Gerhard-Herman et al., 2017).

The AHA/American College of Cardiology recommend supervised exercise at least three times a week, 30-45 minutes per session for at least 12 weeks for patients with PAD (Gerhard-Herman et al., 2017). All sessions should begin and end with a warm-up and cool-down period, respectively. In contrast, the Canadian Guidelines for Cardiac Rehabilitation and Cardiovascular Disease Prevention recommend PAD patients with IC to exercise for 2 to 5 minutes close to their claudication pain threshold with intermittent breaks of 1 to 2 minutes of passive recovery (Canadian Association of Cardiac Rehabilitation, 2009). Patients should be encouraged to exercise at least three times a week with a goal of gradually decreasing resting time while increasing exercise time (Canadian Association of Cardiac Rehabilitation, 2009). Recommendations specifically for asymptomatic PAD patients are currently unclear.

Supervised programs, similar to cardiac rehabilitation, have been recommended for patients with PAD as first-line therapy prior to consideration for surgical interventions (Milani & Lavie, 2007). Previous research has suggested that exercise programs which utilize a mix of aerobic and resistance exercise tend to result in greater improvements in walking capacity for patients with PAD (Parmenter et al., 2015). In addition, vigorous intensity exercise training leads to greater improvements in  $VO_{2peak}$  (mean difference

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1.42 ml/kg/min, 95% CI: 1.04 to 1.80,  $p < 0.00001$ ) compared to moderate intensity exercise (mean difference = 0.43/ml/kg/min, 95% CI 0.01 to 0.85,  $p = 0.05$ ) (Parmenter et al., 2015). Although optimal exercise prescriptions for patients with PAD remain unclear (Parmenter et al., 2015), cardiac rehabilitation programs consisting of progressive intensity aerobic and resistance exercises appear to be a good starting point. Patients with IC may participate in an interval-style walking program where walking duration and rest periods are defined by pain tolerance and the time it takes for the pain to subside (Hamburg & Balady, 2011). Conversely, patients without IC are recommended to exercise continuously for 30 to 60 minutes per session at a moderate intensity (Hamburg & Balady, 2011).

Exercise appears to be an excellent addition to medical therapy and revascularization procedures. In a randomized trial of patients with aortoiliac PAD, peak walking time improved the greatest among patients who underwent supervised exercise and optimal medical therapy for 6 months compared to patients who underwent stent revascularization with optimal medical therapy and patients who underwent medical therapy alone ( $\Delta 5.8 \pm 4.6$ ,  $\Delta 3.7 \pm 4.9$ , and  $\Delta 1.2 \pm 2.6$  minutes, respectively,  $P < 0.05$ ) (Murphy et al., 2012). This suggests that exercise can lead to greater functional improvements than endovascular procedures when combined with optimal pharmacological interventions. In a trial with femoropopliteal PAD patients randomized to angioplasty, supervised exercise or angioplasty and supervised exercise, all participants had an improvement in IC distance when assessed at the three month follow-up (Mazari et al., 2010). Nevertheless, patients randomized to supervised exercise and angioplasty had the greatest improvement compared to patients randomized to exercise alone and angioplasty alone ( $\Delta 108$ ,  $\Delta 61.2$ ,  $\Delta 59$  meters, respectively,  $P < 0.05$ ). A clinically relevant improvement in walking distance for patients with PAD is considered greater than 100m (Hamburg & Balady, 2011). Exercise and endovascular intervention have statistically and clinically significant increases in walking distance. Improvements in QOL were also observed in all groups (effect size  $> 0.5$ ) (Mazari et al., 2010). Considering the strong evidence, exercise should be automatically recommended in combination with endovascular interventions and/or pharmacological therapy.

Exercise rehabilitation has been shown to improve walking ability among PAD patients (Haas, Lloyd, Yang & Terjung, 2012; Januszek et al., 2014; McDermott et al., 2013). Exercise training can result in two-fold increases in walking time (Bonaca & Creager, 2015). Clinically significant improvements in walking time have been defined as an increase of 5 minutes for patients with PAD (Hamburg & Balady, 2011). Januszek et al. (2014) observed a significant change in walking time from  $470.8 \pm 187.1$  seconds at baseline to  $898.0 \pm 358.7$  ( $P < 0.001$ ) 12-week treadmill training program 3 times a week for patients with IC. Remarkably, improvements in maximal walking time were sustained at follow-up (mean 37 weeks) compared to baseline with clinical and statistical significance ( $470.8 \pm 187.1$  seconds vs.  $775.4 \pm 345.4$  seconds,  $P < 0.001$ ). Small but statistically significant improvements in relative  $\text{VO}_{2\text{peak}}$  for PAD patients in exercise rehabilitation have also been observed compared to control patients who did not participate in exercise rehabilitation ( $\Delta = 0.62$  ml/kg/min (95%CI 0.47 to 0.77,  $P < 0.00001$ ) (Parmenter et al., 2015). The training responses across different clinical presentations of

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PAD (asymptomatic, intermittent claudication (IC), critical ischemia (CLI)) are difficult to compare due to various training protocols and limited exercise training data with asymptomatic and CLI patients .

Patients with coronary artery disease (CAD) undergoing exercise rehabilitation also have significant benefits including a lower risk for cardiovascular mortality (RR=0.74, 95%CI 0.63 to 0.87), fewer hospitalizations (RR=0.69, 95%CI 0.51 to 0.93) and improvements in functional capacity as measured by the 6 minute walk test (6MWT) ( $\Delta=60.43\text{m}$ , 95%CI 54.57 to 66.30m) (Bellet et al., 2012; Heran et al., 2011). In a prospective cohort study with 29 CAD patients undergoing cardiac rehabilitation, there was a significant improvement in  $\text{VO}_2\text{peak}$  ( $\Delta=2.45 \pm 0.5 \text{ mL/kg/min}$ ,  $P<0.001$ ) (Lucini et al., 2002). Greater improvements in  $\text{VO}_2\text{peak}$  were observed in a meta-analysis of CAD patients in cardiac rehabilitation compared to CAD patients who did not participate in cardiac rehabilitation (mean difference =  $3.22\text{mL/kg/min}$ , 95%CI 2.42 to 4.03,  $P<0.01$ ) (Tang, Fu, Zhang, & Zhang, 2014). In spite of the results suggesting that CAD patients have greater improvements in  $\text{VO}_2\text{peak}$  following cardiac rehabilitation compared to PAD patients, there is large variability in exercise prescriptions applied limiting the strength of that conclusion.

Although a great deal of research has supported the efficacy of exercise rehabilitation for PAD, it is infrequently implemented into clinical practices (Milani & Lavie, 2007). In an analysis of the medical treatments accessed by PAD patients, exercise or diet counselling were only used in 22% of visits (Berger & Ladapo, 2017). Implementing risk factor education and exercise rehabilitation programs for patients with PAD would be consistent with the Chronic Care Model to help manage chronic diseases (Lovell, Meyers, Forbes, Dresser, & Weiss, 2011). The integration of the Vascular Clinic at the Toronto Rehabilitation Institute (TRI) will help to provide opportunities of exercise rehabilitation for patients with PAD.

To date, no comparison of cardiac rehabilitation efficacy and acute exercise responses has been made between patients with PAD and patients with CAD. Considering some of the parallels between the two conditions, as they are both atherosclerotic conditions, and the strong recommendations for exercise in both populations, it is worthwhile to compare the efficacy of cardiac rehabilitation responses. It is also unclear if the magnitude of response for PAD patients is dependent on biological sex and clinical presentation as this may influence the development of exercise prescriptions. This proposed study, which is in the process of being registered with [clinicaltrials.gov](https://clinicaltrials.gov), hopes to address these gaps in the literature.

## 2.2. Rationale for the study

It is unclear if cardiac rehabilitation will be as effective for patients with PAD as it is for improving the function and health outcomes of patients with CAD. While there are common pathological traits of CAD and PAD, there are some distinct features that are evident in pathology. Acute responses to exercise have yet to be compared between

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patient populations. As well, differences in responses to cardiac rehabilitation based on biological sex and clinical presentation of PAD are not well established. With the newly implemented cardiac rehabilitation program specifically for patients with PAD at TRI, this proposed study is aligned well to address these gaps in the literature. This trial will be conducted in compliance with the protocol described below as well as ICH and GCP standards.

This research is important as the findings from this study may provide further support for the implementation of PAD-specific exercise rehabilitation programs. Determining the efficacy of cardiac rehabilitation for patients with PAD can also help contribute to the understanding of PAD in relation to exercise. Lastly, determining if the magnitude of response is dependent on biological sex and presentation of PAD can help guide future research in determining optimal exercise prescriptions

### 2.3 Potential Benefits

Patients, the community, and the institution will not benefit directly from this research study as the research intervention is standard care procedures which has been provided to all patients of the Cardiovascular Prevention and Rehabilitation Program at TRI for decades.

The research community will likely benefit from the knowledge gained in this research to help better understand exercise for individuals living with PAD. In addition, this research may inform future research regarding exercise prescriptions for individuals living with PAD.

### 2.4 Description of the population to be studied.

Inclusion criteria will include patients over the age of 18 that have been diagnosed with lower extremity PAD or CAD. Patients with concomitant CAD and PAD will also be included in the study. Group allocation will be based on referring diagnosis. In addition, patients must be able to access and participate in the cardiac rehabilitation program at the TRI.

Patients diagnosed with PAD from the University Health Network and Sunnybrook Hospital will be referred by vascular surgeons to the TRI Rumsey Centre for cardiac rehabilitation. Patients with CAD referred to cardiac rehabilitation will be identified through consented chart review and invited to participate in the study.

Patients with vascular aneurysms, chronic heart failure, cancer, stroke, respiratory disease, or chronic kidney disease will be excluded. Patients with foot ulcers or skin breakdowns which may impede ability to exercise will also be excluded. Patients who cannot follow instructions in English will be excluded. Patients who attend less than 70% of sessions of the weekly sessions at TRI (<10 sessions in total) will be excluded from the main analysis and included in an intention-to-treat analysis.

All patients will provide written informed consent prior to study participation. Patients identified with PAD will be referred by their vascular surgeons from Toronto General



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Hospital to the TRI cardiac rehabilitation program. Upon the initial assessment at TRI, PAD patients will be informed about participating in the proposed study by the principal investigator. CAD patients who have attended an initial assessment and have consented to chart review will have their patient file reviewed to determine if the patient is an appropriate match to a PAD patient based on sex, age, presence of diabetes, and assigned cardiac rehabilitation supervisor. One of the study investigators will then inform the patient during their second assessment at TRI about the study and invite the patient to participate in the study.

### **3.0 Study Objectives and Hypothesis**

#### **3.1 A description of the objectives and the purpose of the study.**

The purpose of this study is to compare the efficacy of a 6-month out-patient cardiac rehabilitation program for patients with CAD to patients with PAD.

##### **3.1.1 Primary objective**

The primary objective of this proposed study is to compare the magnitude of the responses to a 6-month cardiac rehabilitation program for patients with PAD in contrast to patients with CAD. The primary variable of interest will be peak oxygen consumption ( $VO_{2peak}$ ) with a secondary variable of interest being functional capacity, as measured by the 6-minute walk test. Tertiary variables of interest will include walking impairment, as measured by the Walking Impairment Questionnaire, and quality of life, as measured by the Short Form-36 health survey (SF-36).

##### **3.1.2 Secondary objectives**

The second objective of this proposed study is to determine if the magnitude of responses to cardiac rehabilitation for patients with PAD are dependent on biological sex or type of PAD (asymptomatic, post-surgical intervention, or intermittent claudication).

##### **3.1.3 Exploratory objectives**

The exploratory objective is to compare acute exercise responses (prescribed exercise training load, actual training load, exercising heart rate and rating of perceived exertion) between PAD and CAD patients.

#### **3.2 Study hypothesis**

The primary hypothesis is that patients with CAD will have greater improvements in  $VO_{2peak}$  and 6-minute walk test compared to patients with PAD (Lucini et al., 2002; Parmenter, et al., 2015). However, considering the walking limitations patients with PAD often have and the improvements observed with exercise training (Milani & Lavie, 2007; Novakovic et al., 2016), it is hypothesized that patients with PAD will have greater improvements in the WIQ and QOL compared with patients with CAD. Furthermore, a secondary hypothesis that the magnitude of response for patients with PAD will be dependent on biological sex and type of PAD. Lastly, it is hypothesized that patients with PAD on average will have a greater exercising heart rate, rating of perceived exertion and rating of pain severity compare to patients with CAD.

## **4.0 Study Design**

### **4.1 Primary and secondary endpoints**

Patients will undergo a baseline assessment with a laboratory technician involving a standard battery of measurements and questionnaires for characteristic purposes including anthropometrics, resting blood pressure, resting heart rate, smoking status, diabetes status, current exercise regimen, and current medications. During this assessment, clinicians will review previous and ongoing medical treatment (i.e. surgical procedures, next physician visit, ankle-brachial index measurement), presence of angina, and conduct resting 12-lead electrocardiograms. This will be followed by a medical assessment by a physician to further review medical history and safety precautions for exercise. Patients will be sent home with a walking impairment questionnaire (WIQ) (McDermott et al., 1998) and a quality of life (QOL) questionnaire (SF-36) (Brazier et al., 1992) to be submitted at their next visit. A requisition for blood work will also be given to patients to be completed prior to their second visit to determine HbA1c and total cholesterol levels.

During the second visit patients will undergo a maximal cardiopulmonary exercise test to determine cardiorespiratory fitness as measured by  $VO_{2peak}$  and will also have an exercising 12-lead electrocardiogram. The cardiopulmonary exercise test will consist of a Bruce or modified Bruce treadmill protocol (Noonan and Dean, 2000).

After determining baseline  $VO_{2peak}$ , an individualized walking exercise prescription will be developed by a cardiac rehabilitation supervisor which corresponds to approximately 60 to 80% of  $VO_{2peak}$ . Patients will be invited to attend weekly 90-minute supervised exercise and education sessions at the same time every week for six months, as per standard care procedures. Patients will be encouraged to gradually increase their exercise time per session as well as frequency of sessions per week.

Clinicians at TRI will record distance walked, rest periods, exercising heart rate (as palpated by the radial pulse), ratings of perceived exertion and ratings of pain severity on a scale of 0 (no pain) to 10 (worst imaginable pain) (Hawker, Mian, Kendzerska, & French, 2011) for each exercise session at TRI. Patients will self-record their other exercise sessions on a weekly basis using standard exercise diaries. Frequency, time, type, exercising heart rate and rating of perceived exertion will be recorded for each exercise session outside of TRI. Patients will wear a non-invasive heart rate monitor (Polar) while walking at the 2<sup>nd</sup> week, 3<sup>rd</sup> month and 6<sup>th</sup> month mark of the program to help determine acute responses to aerobic exercise. Average exercising heart rate will be measured and recorded.  $VO_{2peak}$ , 6MWT, QOL (SF-36), and walking impairment (WIQ) will be re-assessed at the 3 month and 6 month mark of the program.

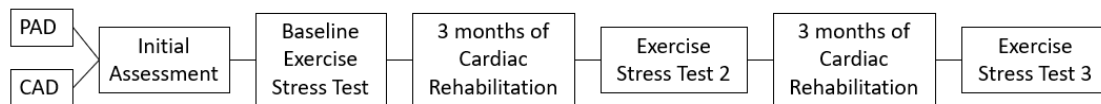
Training volume will be quantified for each group for the prescribed and actual exercise load. For aerobic exercise, training will be calculated as the product of intensity in heart rate reserve, duration, and frequency for both the prescribed and actual exercise. For resistance exercise, training will be calculated as the product of weight, numbers of sets, and number of repetitions for each exercise for both prescribed and actual exercise.

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The primary endpoints of interest include change in  $VO_2$ peak from month 6 to baseline, change in 6 minute walk test distance from month 6 to baseline, as well as change in walking impairment and quality of life as assessed through questionnaires from month 6 to baseline.

#### 4.2 Study Design

This study will be an interventional two-arm prospective cohort study. Both arms (PAD and CAD participants) will undergo the same standard 6 month out-patient cardiac rehabilitation program.



#### 4.3 A description of the measures taken to minimize/avoid bias

The University of Health Network policy requires that all patients be aware of any medical treatment they are receiving and provide informed consent. As a result, it is not possible for patients to be blinded to which treatment they are receiving.

To avoid bias for the ankle brachial index measurement, the order in which blood pressure is measured on each limb will be randomized.

#### 4.4 A description of the trial treatment(s)/ intervention

The standard 6-month out-patient cardiac rehabilitation program consists of weekly 1.5 hour visits to the TRI Rumsey Centre. After determining baseline  $VO_2$ peak from the exercise stress test, an individualized walking exercise prescription will be developed by a cardiac rehabilitation supervisor which corresponds to approximately 60 to 80% of the participant's  $VO_2$ peak. Participants will be invited to to walk around the track and attend education sessions at the same time every week for six months. Patients will be encouraged to gradually increase their exercise time walking speed. Patients will be encouraged to exercise five times a week with four sessions occurring outside of the cardiac rehabilitation program.

#### 4.5 The expected duration of subject participation

Participants will be part of the program for 6 months, as per standard care procedures.

#### 4.6 The expected frequency and duration of study visits (anticipated time commitment) for study participants

There will be six study visits in total which coincide with standard care visits as well as the weekly visits to the cardiac rehabilitation program. Participants will not be required to make any additional visits outside of the standard cardiac rehabilitation program.

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The first visit will take approximately 60 minutes and is consistent with standard care at the TRI Rumsey Centre cardiac rehabilitation program. A cardiac rehabilitation staff member will measure anthropometrics, blood pressure and will review medical history (e.g. smoking status, diabetes status, medications, current exercise regimen). The patient will also meet with a physician to review any concerns with starting the cardiac rehabilitation program. The patient will also be introduced to the study investigator if the patient expresses an interest in participating in the research study. All patients are given a blood work requisition to be completed at their local medical laboratory and if patients choose to consent to participating in the study, they will be given two questionnaires (WIQ and SF-36) to be completed for their next visit (approximately 15 minutes to complete both questionnaires).

The second visit is also consistent with standard care procedures and involves an exercise stress test with cardiac rehabilitation staff members. The exercise test will take approximately 60 minutes including preparation time, exercise time and time for questions. For the exercise stress test, patients will walk on a treadmill or pedal on a bicycle while having their breathing and blood pressure analyzed to measure  $\text{VO}_2\text{peak}$ . Patients will also be attached to a 12-lead electrocardiogram to non-invasively measure activity of the heart.

The third visit will take approximately 30 minutes and will occur before the first cardiac rehabilitation class. While lying down in a private examination room, participants will have their blood pressure measured with an automated machine twice on the right arm, left arm, right ankle and left ankle in a random order. This will allow for calculation of the ankle brachial index for characteristic purposes.

The fourth visit will take approximately 60 minutes with 15 minutes occurring before class and 45 minutes during the exercise portion of the cardiac rehabilitation class. Prior to class, participants will participate in a 6-minute walk test to measure functional capacity. This will consist of participants walking as far as they can in 6 minutes at their own pace. During the 45 minute exercise component of the cardiac rehabilitation class, participants will have a chest strap placed underneath their clothing at the xiphoid-level to measure exercising heart rate.

The fifth visit will take approximately 60 minutes and will be structured exactly like the fourth study visit. Participants will be asked to participate in a 6-minute walk test 15 minutes prior to class and will have a heart rate monitor chest strap attached underneath their clothing while participating in the exercise portion of the cardiac rehabilitation class. Participants will also be given two questionnaires (WIQ and SF-36) to complete for their next visit (approximately 15 minutes).

The sixth and final visit at the 6 month mark of the program will take approximately 30 minutes. Participants will participate in the 6 minute walk test and will be given two questionnaires (WIQ and SF-36) to complete. During class, participants will have a heart rate monitor chest strap attached underneath their clothing.

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#### 4.7 A description of the "stopping rules" or "discontinuation criteria"

Participants can choose to withdraw from the study at any time. If the participant experiences a musculoskeletal injury during the 6-month cardiac rehabilitation program, either alternative exercises will be offered by the cardiac rehabilitation supervisor or they will be asked to discontinue the cardiac rehabilitation program until their injury heals.

#### 4.8 The identification of any data to be recorded directly on the CRFs

All patients are asked during their initial visit to TRI of whether they consent to a chart review by research personnel. All participants of the study will have provided consent to a chart review and will have study data recorded on a data collection sheet with a unique research identification number.

Data to be collected includes age, biological sex, type of PAD or CAD, diabetes status, smoking status, risk factors, current exercise regimen, medications, VO<sub>2</sub>peak, HbA1c levels, total cholesterol, blood pressure, and exercise prescription.

### **5.0 Selection of Subjects**

#### 5.1 Subject inclusion criteria.

Inclusion criteria will include patients over the age of 18 that have been diagnosed with lower extremity PAD or CAD. Patients with concomitant CAD and PAD will also be included in the study. Group allocation will be based on referring diagnosis. In addition, patients must be able to access and participate in the cardiac rehabilitation program at the TRI.

In order to compare patients with PAD to patients with CAD and to control for confounding variables, matching will be based on biological sex, age ( $\pm 5$  years), presence of diabetes (yes or no), smoking status (current, previous, never), and cardiac rehabilitation supervisor.

Patients diagnosed with PAD from the University Health Network and Sunnybrook Hospital will be referred by vascular surgeons to the TRI Rumsey Centre for cardiac rehabilitation. Patients with CAD referred to cardiac rehabilitation will be identified through consented chart review and invited to participate in the study.

#### 5.2 Subject exclusion criteria.

Patients with vascular aneurysms, chronic heart failure, cancer, stroke, respiratory disease, or chronic kidney disease will be excluded. Patients with foot ulcers or skin breakdowns which may impede ability to exercise will also be excluded. Patients who cannot follow instructions in English will be excluded. Patients who attend less than 70% of sessions of the weekly sessions at TRI (<10 sessions in total) will be excluded from the main analysis and included in an intention-to-treat analysis.

#### 5.3 Withdrawal of Subjects

Participants may choose to withdraw from the study at any time. Any data collected will be discarded immediately.

## **6.0 Study Intervention**

The study intervention is consistent with the standard 6-month out-patient cardiac rehabilitation program consists of weekly 1.5 hour visits to the TRI Rumsey Centre. After determining baseline  $\text{VO}_2\text{peak}$  from the exercise stress test, an individualized walking exercise prescription will be developed by a cardiac rehabilitation supervisor which corresponds to approximately 60 to 80% of the participant's  $\text{VO}_2\text{peak}$ . Participants will be invited to walk around the track and attend education sessions at the same time every week for 6 months. Patients will be encouraged to gradually increase their exercise time walking speed. Patients will be encouraged to exercise five times a week with four sessions occurring outside of the cardiac rehabilitation program.

Clinicians at TRI will record distance walked, rest periods, exercising heart rate (as palpated by the radial pulse), ratings of perceived exertion (Borg scale) and rating of pain severity on the Numeric Rating Scale for Pain (numeric scale from 0 to 10, 0 being no pain and 10 being worst pain imaginable) (Hawker, Mian, Kendzerska, & French, 2011) for each exercise session at TRI. Patients will self-record their other exercise sessions on a weekly basis using exercise diaries. Frequency, time, type, exercising heart rate and rating of perceived exertion will be recorded for each exercise session outside of TRI.

## **7.0 Assessment of Efficacy**

Peak oxygen consumption ( $\text{VO}_2\text{peak}$ ) measured through a treadmill test is a standard measure of cardiorespiratory fitness. A meta-regression analysis of various treadmill protocols for patients with PAD found that continuous protocols had an intraclass correlation coefficient (ICC) of 0.85 (95% CI 0.82 to 0.88) and graded protocols had an ICC of 0.83 (95% CI 0.80 to 0.85). Graded protocols were more reliable than continuous protocols for absolute claudication distance (ICC=0.95, 95% CI 0.94 to 0.96).

Continuous protocols had the greatest reliability at a grade of 12 % (ICC=0.91, 95% CI 0.88 to 0.92) (Nicolai et al., 2009). In addition to being used for characteristic purposes,  $\text{VO}_2\text{peak}$  can also be an outcome measure to determine the effectiveness of interventions. In a systematic review and meta-analysis, the mean difference in relative  $\text{VO}_2\text{peak}$  for PAD patients who underwent exercise training compared to control patients was 0.62 ml/kg/min (95%CI 0.47 to 0.77,  $P<0.00001$ ) (Parmenter et al., 2015). This suggests that  $\text{VO}_2\text{peak}$  is responsive to changes following exercise interventions. It should be noted that although  $\text{VO}_2\text{peak}$  is one parameter used to define intensity in exercise prescriptions, PAD patients with IC often exercise according to pain tolerance (Hamburg & Balady, 2011).

The walking impairment questionnaire (WIQ) is a validated method of quickly measuring walking ability in men and women with PAD (McDermott et al., 1998). The WIQ consists of 14 items related to walking distance, walking speed and stair climbing ability using a scale from 0 to 4 to rank degree of difficulty. An overall score below 42.5 suggests a patient with low walking ability (sensitivity 0.90, specificity of 0.73) whereas a score above 75.5 suggests a patient with a high walking ability (sensitivity 0.41, specificity 0.90) (Sagar, Brown, Zelt, Pickett & Tranmer, 2012). In a cross-sectional

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study validating the WIQ, the WIQ distance score was moderately correlated with 6MWT times with a Spearman rank correlation coefficient of 0.557 for patients with PAD (McDermott et al., 1998). Considering the evidence, the WIQ is a useful clinical tool to assess walking ability.

Montgomery and Gardner (1998) determined test-retest reliability using multiple 6MWT trials among 64 PAD patients. The distance walked and number of steps taken were similar between trials with a reliability coefficient of  $R=0.94$  and  $R=0.90$ , respectively. QOL can be measured through standardized general questionnaires such as the Short-Form 36 health survey (SF-36). The SF-36 is the most common instrument used to measure health related QOL in physical activity research (Hart & Kang, 2015; Novakovic et al., 2016; Stoner et al., 2016). It has high internal consistency (Cronbach's  $\alpha>0.8$ ), with the exception of social functioning likely due to having only two items in that domain ( $\alpha=0.79$ ), among older adults (Brazier et al., 1992; Walters, Munro & Brazier, 2001). A meta-analysis of the reliability of the SF-36 in physical activity research with various research designs and patient populations found strong effect sizes (ES) for physical health (ES=0.90, 95% CI: 0.88 to 0.92,  $P<0.001$ ) and mental health (ES=0.90, 95% CI: 0.89 to 0.91,  $P<0.001$ ) domains (Hart & Kang, 2015). This suggests that the SF-36 is a responsive measure of QOL for physical activity research. The SF-36 is also considered to be a suitable general measure of QOL for patients with PAD (Mehta, Subramaniam & McCollum, 2003).

## **8.0 Statistics**

### **8.1 A description of the statistical methods to be employed**

Primary analysis to determine if patients with CAD or patients with PAD have greater improvements in  $VO_{2peak}$ , 6MWT, WIQ, and QOL will be tested with a series of two factor 2 (time: Baseline, End) by 2 (group: PAD, CAD) analyses of variances with Tukey's Honest Significant Difference (HSD) test for post-hoc corrections. This analysis will include patients who attended  $>70\%$  of on-site cardiac rehabilitation sessions. An intention-to-treat analysis will be conducted to include patients who attended less than 70% of the cardiac rehabilitation program sessions.

The secondary hypothesis that the magnitude of responses for patients with PAD will be dependent on biological sex will be tested through conducting a 3 factor 2 (time: Baseline, End) by 2 (group: PAD, CAD) by 2 (sex: men, women) analysis of variance. In addition to determine if the magnitude of responses are dependent on clinical presentation of PAD, a 2 factor 2 (time: Baseline, End) by 2 (type: asymptomatic, post-surgical intervention, IC) analysis of variance will be conducted.

To determine if PAD patients have greater exercising heart rate, rating of perceived exertion (Borg scale), rating of pain severity, and training volumes than CAD patients, tertiary analysis will involve independent t-tests for these variables.

### **8.2 The number of subjects planned to be enrolled**

Sample size calculations were conducted using an alpha of 5% and a power of 0.8. Calculations were based on the primary and secondary variables of interest ( $VO_{2peak}$

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and 6MWT distance) for PAD and CAD patients. To be conservative, the largest sample size (6MWT) was selected.

Previous literature has found that patients with PAD undergoing exercise training compared to PAD patients who did not undergo exercise training had improvements in the 6MWT of 34.9m (95 % CI 25.6–44.1 m,  $P < 0.00001$ ) (Parmenter et al., 2015). In contrast, patients with CAD had improvements of  $29.6 \pm 12$ m following exercise training (Jaureguizar et al., 2016). Clinically significant changes have been defined as 20m for the 6MWT (Perera et al., 2006). A difference of 10 meters between groups is a conservative average between what is observed in the literature and the defined clinically significant change. The sample size calculation for a power of 0.8 would be 23 participants per group. Accounting for a 20% drop out, 28 patients with CAD and 28 patients with PAD will be recruited. Statistical significance will be set at a P value of 0.05.

A sample size of 28 participants per group is powered to detect a difference of 1.6 ml/kg/min between groups for  $VO_{2peak}$ .

### 8.3 Procedure for accounting for missing, unused, and spurious data.

If data variables are missing, the whole participant data set will be excluded from the main statistical analysis. If some data is available, the participant's data will be included in the intention to treat analysis.

## **9.0 Direct Access to Source Data/Documents**

Only study investigators (Dr. Paul Oh, Dr. Scott Thomas, and Cindy Nguyen) will have direct access to study related documents.

## **10.0 Quality Control and Quality Assurance Procedures**

Study investigators will review data collection forms as well as the completeness of the questionnaires when data is collected to ensure accuracy and completeness.

## **11.0 Ethics**

### 11.1 Consent process

All patients will provide written informed consent prior to study participation. Patients identified with PAD will be referred by their vascular surgeons to the TRI cardiac rehabilitation program. Upon the initial assessment at the Rumsey Centre, PAD patients will be informed about participating in the proposed study by a cardiac rehabilitation staff member. If the patient is interested, the cardiac rehabilitation supervisor will introduce the patient to one of the study investigators to provide the potential participant with further study details. If the patient wishes to participate in the study, they will provide written informed consent.

CAD patients who have attended an initial assessment and have consented to chart review will have their patient file reviewed to determine if the patient is an appropriate match to a PAD patient based on sex, age ( $\pm 5$  years), presence of diabetes, and assigned



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cardiac rehabilitation supervisor. A cardiac rehabilitation staff member will inform the patient about the research study. If the patient expresses interest, they will be introduced to one of the study investigators who will provide further study details during their second assessment.

#### 11.1.1 A description of the identification process

TRI is launching a Vascular Program designed to support patients with PAD seeking opportunities to manage their condition. All patients part of the Vascular Program will be referred by vascular surgeons. The cardiac rehabilitation staff helping with the Vascular Program will be informed about this proposed research study and will introduce all PAD patients to the opportunity. If patients express an interest in learning further details, the staff member will introduce the patient to one of the study investigators.

CAD patients will be identified through consented chart review. All patients in the cardiac rehabilitation program at TRI are asked during the initial assessment whether they would like to consent to a chart review by research personnel as part of standard procedures. The study investigators will review the patient charts to find a match to a participant with PAD. The study investigator will notify the cardiac rehabilitation staff members conducting the exercise stress test to inform the patient about the study. If the patient expresses interest in learning further details, the staff member will introduce the patient to one of the study investigators.

#### 11.1.2 A description of who will make initial contact with research participants

Potential research participants will be informed about the study through a cardiac rehabilitation staff member. If interested, the individual will be introduced to one of the study investigators.

#### 11.1.3 A description of who will obtain informed consent from research participants.

Cindy Nguyen, MSc candidate, will obtain written informed consent from the research participants. Ms. Nguyen has over 4 years of research experience as a research assistant at the University of Toronto's Training and Performance Laboratory under supervision by Dr. Scott Thomas.

#### 11.2 A statement of review and approval of the study by the Research Ethics Board before any study related procedures commenced.

Participant recruitment and data collection for this study will only begin when approval is given by the Research Ethics Board.

#### 11.3. A statement of review and approval of any amendment to the study by the Research Ethics Board before any changes implemented beside these to eliminate immediate hazard to the study participants.

If any changes to the study protocol are planned, the Research Ethics Board will be contacted and informed through an amendment prior to the change being implemented.

## **12.0 Data Handling and Record Keeping**

12.1.A description of the process for data recording to ensure accuracy, completeness, legibility, and timeliness of the data.

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Data will be recorded on a data collection sheet and will be reviewed following each study visit to ensure accuracy, completeness, and legibility. We hope to begin data collection in January 2018 and complete data collection by December 2018.

#### 12.2 A description of where the data will be recorded

Data will be recorded on a data collection sheet and will be stored in a locked cabinet in the TRI Rumsey Centre room 231.

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