The Selection of Cardiopulmonary Exercise Testing Protocols for Patients with Coronary Artery Disease

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Preface

This thesis contains data from an observational study, “Selection of Cardiopulmonary Exercise Testing Protocols in Cardiovascular Rehabilitation centres across Canada” (TRADE), and a randomized single blind cross-over trial, “Comparing Peak $\dot{V}O_2$ Values of Exercise Testing Protocols for Females and Males with CAD” (PACED), that was designed and conducted by the student (Jennie Wong) with guidance from supervisors Dr. Jennifer Reed and Dr. Kristi Adamo. All data were collected and stored at the University of Ottawa Heart Institute. TRADE was approved as a quality improvement (QI) project by the Ottawa Health Science Network Research Ethics Board and was registered as a QI project with the University of Ottawa Heart Institute (QI-167). Ethics approval for the PACED trial was obtained from the Ottawa Health Science Network Research Ethics Board (OHSN-REB#: 20230327-01H) and the University of Ottawa Office of Research Ethics and Integrity (H-02-25-11335). The equipment and consumables for the PACED trial were supported by Dr. Jennifer Reed’s research program. The student received funding from the University of Ottawa Heart Institute and the University of Ottawa in the form of academic scholarships for the first three years of the master’s program.

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List of Abbreviations

6MWT: 6-minute walk test
ACE: Angiotensin-converting enzyme
ACSM: American College of Sports Medicine
AHA: American Heart Association
ATP: Adenosine triphosphate
A-$\dot{V}$O2: Arteriovenous oxygen difference
BMI: Body mass index
BP: Blood pressure
CABG: Coronary artery bypass graft
CACPR: the Canadian Association of Cardiovascular Prevention and Rehabilitation
CAD: Coronary artery disease
CCS: Canadian Cardiovascular Society
CI: Confidence interval
COPD: Chronic obstructive pulmonary disease
CPET: Cardiopulmonary exercise test
CR: Cardiac rehabilitation
CRF: Cardiorespiratory fitness
CVD: Cardiovascular disease
DBP: Diastolic blood pressure
ECG: Electrocardiogram
eNOS: endothelial nitric oxide synthase
EPCHL: Exercise Physiology and Cardiovascular Health Lab
FITT: Frequency, Intensity, Time, Type
GERD: gastroesophageal reflux disease
HDL: high density lipoprotein
HR: Heart rate
HRR: Heart rate reserve
ICD: Implantable cardioverter-defibrillator
IPAQ: International Physical Activity Questionnaire
IQR: interquartile range
LDL: Low-density lipoproteins
LDL-C: Low density lipoprotein cholesterol
MCID: Minimal clinically important difference
MET: Metabolic equivalent
MI: Myocardial infarction
NSTEMI: Non-ST-elevation myocardial infarction
OHSN-REB: Ottawa Health Science Network Research Ethics Board
PA: Physical activity
PACED: Comparing Peak $\dot{V}O_2$ Values of Exercise Testing Protocols for Females and Males with CAD
PCI: Percutaneous coronary intervention
$\dot{Q}$: Cardiac output
QI: Quality improvement
RER: respiratory exchange ratio

R.Kin: Registered Kinesiologist
RPE: Rating of perceived exertion
SBP: Systolic blood pressure
SCAD: Spontaneous coronary artery dissection
SOP: Standard operating procedure
STEMI: ST-elevation myocardial infarction
SV: Stroke volume
TRADE: Selection of Cardiopulmonary Exercise Testing Protocols in Cardiovascular Rehabilitation centres across Canada
UOHI: University of Ottawa Heart Institute
$\dot{V}O_2$: Oxygen consumption
$\dot{V}O_{2\ peak}$: Peak oxygen consumption
$\dot{V}O_{2\ max}$: Maximal oxygen consumption
VT: Ventilatory threshold
VT1: First ventilatory threshold
VT2: Second ventilatory threshold

Thesis Abstract

Coronary artery disease (CAD) is the most common type of cardiovascular disease (CVD). Cardiorespiratory fitness (CRF), which can be measured using cardiopulmonary exercise testing (CPET), is a strong independent predictor of mortality. Maximal and submaximal exercise tests are commonly used to assess the CRF of patients in cardiovascular rehabilitation (CR) programs. Maximal exercise tests are performed until volitional exhaustion, whereas submaximal exercise tests are usually terminated at 85% of age-predicted maximal heart rate (HR). Over the past 75 years, several protocols have been developed for measuring CRF. However, most of these were created and validated in predominantly male populations (males = 85.7%, females = 14.3%). Due to anatomical and physiological differences between males and females, it should not be assumed that the most optimal maximal and submaximal exercise testing protocols would be the same for females and males. The overall aim of my thesis was to investigate the exercise testing practices in CR programs across Canada and the optimal maximal and submaximal exercise testing protocols for assessing peak $\dot{V}O_2$ in females and males with CAD.

Study 1, TRADE, was an observational pan-Canadian survey to determine (i) which maximal and submaximal exercise testing protocols are most frequently used in CR programs across Canada; (ii) how many maximal and submaximal protocols are used at each CR centre; (iii) how many maximal and submaximal tests are completed per year; (iv) the number of times each maximal and submaximal protocol is used per year; (v) which healthcare professional is most often selecting the exercise testing protocol; and (vi) the decision making process and criteria used for selecting an exercise testing protocol. The TRADE survey was completed by 118 CR programs (30.4% of programs in Canada). Of the 85 centres (72.6%) which perform

exercise testing, 13 (14.9%), 42 (49.4%), and 26 (29.9%) complete maximal, submaximal, and both maximal and submaximal exercise testing, respectively. The Bruce treadmill and 6-minute walk tests were the most frequently used maximal (82.1%) and submaximal (75.0%) exercise tests, respectively. It was estimated that 3,610 – 4,910 and 18,000 – 22,710 maximal and submaximal exercise tests, respectively, were performed annually across Canada. The Bruce test was used approximately 3,560 – 4,790 times per year and the 6MWT was used approximately 13,940 – 16,650 times per year. Physicians were the leading decision-makers, overseeing testing protocols in 38 of the 118 programs, and the most common criteria for selecting an exercise testing protocol included standard procedures developed by management (n = 18).

Study 2, PACED, was a randomized single blind cross-over trial to determine if peak $\dot{V}O_2$ varied between different maximal and submaximal treadmill exercise testing protocols for females and males with CAD. Key secondary research questions examined: (i) how cardiometabolic responses and ratings of perceived exertion (RPE) compare between different maximal and submaximal protocols; (ii) how different increments of grade speed affect test duration for maximal and submaximal exercise tests; and (iii) the most common reason for test termination for maximal exercise tests for females and males with CAD. The study included 20 participants (7 females [age: 64 ± 7 years] and 13 males [age: 64 ± 8 years]). For females, there was a significant difference in peak $\dot{V}O_2$ across the protocols ($F = 9.222$, $p = 0.001$); however, the location of the difference in peak $\dot{V}O_2$ could not be identified, likely due to insufficient power as few females completed the modified Balke protocol. No difference in peak HR was observed across the protocols ($F = 3.079$, $p = 0.425$). Females appeared to achieve greater peak systolic BP during the modified Balke protocol (SBP: 190 ± 21 mmHg, $F = 0.40$, p = N/A) and higher peak blood lactate concentrations (5.2 ± 1.1 mmol/L, $F = 1.395$, p = N/A) using the

Modified Balke protocol; yet, due to a small sample size, there was an insufficient power for this analysis. Females achieved a higher RPE using the UOHI Slow Ramp protocol (18 ± 3 points, $F = 0.594$, $p < 0.05$). For females, 67% cited speed as the primary reason for test termination for the modified Balke, 29% and 50% cited shortness of breath for the modified Bruce and UOHI Slow Ramp, respectively, and 33% cited musculoskeletal fatigue for the modified Naughton. For males, no difference in peak $\dot{V}O_2$ was observed across the protocols ($F = 0.189$, $p = 0.75$). Also, no differences in peak HR ($F = 0.2023$, $p = 0.649$), systolic BP ($F = 1.015$, $p = 0.420$), diastolic BP ($F = 0.786$, $p = 0.524$), blood lactate concentrations ($F = 1.015$, $p = 0.409$), or RPE ($F = 1.701$, $p = 0.197$) was observed across the protocols. For males, 20% cited speed as the primary reason for test termination for the modified Balke, while 28% cited muscuolskeletal fatigue for the modified Bruce, and 23% and 50% cited shortness of breath for the modifed Naughton and UOHI Slow Ramp, respectively.

These thesis findings suggest that although the Bruce protocol is the most used maximal exercise testing protocol for measuring CRF in patients with CVD across Canada, the modified Naughton protocol should be used for females with CAD to achieve their highest peak $\dot{V}O_2$. These findings contribute to our understanding of how different CPET protocols can impact individual CRF and cardiometabolic responses in patients with CAD, though future studies should explore larger sample sizes to adequately (with sufficient sample sizes) capture these sex-specific responses.

Chapter 1: Background and Review of Literature

1.1 Coronary Artery Disease

1.1.1 Epidemiology

Cardiovascular disease (CVD) is the leading cause of death worldwide with approximately 9.4 million deaths annually.[1,2] Coronary artery disease (CAD), also referred to as ischemic heart disease or coronary heart disease, is the most common type of CVD[2] and constitutes 20.3% of the 620 million CVD cases worldwide.[1,3] CAD is an atherosclerotic disease characterized by the buildup of plaque in the artery walls causing the arteries to become narrow or blocked.[4] In 2017, it was estimated that 2.4 million (8.5%) of Canadians aged 20 years and older were living with CVD[5] and CAD, in particular, affected 244.1 million individuals globally (141.0 million males and 103.1 million females). This is approximately 3.03% of the world's population.[6] Genetics, environmental (e.g., tobacco smoke and inhaled pollutants), and lifestyle factors (i.e., sedentary behaviour and physical inactivity) have been found to play a role in the development of CAD.[4]

1.1.2 Pathophysiology

1.1.2.1 Risk Factors

Major risk factors for CAD include being physically inactive (i.e., defined as not meeting physical activity [PA] guidelines) (see section 1.2), diabetes, hypertension, sex hormones, hyperlipidemia, hyperglycemia, obesity, poor dietary choices, excessive alcohol consumption, and smoking.[7–9] While both males and females share common risk factors for cardiovascular disease, the influence or significance of these factors can differ between sexes such that certain factors may have a greater impact on the heart health of males compared to females, and vice

versa.[8] This variation in the presence and severity, often referred to as "weighting," helps to understand why clinical symptoms and the manifestation of CAD differs between males and females. These variations can help explain why women may not be diagnosed with CAD as often as men, even though they share some common risk factors.[8–10]

Females compared to males with diabetes are 50% more likely to develop CAD and the reasons are multifactorial; less aggressive treatment of diabetes in women, greater activation of inflammatory markers and smaller vessel size of coronary arteries.[10] Growing research has highlighted the dynamic relationship between diabetes, inflammation, and risk of CAD.[11] Females with diabetes often exhibit a greater activation of inflammatory markers than their male counterparts.[11] This hyperactive inflammatory response may significantly contribute to the accelerated progression of atherosclerosis, ultimately elevating the likelihood of CAD development in women.[11] Studies have consistently demonstrated that women generally possess smaller coronary vessels than men,[12,13] and this unique anatomical characteristic has emerged as a relevant factor in the development of CAD.[14] This difference in vessel size not only influences hemodynamics but also contributes to the susceptibility for atherosclerotic plaque formation, thereby amplifying the risk of CAD in women with diabetes.[12,13] Equally important is the gender/sex-based disparity in the management of diabetes. Existing evidence suggests that women with diabetes may receive less aggressive treatment when compared to men for their CAD.[15] Disparities in medication dosages, glycemic control strategies, and lifestyle interventions contribute to differences in the management of diabetes, potentially leaving women more vulnerable to CAD.[10,16] Therefore, the combined effect of increased inflammation, smaller coronary artery size, and less aggressive diabetes management creates a complex web of influences that can lead to elevated CAD risk in females with diabetes.

Hypertension is a more significant risk factor for CAD in females than in males due to biological, hormonal, and epidemiological differences.[17] Studies have shown that women experience more severe vascular damage from elevated blood pressure (BP) when compared to men, even at similar levels of hypertension (i.e., comparable systolic and diastolic BP values between men and women).[17] This is partly due to sex-specific differences in vascular physiology, such as smaller arterial diameters and less compliant vascular walls in women, which leave their arteries more susceptible to adverse effects of elevated BP.[17] In addition, females who have experienced a pregnancy complication (i.e., preeclampsia, gestational diabetes, and pre-term delivery) are at a heightened risk for CVD.[18,19] Furthermore, the protective role of estrogen in premenopausal women helps to regulate vascular tone and reduce oxidative stress; however, following menopause, this protection diminishes, exacerbating the impact of hypertension on cardiovascular health.[20,21] CVD risk after menopause increases due to a variety of factors including changes in endogenous sex hormones[8,21] (i.e., a decrease in estrogens contributes to endothelial dysfunction, increased arterial stiffness, and a greater risk of atherosclerosis; a decrease in progesterone exacerbates vascular changes, as progesterone modulates smooth muscle relaxation and inflammatory processes; and androgens may contribute to visceral fat deposition and insulin resistance),[21] body composition[8] (i.e., increase in visceral fat and decrease in lean muscle mass),[21] lipid profiles[8] (increases in total cholesterol and low-density lipoprotein cholesterol [LDL-C] accelerates plaque formation in arterial walls and an increase in triglycerides increases atherogenic risk),[21] and vascular health[8] (loss of estrogen reduces endothelial nitric oxide synthase [eNOS] activity, impairing vasodilation and increasing vascular stiffness).[8,21] It is crucial to recognize that these factors do not act in isolation; rather, they interact synergistically.

It has been widely established that hyperglycemia is a significant risk factor for CVD.[22–25] Blood glucose concentrations in patients without diabetes exceeding 100mg/dL has been associated with a significant increase in CAD risk with a hazard ratio of 1.24 (95% confidence interval [CI] 1.16 to 1.33).[25] Prolonged exposure to hyperglycemia is a major factor in the pathogenesis of atherosclerosis.[24] Elevated blood glucose concentrations drive three key cellular alterations in vascular tissue that accelerate atherosclerotic plaque formation.[24] First, non-enzymatic glycosylation of proteins and lipids can interfere with normal function of cells by altering enzymatic activity and interfering with receptor recognition.[24] Secondly, an increase in oxidative stress occurs from the interaction of glycosylated proteins with their receptors which results in an increase in oxidative stress and proinflammatory responses.[24] Thirdly, the activation of protein kinase C can alter the growth factor expression.[24] These three alterations can be interrelated and can trigger a chain reaction whereby these changes contribute to an increased risk of CAD.[24]

Other well established risk factors for the development of CAD include but are not limited to obesity, poor dietary choices, excessive alcohol consumption and smoking.[7–9] Obesity is linked with an elevated risk of CVD due to mechanisms that are associated with CAD such as dyslipidemia, hypertension, and type 2 diabetes.[26] Obesity, particularly visceral adiposity, is associated with increased inflammation and metabolic dysfunction which leads to endothelial dysfunction, a process within the pathogenesis of CAD which leads to the narrowing of blood vessels which can result in cardiac related events such as a myocardial infarction (MI) or stroke.[26] Poor dietary choices such as diets high in saturated fats and refined sugars, and low in fruits and vegetables can also contribute to the development of atherosclerosis by promoting dyslipidemia and insulin resistance.[27] Evidence has shown that a reduction in saturated fat is

important for lowering low-density lipoprotein (LDL) cholesterol which is key for preventing CVD and improving cardiovascular health.[27] High carbohydrate diets coupled with obesity favours the development of atherogenic dyslipidemia and increases the risk for CVD.[27]

Lifestyle factors such as alcohol consumption and smoking can also increase CVD risk.[28] High levels of alcohol consumption (i.e., three to seven or more drinks per week) are associated with an increased cardiovascular risk.[28,29] Alcohol consumption of greater than 2.5 drinks per day for females and greater than 4 drinks per day for males are associated with higher death rates in a dose-dependent relationship.[28] These high levels of alcohol consumption increase the risk of CAD through several harmful mechanisms: (1) hypertension (excessive alcohol intake raises BP and chronic high BP will cause damage to the artery walls and lead to atherosclerosis);[17] (2) elevated triglycerides (heavy drinking increase triglycerides in the blood and lowers high-density lipoprotein [HDL] cholesterol,[30] which contributes to the build-up of plaque in the arteries, increasing the risk for CVD);[30] and (3) inflammation and oxidative stress[30] (high consumption of alcohol triggers inflammation and oxidative stress within the cardiovascular system, liver, and gut which leads to damage to the blood vessels and the promotion of atherosclerotic plaque, therefore restricting blood flow to the heart).[30] Finally, the harmful effects of smoking on the cardiovascular system are multifaceted and involve several mechanisms. Females who smoke are 25% more likely to develop CVD when compared to their male counterparts due to greater absorption of toxic agents from cigarettes.[31,32] Smoking releases many toxins into the bloodstream and the absorption of these products can result in an increase in endothelial dysfunction and promotion of atherosclerosis.[33,34] Smoking elevates systemic catecholamine levels, which subsequently impair oxygen-carrying capacity.[34] This cascade leads to atherosclerosis through mechanisms such as endothelial damage, oxidative stress, and

thrombosis.[34] Smoking promotes atherosclerosis from its direct effects on the vascular wall and circulating lipoproteins and platelets.[33] Endothelial and platelet adhesions contribute to atherogenesis by promoting lipid infiltration and smooth muscle cell proliferation.[33] Smoking is further associated with reduced levels of HDL which affects total cholesterol and triglyceride levels, leading to the formation of atherosclerotic plaque.[33] The interplay of these lifestyle factors and pathophysiological mechanisms necessitates a holistic understanding to develop targeted interventions addressing the unique challenges faced by women and men.

1.1.2.2 Symptoms

Although CAD affects the global population, CAD is frequently underrecognized in women due to differences in clinical presentation.[10] Females and males with CAD report different clinical symptoms.[35] For example, females are generally more likely to report unusual chest pain, sweating, dyspnea, nausea, and vomiting,[35] while men are more likely to report angina, dyspnea, fatigue, heart palpitations, and weakness and or numbness in the limbs.[10] These differences in CAD symptoms can lead to physicians frequently failing to recognize and subsequently correctly diagnose CAD in females.[8,9,36] This oversight may contribute to less aggressive treatment strategies and, in turn, result in the underrepresentation of women with CAD in clinical trials.[10,16,37]

1.1.3 Treatment

The Canadian Cardiovascular Society (CCS) recommends that initial steps to treating and managing CAD include medications (e.g., anticoagulants, statins, β-blockers, nitrates angiotensin-converting enzyme [ACE] inhibitors, and calcium channel blockers),[38,39] and medical procedures (e.g., coronary angioplasty or coronary artery bypass graft [CABG] surgery

to open or bypass blocked arteries.).[38,39] Clinical guidelines for the management of CAD with severe blockages recommend that a primary percutaneous coronary intervention (PCI) should be performed as soon as possible following diagnosis.[39] If PCI is not available, fibrinolytic therapy should be used.[39] CABG surgeries are performed in cases of complex CAD, specifically when there are multiple or diffuse blockages, and when the left main coronary artery is involved.[40] For further information regarding the treatment of CAD, readers are referred to CCS guidelines[39] as this is beyond the scope of this thesis. Lifestyle changes such as engaging in regular PA and exercise, nutrition (healthy food choices), managing weight (consuming fewer calories than expended), limiting alcohol, and cessation of smoking are also recommended.[38,39]

1.2 Coronary Artery Disease and Physical Activity

PA and exercise are key in the prevention and management of CAD.[41] PA is defined as any bodily movement that is produced by skeletal muscle contraction that increases energy expenditure above resting state.[42] PA performed on a regular basis (i.e., >150 minutes of weekly moderate-to-vigorous intensity exercise) can reduce CAD-related symptoms (i.e., angina, dyspnea) and improve myocardial perfusion and reduce mortality in patients with CAD.[41,42] Epidemiological studies have identified that insufficient PA or not meeting recommended PA guidelines (> 150 minutes of weekly moderate-to-vigorous intensity exercise) is an important risk factor for the development of CAD,[41] morbidity,[41] and CVD and all-cause mortality.[41,43] The well-known Harvard Alumni Health Study published in 2000 found an inverse linear relationship between PA and incidence of CAD such that individuals who expended at least 1,000-2,000 kcal/week from engaging in PA had the lowest relative risk for the development of CAD.[44] Warburton et al. later reported in 2010 that 22% of premature deaths due to physical inactivity (not defined in the publication) were in patients with CAD.[45] Exercise is a type of PA that is

structured and repeated to improve or maintain at least one component of physical fitness (i.e., cardiorespiratory endurance, muscular strength, muscular endurance, flexibility, and body composition).[42] Exercise is beneficial for the secondary prevention of CAD.[41] As cardiorespiratory fitness (CRF) levels increase due to regular PA and/or exercise participation in patients with CAD (30-60 minutes of aerobic PA at moderate intensity [60-85% of maximum heart rate (HR)] 5 days per week), cardiac-specific adaptions occur (i.e., increase in coronary blood flow and oxygen supply), leading to a reduction in the risk of angina and cardiac events.[46,47]

1.2.1 Physical Activity Mechanisms for Patients with CAD

Some adaptations following regular exercise over several weeks that have been identified in patients with CAD include but are not limited to modulation of the autonomic nervous system, increased vagal activity, and augmented baroflex sensitivity.[41,46,47] Autonomic balance can be restored in addition to improved peripheral endothelial function and decreased BP, which results in improved left ventricular diastolic function.[41,46,47] In addition, regular PA has a positive effect on lipid profiles,[48] therefore reducing the risk of dyslipidemia and can also lead to weight loss and improved insulin sensitivity, all of which contribute to lowering the risk of CVD.[48] These exercise-produced physiological changes are important in managing and preventing CAD.

1.2.2 Exercise Prescription for Patients with Coronary Artery Disease

Regular exercise, as outlined by the American Heart Association (AHA) guidelines, involving 150 minutes of moderate-intensity aerobic exercise per week or 75 minutes of vigorous-intensity aerobic exercise per week, coupled with 2 days of muscular strength activities, has been a cornerstone in the prevention and treatment of CAD.[41] The American College of

Sports Medicine (ACSM), a prominent authority in exercise prescription, recommends aerobic training 3-5 days per week, resistance training 2-3 non-consecutive days per week, and flexibility training 2-3 days per week.[49] Specific to Canadians, the Canadian Association of Cardiovascular Prevention and Rehabilitation (CACPR) recommends 3 days per week of aerobic training at 40-85% of HR reserve or $\dot{V}O_2$ reserve for patients with CVD.[50] Both the ACSM and CACPR share a common objective of a multidisciplinary approach prioritizing safety and tailoring exercise prescriptions to the unique health status of individuals with CAD, underscoring their efforts to promote effective and safe PA for the management and improvement of cardiovascular health.[41,49] Before beginning an exercise training program, a baseline measure of CRF and physical wellness (muscular strength and endurance, flexibility, and body composition) is helpful to guide the development of exercise training programs.[42] The FITT principle (frequency, intensity, time, and type of exercise) is used by exercise professionals to create exercise prescriptions that can be tailored to an individual's needs and abilities. These baselines measures can also suggest possible responses to an exercise training program. Individuals with lower initial fitness levels often exhibit more significant relative improvements in CRF and other fitness domains compared to those with higher baseline fitness levels.[51] For patients with CAD, improving CRF is critical, as even modest increases are associated with substantial reductions in cardiovascular mortality and morbidity.[52] Baseline measures can identify low CRF, which serves as both a modifiable CVD risk factor and a predictor of training adaptability (i.e., patients with lower CRF may experience more pronounced increases in oxygen consumption [$\dot{V}O_2$] following aerobic training).[51] Moreover, these measures provide critical data for tailoring program intensity and progression.[53] For patients with CAD, starting exercise at an appropriate level is vital to avoid undue cardiovascular strain.[53] Baseline data allow clinicians to set individualized

thresholds that promote safety while maximizing potential benefits.[54] They also enable the monitoring of progress and adjustments in training prescriptions, ensuring sustained improvement over time. Thus, comprehensive baseline testing is not only foundational for personalized care but also pivotal in optimizing the therapeutic outcomes of exercise training for patients with CAD by enhancing overall functional capacity and quality of life.[54]

1.3 Exercise Testing

CRF is defined as the ability of the body's circulatory and respiratory system to supply the body and muscles with oxygen to produce energy during PA and exercise.[55] CRF is a strong independent predictor of mortality.[56] A CRF less than 5 metabolic equivalents (METs), greater than 8 METs, and of 14 METs has been associated with a high risk of mortality,[57] increased likelihood (10-25%) of survival,[57,58] and lowest risk for mortality, respectively.[57–59] Further, a 1 MET increase in CRF has been shown to be associated with a 15% decrease in CVD and a 13% decrease in risk of all-cause mortality.[58,59] Cardiopulmonary exercise tests (CPETs) are the gold standard for measuring CRF in patients with CAD and provide clinicians important information regarding the health status of patients during exercise.[60] Oxygen consumption ($\dot{V}O_2$) which is measured throughout the test provides clinicians insight about the integrative function of multiple systems of the body during exercise (i.e., musculoskeletal, cardiovascular, respiratory, and nervous). Peak $\dot{V}O_2$, the highest value that is measured, often during the last minute of an incremental exercise test to volitional exhaustion,[14,20] is the product of cardiac output ($\dot{Q}$) and arterial-venous oxygen difference (A-$\dot{V}O_2$). The Fick equation shows that the rise in $\dot{V}O_2$ during exercise occurs as a result of increases to the central (rise in $\dot{Q}$ from changes in HR and stroke volume [SV]) and peripheral (increase in A-$\dot{V}O2$) cardiovascular systems.[47] Exercise intensity (i.e., by using changes in speed, grade, and or workload) is gradually increased during CPETs

while HR, BP, $\dot{V}O_2$ (measured in mL/min or /mL/kg/min, represents the ability of an individual to perform exercise based on their cardiovascular and skeletal muscle oxidative function and pulmonary ventilation[61]), volume of carbon dioxide ($\dot{V}CO_2$), and respiratory rate are measured.[61,62] The designation of $\dot{V}O_{2\ max}$ has been applied by clinicians and researchers to indicate that an individual has reached their physiological limit. Although widely debated,[63–65] suggested criteria by the ACSM for the designation of $\dot{V}O_{2\ max}$ are achieving at least 3 of the 5 following criteria (Table 1.1):

Table 1.1: Criteria for the designation of $\dot{V}O_2$ max[49]

Measure	Criteria
$\dot{V}O_2$	Plateau in $\dot{V}O_2$ (≤150mL/min) with increased workload
RER (respiratory exchange ratio)	RER ≥1.10
HR	Failure of HR to increase with increasing workload
Lactate	Post-exercise venous lactate concentration >8.0mmol/L
RPE (rating of perceived exertion)	RPE at peak exercise >17 on the 6-20 RPE scale

HR, heart rate; RER, respiratory exchange ratio; RPE, rating of perceived exertion; $\dot{V}O_2$, oxygen consumption.

In the absence of data that supports that a patient has reached their physiological maximum, as commonly seen in patients with CAD,[66–69] peak $\dot{V}O_2$ terminology is frequently used. Therefore "peak" will be used throughout this thesis. "Peak" will be defined as the highest value that a patient achieved during a test. It should be noted that peak may be the max for some but not all patients.[68,69] CPETs are used in various healthcare and research settings. The data obtained from a CPET provides health care professionals with the necessary information to design, prescribe, and monitor exercise programs that are safe and effective.[60]

Maximal exercise tests, although beneficial as described above, pose a higher risk for adverse events (0.8 complications per 10,000 tests in healthy adults,[70] and 0.3 to 2.7 and 0.6 to

6.0 events per 10,000 testing hours for men and women, respectively),[42] and for experiencing cardiac signs and/or symptoms for patients with CAD when compared to submaximal tests.[60] There are several criteria to determine if a CPET should be terminated (Table 1.2).

Table 1.2: Criteria for CPET termination[49]

Symptoms	Criteria
Angina	Onset of angina or angina-like symptoms
Blood Pressure	• drop in systolic blood pressure (SBP) of ≥ 10 mmHg with an increase in work rate or a decrease in SBP below the value obtained prior to testing • excessive rise in BP (systolic pressure > 250 mmHg or diastolic blood pressure [DBP] > 115 mm Hg)
Heart rate	No increase in HR with an increase in exercise intensity
Fatigue	Sever fatigue
Other	Dyspnea, wheezing, leg cramps, light-headedness
Request	Patient requests to stop
Equipment	Testing equipment malfunction

BP, blood pressure; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.

While the above-mentioned stopping criteria are generally accepted, there are many CPET modalities and protocols and there is no consensus as to which CPET protocol should be used in patients (females vs. males) with CAD to attain their peak $\dot{V}O_2$.

1.3.1 Maximal Exercise Test Protocols

During the past 75 years, several protocols have been developed for measuring CRF.[71–76] Some of the most frequently used protocols include the Bruce, Balke, and Naughton as they can be used for a wide range of populations (i.e., clinical and athletic) and for diagnostic purposes.[49] The Bruce protocol was developed in 1949 by Bruce and colleagues using 15 females and 20 male healthy adult participants with no known diseases or medical conditions (see Appendix B).[33] The Balke protocol was developed in 1959 to obtain further information regarding the normal range of physical performance capacity (i.e., pulse rate, BP, and gas exchange) of 500

men within the air force (see Appendix B).[71] The Naughton protocol was developed in 1963 by Naughton and colleagues and is a modification of the previously published Balke protocol.[72] This approach was validated using four male participants: a healthy untrained male, a patient with known CAD, a patient with clinically significant aortic stenosis, and a well-trained male. BP, pulse rate, $\dot{Q}$, respiratory gas exchange and electrocardiograms (ECG) were recorded throughout the test (see Appendix B). Naughton et al. found that this approach allowed for careful monitoring for signs of cardiopulmonary decompensation and that the same principles used to test physical fitness in people with optimal physical training can be applied to individuals with heart disease.[72]

In 1983, Buchfuhrer and colleagues examined differences in cardiorespiratory responses to determine the optimal work rate to standardize exercise testing.[77] $\dot{V}O_2$ max was significantly higher on tests where the increment of work was large enough to induce test durations of 8-12 minutes.[77,78] Test durations beyond this range often resulted in a mean reduction of approximately 10% in maximal $\dot{V}O_2$ (mL/kg/min).[77] Almost 20 years later, Myers and Berlin expanded on the findings of Buchfuhrer[77] and found that large (i.e., > than 5 METs) and unequal workload increments (i.e., changes in speed/grade) resulted in less accurate estimates of CRF, particularly for patients with CAD.[79] The University of Ottawa Heart Institute (UOHI) Slow Ramp treadmill protocol developed for the purpose of testing CRF in those with CVD has been used for over 20 years at our facility (see Appendix B). Table 1.3 describes popular CPET protocols and population characteristics of validated protocols.

Table 1.3: Protocol validation population characteristics

Year	Authors	Publication	Protocol	Population		Participant Characteristics
				Females n (%)	**Males n (%)**	
1949	Bruce, R., Lovejoy, F., Pearson, R., Yu, P., Brothers, G., Velasquez, T.	Variability of Respiratory and Circulatory Performance During Standardized Exercise	Bruce	15 (43)	20 (57)	Adults ages 20 to 57 years old. All participants were apparently healthy, employed, and had no detectable history of any previous cardiac or pulmonary disease.
1955	Taylor HL, Buskirk E, Henschel A	Maximal Oxygen Intake as an Objective Measure of Cardio-respiratory Performance	Taylor	0	73 (100)	Males ages 18-35 years who passed vigorous physical examinations and were in good health (27 male soldiers from the Quartermaster Corps at Fort Lee and 46 volunteer students from the University of Minnesota).
1959	Balke, B., Ware, R.	An Experimental Study of "Physical Fitness" of Air Force Personnel	Balke	0 (0)	500 (100)	500 male military and civilian Air Force personnel.
1960	Astrand, I.	Aerobic Work Capacity In Men and Women With Special Reference To Age	Astrand	44 (32.8)	90 (67.2)	Females ages 20-65 years (41 were housewives, 3 were unmarried). 81 males between the ages of 50-64 years, all truck drivers for approx. 21.2 years. 9 men between 56-68 years old from the YMCA health club in Philadelphia who were well trained

						and accustomed to heavy exercise
1963	Naughton J, Sevelius G, Balke B.	Physiological Responses of Normal And Pathologic Subjects To A Modified Work Capacity Test.	Naughton	0 (0)	4 (100)	4 males (1 presumably healthy untrained patient, 1 patient with known CAD, 1 patient with clinically significant aortic stenosis, 1 patient who was a healthy trained male).
1969	Ellestad, M., Allen, W., Wan, M., Kemp, G.	Maximal Treadmill Stress Testing For Cardiovascular Evaluation	Ellestad	205 (20.5)	795 (79.5)	Patients ages 7 to 83 years who were referred to the division of clinical physiology of Memorial Hospital, Long Beach, for maximal treadmill stress testing.
~2000	UOHI diagnostics department		UOHI Slow Ramp			UOHI patients

CAD, coronary artery disease; UOHI, University of Ottawa Heart Institute.

Many protocols exist for many populations (i.e., athletic, sedentary, and clinical) by adapting the speed, percentage of incline and resistance, and equipment modality. It is important that protocols selected for patients with CAD do not have large and unequal increments in workload to most accurately measure or estimate peak $\dot{V}O_2$.[60] There are many exercise testing protocol options (i.e., modality and changes in speed, grade, peak power output, etc.) that could be evaluated in females and males with CAD. However, for the purpose and reasonable scope of this thesis, I will focus on treadmill protocols as they require minimal learning as walking is more familiar than cycling. Further, as cycle ergometer tests are self-paced (i.e., rpm will vary), this can lead to more work than intended resulting in an increase in localized muscle fatigue in the patient’s legs which can limit the patient to perform exercise at higher intensities.[60] Poor

muscle strength and endurance are often cited as reasons why patients are unable to cycle at sufficient workloads to produce exercise HRs within an appropriate range to calculate an estimated peak $\dot{V}O_2$.[60,80] Lower peak $\dot{V}O_2$ can result in lower exercise prescription (i.e. lower exercise intensity since the target intensity is calculated as a percentage of peak values).

Most of the above-mentioned protocols were created and validated in predominantly male populations (males = 84.9%, females = 15.1%) (see Table 1.3).[71–74] Due to anatomical and physiological differences between males and females (see section 1.4), it should not be expected that the most optimal exercise test protocol would be the same for males and females.[81] These testing protocols have been used in various clinical and research settings with different populations worldwide;[80,82,83] however, maximal exercise testing is not without limitations when considering requirement equipment, space, and trained personnel.

1.3.2 Submaximal Exercise Tests

Maximal exercise testing is not as widely available in some cardiovascular rehabilitation (CR) settings due to the equipment (i.e., cycle ergometer or treadmill, ECG), cost (metabolic cart: approx. $40,000) and certified personnel (i.e., registered kinesiologist, R.Kin, certified exercise physiologist, stress test technician) required to administer the tests. Submaximal tests are, therefore, frequently used to predict CRF.[84–88] Submaximal exercise tests that are frequently reported in the literature include the Astrand-Rhyming cycle ergometer test,[75] the Chester step test,[89] the Astrand-Rhyming step test,[75] the 6-minute walk test (6MWT),[90] and the incremental shuttle walk test.[91] Such tests can be performed at a lower cost, are more time efficient, require fewer resources (i.e., equipment, personnel), and appear to be safer for patients[92] (i.e., the BEST study reported no adverse events, n_{tests}= 176[80] , Skalski *et al*, reported an adverse event rate of approximately 0.04% or 1 in 2,500 tests).[93] Submaximal tests are routinely administered to

predict peak $\dot{V}O_2$ for patients with known signs and/or symptoms that would be a contraindication for a maximal exercise test (e.g., unstable angina, uncontrolled cardiac arrythmia, endocarditis, severe aortic stenosis, heart failure, pulmonary embolism, pulmonary infarction, deep venous thrombosis, myocarditis, pericarditis, acute aortic dissection, known obstructive left main coronary artery stenosis, tachyarrhythmias with uncontrolled ventricular rates, acquired advanced or complete heart block, recent stroke or transient ischemia attack, resting hypertension with systolic >200 mm Hg or diastolic >110 mm Hg, and/or physical disability that precludes safe and adequate testing).[42] Submaximal tests are terminated and are considered successful if participants complete at least 2 stages of the test and reach 85% of their age-predicted peak HR.[49] However, submaximal testing tends to be less accurate as it uses a patient's HR response to a submaximal workload to predict $\dot{V}O_{2\,max}$.[80,92] There are many protocols that exist in the literature, but for the scope of this thesis we selected one modality (i.e., treadmill) that would be accessible and a number of protocols that would be feasible.

Modified submaximal versions of the well-known Bruce, Naughton, and Balke protocols have been used as a proxy to predict peak $\dot{V}O_2$ when maximal exercise testing protocols are not recommended or available (i.e., for individuals who are less fit or have medical conditions that would preclude them from completing a maximal exercise test [i.e., unstable angina, uncontrolled symptomatic heart failure, cardiac arrythmias causing hemodynamic compromise][87]). The modified Bruce is most often used for older individuals whose CRF may be limited due to CAD. This modified submaximal exercise test starts at a lower workload (e.g., 1.7 mph and 0% grade), with the third stage of this modified protocol corresponding to the first stage of the standard Bruce protocol (see Appendix B).[42] The modified Naughton protocol has become a popular treadmill test for patients with CAD since its use in the National Exercise and Heart

Disease Project (see Appendix B).[94] The modified Balke treadmill test was developed to be a clinical test to measure peak $\dot{V}O_2$ in cardiac patients, while also being able to estimate CRF in athletes (see Appendix B).[72]

1.3.3 Exercise Test Selection at Cardiac Rehabilitation Centres in Canada

Maximal and submaximal exercise tests are completed at CR centres across Canada. There are many different protocols and practitioners are often unsure which one(s) are the most appropriate for patients with CAD. It is also unknown which maximal and submaximal protocols are most appropriate for testing peak $\dot{V}O_2$ in females and males with CAD. Following thorough literature searches, no quantitative or qualitative studies were identified that determined the reason as to why certain tests are conducted for CVD patients. The decision-making process of which maximal and submaximal exercise tests are selected for each patient remains unknown. Therefore, my first study will examine which CPET protocol and which submaximal exercise test is the most frequently used to measure peak $\dot{V}O_2$ and estimated peak $\dot{V}O_2$, respectively, in patients with CVD at CR centres in Canada.

1.4 Anatomical and Physiological Sex Differences

Central Differences

Many anatomical and physiological differences in the cardiovascular system exist between females and males (Figure 1.1). Females typically have smaller hearts than males, resulting in an average resting HR of 78-82 bpm for females and 70-72 bpm for males.[95] Due to the smaller size of their hearts, approximately 10% less blood is ejected per beat in females. Therefore, a female's heart beats faster to achieve the same $\dot{Q}$ (SV x HR)[96] as the larger heart of a male.[97] During both maximal and submaximal exercise at the same absolute workload, females

tend to have higher HRs than their male counterparts to compensate for their lower SV to maintain a similar $\dot{Q}$.[98] The difference in cardiovascular responses between females and males is also reflected in BP.[93,96] At maximal exercise females exhibit lower SBP due to a reduced sympathetic response and higher vasodilatory state.[98,99] At submaximal exercise and rest, SBP is lower for females compared to males,[100] however there are no differences in DBP.[100]

Peripheral Differences

$\dot{V}O_2$ is higher in males than females for both maximal and submaximal efforts[101] as males naturally have a greater aerobic capacity,[101,102] more muscle mass[102] and higher hemoglobin concentrations.[102] The increased muscle mass in males leads to a higher metabolic demand and greater oxygen utilization during both submaximal and maximal exercise.[101] The increased levels of hemoglobin further help males enhance oxygen transport to the working muscles, supporting greater aerobic performance.[102] Therefore, during both maximal and submaximal loads, females are required to perform greater cardiac work to meet the same external work demand as males.[100] In addition, at peak exercise, females have a lower A-$\dot{V}O_2$ content.[103] This can be attributed to a lower concentration of hemoglobin and the inability to decrease mixed venous oxygen at the same rate as males, as well as females lower capillary density and oxidative potential.[103] Finally, there is no difference at maximal and submaximal efforts or rest between females and males with regards to blood lactate concentrations.[98,104] Although these anatomical and physiological

differences exist between females and males, exercise testing protocols fail to account for these differences despite well-documented sex-differences in cardiovascular function.

A	Resting		Submaximal Exercise		Maximal Exercise	
Central Differences	♀	♂	♀	♂	♀	♂
HR	↑		↑		↑	
SV		↑		↑		↑
CO	–	–	–	–		↑
Systolic BP		↑		↑		↑
Diastolic BP	–	–	–	–	–	–

B	Resting		Submaximal Exercise		Maximal Exercise	
Peripheral Differences	♀	♂	♀	♂	♀	♂
A-$\dot{V}O_2$		↑		↑		↑
$\dot{V}O_2$	–	–		↑		↑
Hemoglobin Concentration		↑		↑		↑
Capillary Density		↑		↑		↑
Blood Lactate	–	–	–	–	–	–

Figure 1.1: Central (A) and peripheral (B) system sex differences at rest and during submaximal and maximal exercise.
A-$\dot{V}$O2, arteriovenous oxygen difference; HR, heart rate.
Note: " ↑ " indicates that the variable is higher for a sex. " – " indicates no difference between sexes.

1.5 The Rationale and Statement of Problem

The extant literature shows an underrepresentation of females when compared to males in the development and validation of exercise testing protocols (Table 1.3). Given the above-mentioned anatomical and physiological differences between sexes, females and males with

CAD may respond differently to exercise testing protocols of varying increases in speeds and grades.[81] The overall aim of my thesis was to investigate the exercise testing practices in CR programs across Canada and the optimal submaximal and maximal exercise testing protocols for assessing peak $\dot{V}O_2$ in females and males with CAD.

1.6 Research Objectives

Study 1: The Selection of Cardiopulmonary Exercise Testing Protocols in Cardiovascular Rehabilitation Centres Across Canada (TRADE)

Primary Research Question: Which maximal and submaximal exercise testing protocols are the most frequently used to measure or estimate peak $\dot{V}O_2$, respectively, in patients with CVD at CR centres across Canada?

Secondary Research Questions: The secondary research questions include:

(1) How many maximal and submaximal exercise testing protocols does each CR centre use?

(2) How many maximal and submaximal exercise tests are completed per year?

(3) How many times is each maximal and submaximal exercise testing protocol used per year?

(4) Which healthcare professional (e.g., physician, registered kinesiologist, exercise physiologist, cardiovascular technologist, etc.) is most often deciding the exercise testing protocol? and

(5) What is the decision-making process and criteria used for selecting an exercise testing protocol for patients with CVD to reach their peak $\dot{V}O_2$?

Study 2: Comparing Measured and Estimated Peak $\dot{V}O_2$ Values of Maximal and Submaximal Exercise Testing Protocols of Females and Males with Coronary Artery Disease (PACED)

Research Questions: Maximal Exercise Testing

Primary research question: Does peak $\dot{V}O_2$ vary between different maximal treadmill exercise testing protocols in females and males with CAD?

Hypothesis: Maximal exercise testing protocols with lower starting grade and or speed and lower incremental magnitudes will yield a higher peak $\dot{V}O_2$ in females and males with CAD.

Secondary research questions: The secondary research questions include:

(1) How do peak cardiometabolic responses (i.e., HR, BP, and blood lactate concentrations) and RPE compare between different maximal treadmill exercise testing protocols for females and males with CAD?

(2) Do different increments of grade/speed affect test duration for females and males?

(3) What is the most common reason for test termination for females and males?

(4) Does higher patient enjoyment of a test protocol yield a higher peak $\dot{V}O_2$ for females and males?

(5) Which test was most frequently ranked as the most enjoyable test by female and male patients? and

(6) Which of the tested protocols (i.e., modified Bruce, modified Balke, modified Naughton, and UOHI Slow Ramp) achieves a greater number of ACSM criteria for maximal test termination for females and males with CAD?

Research Questions: Submaximal Exercise Testing

Primary research question: Does estimated peak $\dot{V}O_2$ vary between different submaximal treadmill exercise testing protocols in females and males with CAD?

Hypothesis: Submaximal exercise testing protocols with lower starting grade and or speed and lower incremental magnitudes will yield a higher peak $\dot{V}O_2$ in females and males with CAD.

Secondary research questions: The secondary research questions include:

(1) Does the test duration differ between submaximal exercise testing protocols for males and females with CAD? and

(2) Do peak cardiometabolic responses (i.e., BP, HR, and blood lactate concentrations) and RPE differ between submaximal exercise testing protocols for males and females with CAD?

Chapter 2

Study 1: The Selection of Cardiopulmonary Exercise Testing Protocols in Cardiovascular Rehabilitation Centres Across Canada

2.1 Introduction

2.1.1 Cardiac Rehabilitation

Cardiac rehabilitation (CR) is a structured and supervised multi-component program, led in person, remotely, or as a hybrid model.[105–108] CR plays a critical role in the care and management of individuals recovering from cardiovascular conditions, events, or procedures (e.g., patients with CAD,[109] who have experienced a MI,[110] or who have undergone a PCI[110,111] or coronary artery bypass graft [CABG] surgery).[112] Specifically, this programming has been shown to optimize the management of modifiable CVD risk factors such as physical inactivity, sedentary behaviour, smoking cessation, hypertension, hyperlipidemia, diabetes, and obesity.[113,114] Patients participating in CR frequently report better physical health, functional capacity, and psychological well-being.[115,116] And, Cochrane systematic reviews have shown that CR improves patients' quality of life[115,117–119] and reduces their all-cause and cardiovascular morbidity[41,43,118–120] and mortality.[43,117–119,121]

Exercise training is a core component of CR, involving supervised, structured physical activity and personalized exercise prescription according to patients' individual needs and abilities.[122–124] Healthcare professionals closely monitor patients' progress, make necessary adjustments to exercise routines, and offer ongoing encouragement throughout the program.[116] This targeted approach aims to enhance patients' cardiovascular fitness, strength, and endurance.[125,126] Other key components of a CR program typically include education, nutritional,

psychosocial, and vocational counselling, and cardiovascular disease risk factor awareness and modification.[108] The participation in these services (offered by a physiotherapist, kinesiologist, dietitian, vocational counsellor, and or psychologist) vary based on an individual's health condition, needs, and goals.[108] Education focuses on heart-healthy living, including strategies to manage CVD risk factors such as hypertension, hyperlipidemia, obesity, and diabetes through improving PA, reducing sedentary time, choosing healthy food choices, consuming less alcohol, and medication adherence.[114,120,127,128] Counseling extends to stress management, emotional well-being, and psychological support, assisting patients in coping with the psychological impacts of cardiovascular-related conditions such as depression, anxiety, and stress.[126] It is not only essential to offer a comprehensive CR program, but also to integrate exercise testing as a key element in evaluating and monitoring patients' cardiovascular health.

2.1.2 Exercise Testing in CR

Exercise testing supports the evaluation of the CRF and functional capacity of patients with CAD.[85,122] The primary purpose of incorporating exercise testing into CR programs is to assess patients' baseline fitness levels and then individualize exercise prescriptions accordingly.[85,122] Exercise testing provides valuable insights into patients' exercise tolerance and cardiovascular responses, guiding healthcare professionals in designing safe and effective exercise programs.[67,85] It also allows for the monitoring of patients' progress throughout the rehabilitation process, enabling timely adjustments to the frequency, intensity, time, and type of exercise modality of exercise interventions as patients' cardiovascular health hopefully improves.[122,129] By systematically incorporating exercise testing into CR, healthcare providers can optimize the therapeutic benefits of exercise while minimizing the risk of adverse events during and or following exercise session (e.g., MI, cardiac arrest, stroke, transient ischemic

attack, serious adverse arrhythmias [i.e., ventricular tachycardia, ventricular fibrillation, supraventricular tachycardia], hospitalizations, death, etc.).[130] Although exercise testing and training are critical elements of CR programs and widely used across Canada and beyond, it is unknown which maximal and submaximal exercise testing protocols are most frequently used in CR programs across Canada.

2.1.3 Exercise Test Selection at Cardiac Rehabilitation Centres in Canada

Exercise testing including maximal and submaximal exercise tests are completed at CR centres across Canada. The goal of maximal exercise tests is to determine the maximum physiological response to exercise, [80,131,132] typically assessed by reaching an individual's maximal HR or achieving volitional exhaustion. Common graded maximal exercise tests in CR which consist of 1,2 or 3-minute stages of increasing speeds and grades of varying degrees include the Bruce,[73] Naughton,[133] and Balke[71] treadmill protocols. Submaximal exercise testing will often be used in lieu of maximal exercise testing as it is less expensive and does not requires specialized personnel or equipment (i.e., metabolic cart, ECG, treadmills with high load capabilities) to perform.[84–88] These exercise tests are designed to evaluate cardiovascular responses to exercise at a submaximal workload (typically terminated at or below 85% of age-predicted maximal HR).[80] Common submaximal tests reported in the literature include but are not limited to the Chester Step test, the modified Bruce, and the 6MWT.[80,134–136] The Chester step test is a submaximal, multi-stage aerobic capacity test that requires the patient to step on and off a step to the beat of a metronome until 80% of age-predicted of maximal HR is attained or all 5 stages of the test are completed.[89] The modified Bruce protocol is used as a clinical tool to estimate CRF.[137] Patients walk on a treadmill for 3-minute stages of increasing speeds and grades until the test is terminated when a patient has reached 85% of their age-predicted maximal

HR.[137] The 6MWT is widely used in CR to assess aerobic capacity due to its simplicity and accessibility.[90] The 6MWT measures the farthest distance a patient can walk on a hard, flat surface in 6 minutes without jogging or running.[90] These tests are useful for assessing exercise tolerance, monitoring progress during rehabilitation, and prescribing individualized exercise programs based on the patient's fitness level and cardiovascular responses.

Exercise testing protocols are structured procedures designed to assess an individual's response to exercise.[42] Protocols can vary with regards to intensity, speed, grade, incline, stage duration, and modality (i.e., treadmill, cycle ergometer, step, track)[42] which can impact the total test time and, consequently, the attainment of peak $\dot{V}O_2$. It is well established that peak $\dot{V}O_2$ is a key indicator of aerobic power[129] and functional capacity[122,138,139] in patients with CVD.[42] With the variety of available protocols, practitioners often face uncertainty in selecting the most appropriate maximal or submaximal exercise testing protocol to assess peak $\dot{V}O_2$ in patients with CVD. Protocol selection is a critical consideration due to its significant implications for patient safety, assessment accuracy, and evaluating the effectiveness of exercise interventions.[140] The choice of exercise testing protocol can also influence the physiological responses, including $\dot{V}O_2$, HR, and BP, elicited during exercise testing.[129,138,139] The selection of an inappropriate protocol may result in an underestimation or overestimation of peak $\dot{V}O_2$.[141] For instance, protocols of shorter durations or inadequate workload increments may fail to elicit a true maximal effort, resulting in lower peak $\dot{V}O_2$ values and potentially suboptimal exercise prescriptions based on underestimated aerobic capacities. Conversely, protocols of prolonged test durations with aggressive workload increments may induce premature fatigue or safety concerns, compromising the accuracy of peak $\dot{V}O_2$ assessment and leading to inappropriate exercise prescriptions that exceed patients' physiological capacities for those with CVD.[142,143] Careful consideration of

protocol selection is, therefore, paramount in CR to ensure an accurate assessment of CRF, safe conduct of exercise testing, and appropriate prescription of individualized exercise program intensity tailored to patients' cardiovascular health and fitness levels.

Following a thorough literature search, no quantitative or qualitative studies were identified that determined the decision-making process, guidelines, or criteria as to why certain maximal or submaximal exercise tests are performed for patients with CVD. Study 1 of my thesis will therefore examine which maximal and submaximal exercise tests are the most frequently used to measure peak $\dot{V}O_2$ or estimate peak $\dot{V}O_2$, respectively, in patients with CVD at CR centres across Canada.

2.1.4 Research Objectives

Primary Research Question: Which maximal and submaximal exercise testing protocols are the most frequently used to measure or estimate peak $\dot{V}O_2$, respectively, in patients with CVD at CR centres across Canada?

Secondary Research Questions: The secondary research questions include:

(1) How many maximal and submaximal exercise testing protocols does each CR centre use?

(2) How many maximal and submaximal exercise tests are completed per year?

(3) How many times is each maximal and submaximal exercise testing protocol used per year?

(4) Which healthcare professional (e.g., physician, registered kinesiologist, exercise physiologist, cardiovascular technologist, etc.) is most often deciding the exercise testing protocol? and

(5) What is the decision-making process and criteria used for selecting an exercise testing protocol for patients with CVD to reach their peak $\dot{V}O_2$?

2.2 Methods

2.2.1 Design and Setting

This was an observational pan-Canadian study led from the UOHI.

2.2.2 CR Centre Recruitment Process

Several methods were used to identify all current CR programs across Canada. A Google search was first used to identify CR centres in Canada. These centres were then cross-referenced with a former Canadian Association of Cardiovascular Prevention and Rehabilitation (CACPR) database of CR programs. All identified CR centres in Canada were contacted via emails and phone calls in English and French to request their participation in the study. Facilities were contacted up to 3 times to request participation by either email, phone, or a combination of both. Once recruited, an email containing the link to the REDCap (secure web application for building and managing online surveys and databases) "Selection of Cardiopulmonary Exercise Testing Protocols in Cardiovascular Rehabilitation centres across Canada (TRADE)" nationwide CR survey was sent for completion.

2.2.3 Eligibility Criteria

All CR facilities in Canada were eligible to complete the survey.

2.2.4 Outcomes

Primary Outcome

The primary outcome was the most frequently used maximal and submaximal exercise testing protocol in CR facilities across Canada.

Secondary Outcomes

The secondary outcomes included the: (1) number of protocols used at each CR centre, (2) number of exercise tests completed annually, (3) frequency each protocol is used annually, (4) healthcare professional responsible for protocol decision, and (5) decision-making process and criteria used for selecting a maximal and submaximal exercise testing protocol for patients with CVD.

2.2.5 Statistical Analysis

All analyses were performed using SPSS for Windows (Version 29.0.1.0 [171]) (IBM Corp., Armonk, NY, USA). Descriptive statistics (i.e., means and standard deviations if normally distributed or medians and 95% confidence intervals (CIs) if not normally distributed, or absolute numbers and percentages) were used to compare patient volume, the number of centres that offer each type of CR, program duration, program cost, program and number of education centres and number of protocols used. Descriptive statistics were used to compare categorical variables (i.e., maximal exercise testing protocols used, submaximal exercise testing protocols used, number of times each test is performed, role of person administering the tests). Content analysis was used to assess open text responses and thematic topics and were categorized.

2.3 Results

Recruitment occurred between September 26th, 2023, and June 30th, 2024. Figure 2.1 shows the number of CR centres included in the study. Of the 388 CR facilities that were identified and contacted, 118 completed the survey and 92 no longer offered CR programs.

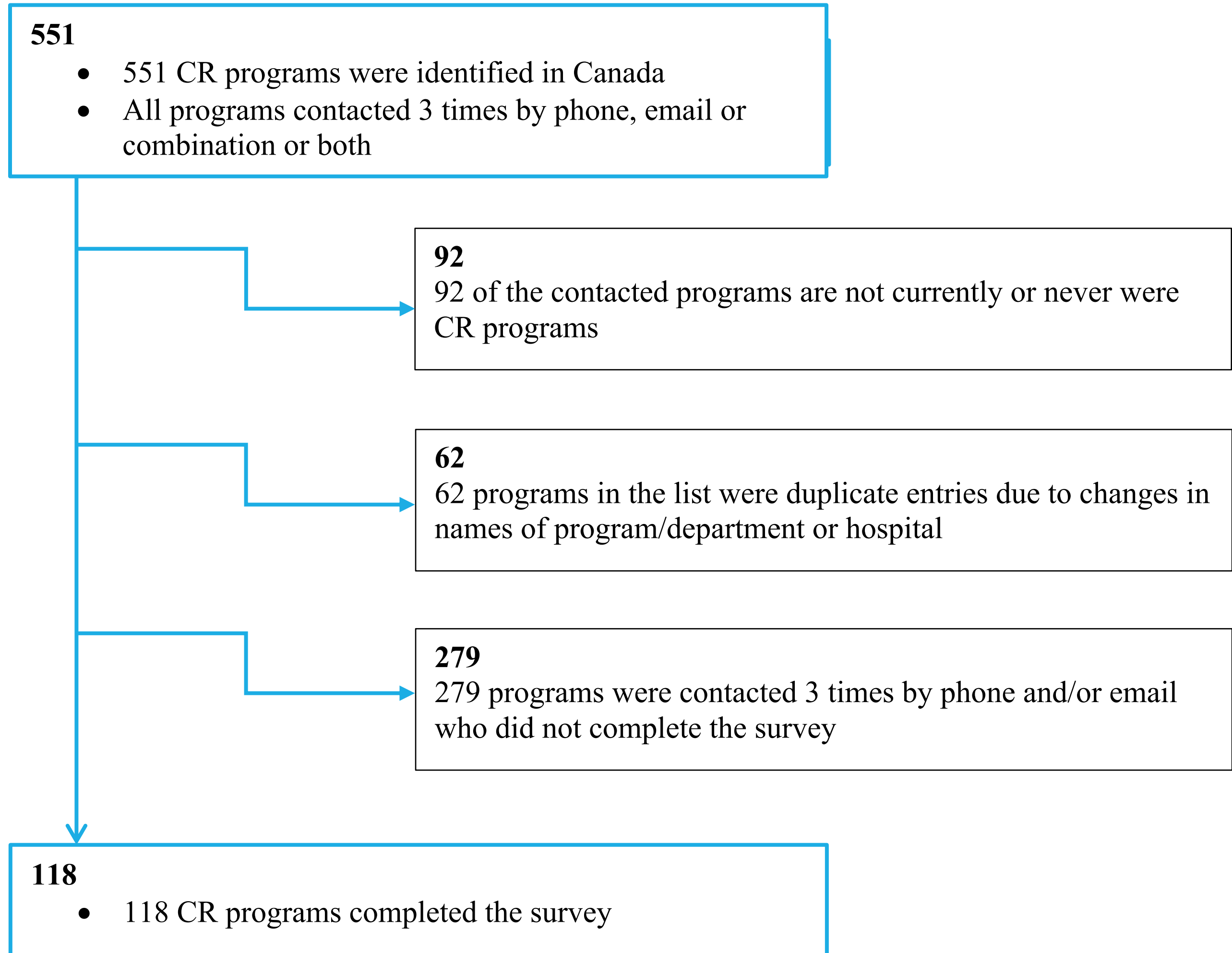

Figure 2.1: Flow diagram of CR program recruitment process.
CR, cardiac rehabilitation.

CR programs in Canada vary in terms of patient volume, program duration, and delivery methods. The median patient volume per centre per year ranged from 192.5 to 200.0. Most CR programs (84.7%) offered in person exercise. Virtual exercise and virtual education options were also available at nearly 80% of programs. Hybrid models which incorporated in person and virtual components were also common with 37.3% offering both in-person and virtual exercise and 18.6% offering a combined virtual exercise with in-person education delivery. Other

program delivery formats were available at 11.9% of the centres. The average program duration ranged from 12.4 ± 8.4 to 14.4 ± 12.4 weeks with a median program cost of $0 for patients.

The response rate per province/territory varied. Provinces and territories with 100% completion rates were Newfoundland, Prince Edward Island, and the Yukon. New Brunswick followed by Manitoba had the next highest completion rates of 66.7% and 63.6%, respectively. Ontario, Saskatchewan, and British Columbia reported completion rates of 35.4%, 32.0%, and 28.8%, respectively. Alberta and Quebec recorded the lowest survey completion rates of 21.6% and 12.7%, respectively.

A total of 85 CR programs (72.6%) performs exercise testing. Of these 85 centres, 13 programs (15.3%) complete only maximal exercise testing, 42 (49.4%) complete only submaximal exercise testing, 26 (30.6%) complete both submaximal and maximal exercise testing, and 4 (4.7%) did not specify which type of exercise testing they use.

The demographics of the participating centres are shown in Table 2.1 and their locations in Figure 2.2.

Table 2.1: CR centre demographics

	Minimum	**Maximum**
Patient volume (median, interquartile range [IQR])	192.5, 688.3	200.0, 678.3
Number of centres that offer each type of cardiac rehabilitation offering (n, %):		
In person exercise	100/118, 84.7%	
Education only, in person	39/118, 33.1%	
Virtual exercise (home-based setting)	62/118, 52.5%	
Education only, virtual	32/118, 27.1%	

Hybrid (in person and virtual exercise)	44/118, 37.3%	
Hybrid (in person exercise with virtual education)	44/118, 37.3%	
Hybrid (virtual exercise with person education)	22/118, 18.6%	
Other	14/118, 11.9%	
Duration of program (weeks) (mean ± standard deviation)	12.4 ± 8.4	14.4 ± 12.4
Cost of program (median, IQR)	0, 2.5	
Number of education sessions (mean ± standard deviation)	7.8 ± 5.8	

IQR, interquartile range.
N=118 denotes the total number of completed surveys.

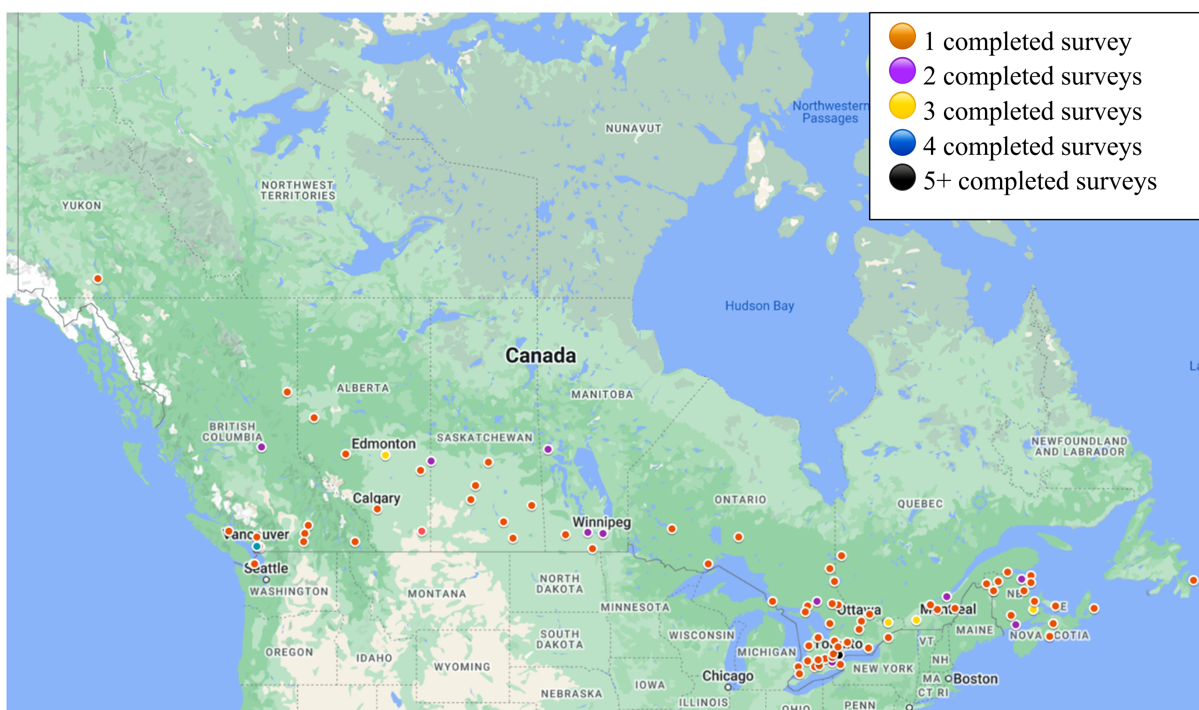

Figure 2.2: Map showing the distribution of cardiac rehabilitation centres across Canada that completed the TRADE survey.
TRADE, Selection of Cardiopulmonary Exercise Testing Protocols in Cardiovascular Rehabilitation centres across Canada.

Primary outcome

Within the 39 programs that complete maximal exercise testing, the Bruce treadmill test was the most frequently used (82.1% in CR programs across Canada) (Figure 2.3). Of the 68 CR programs that complete submaximal exercise testing, the 6MWT was the most used (75.0%) and the modified Bruce was the second most used (39.71%) in CR programs in Canada (Figure 2.4).

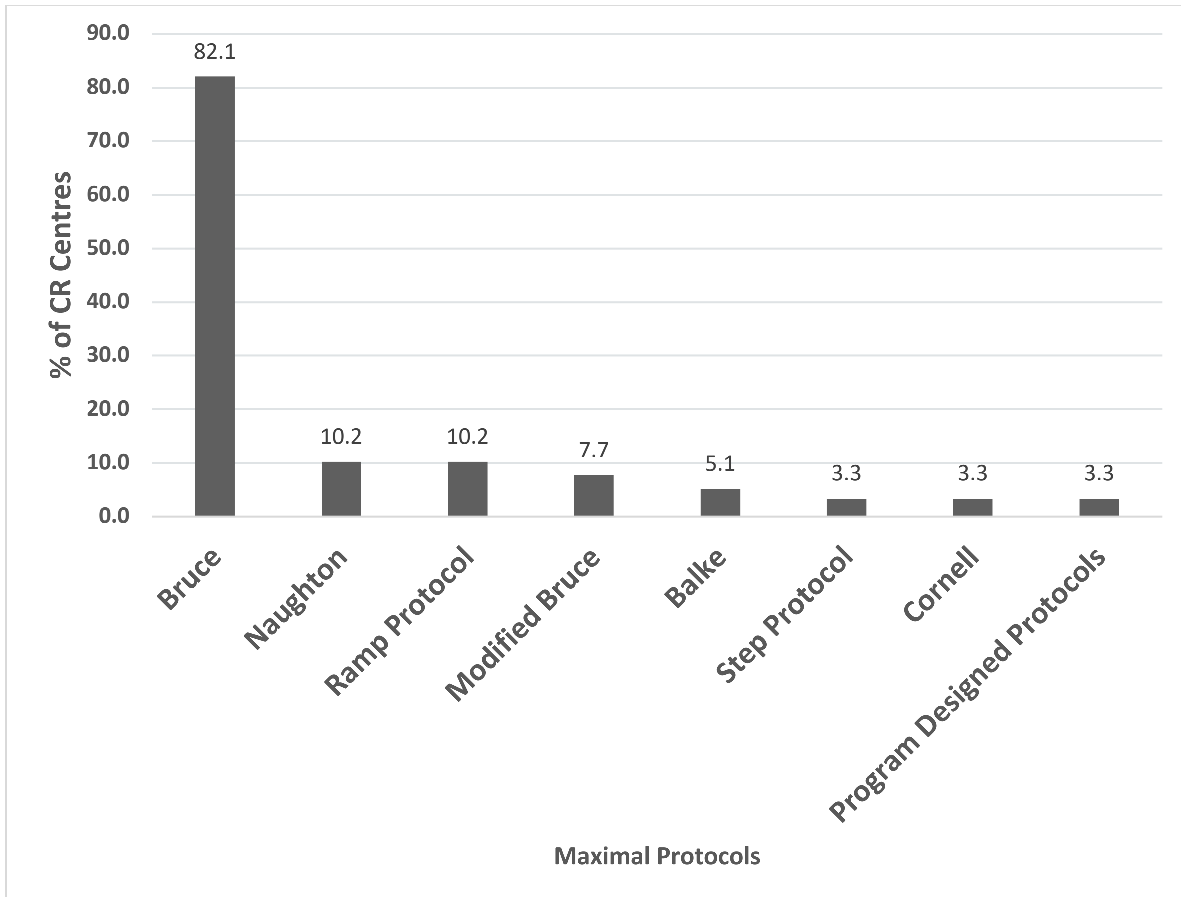

Figure 2.3: Most frequently used maximal exercise testing protocols at CR programs across Canada.
CR, cardiac rehabilitation.
Multiple answers from the same CR program were accepted.

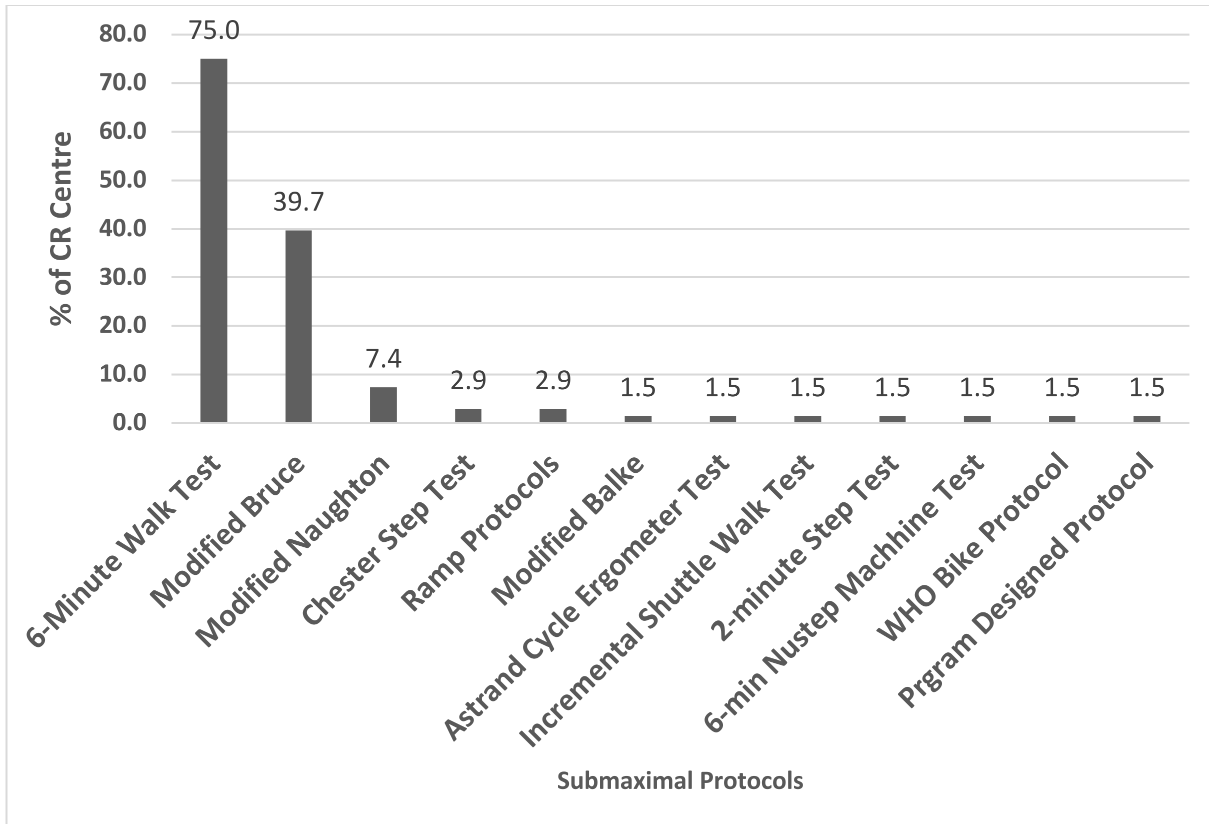

Figure 2.4**:** Most frequently used submaximal exercise testing protocols at CR programs across Canada.
CR, cardiac rehabilitation.
Multiple answers from the same CR program were accepted.

Secondary outcomes

It was estimated that 3,610 – 4,910 maximal exercise tests were performed annually at CR centres across Canada (Figure 2.5) and 18,000 – 22,710 submaximal exercise tests were performed annually (Figure 2.6).

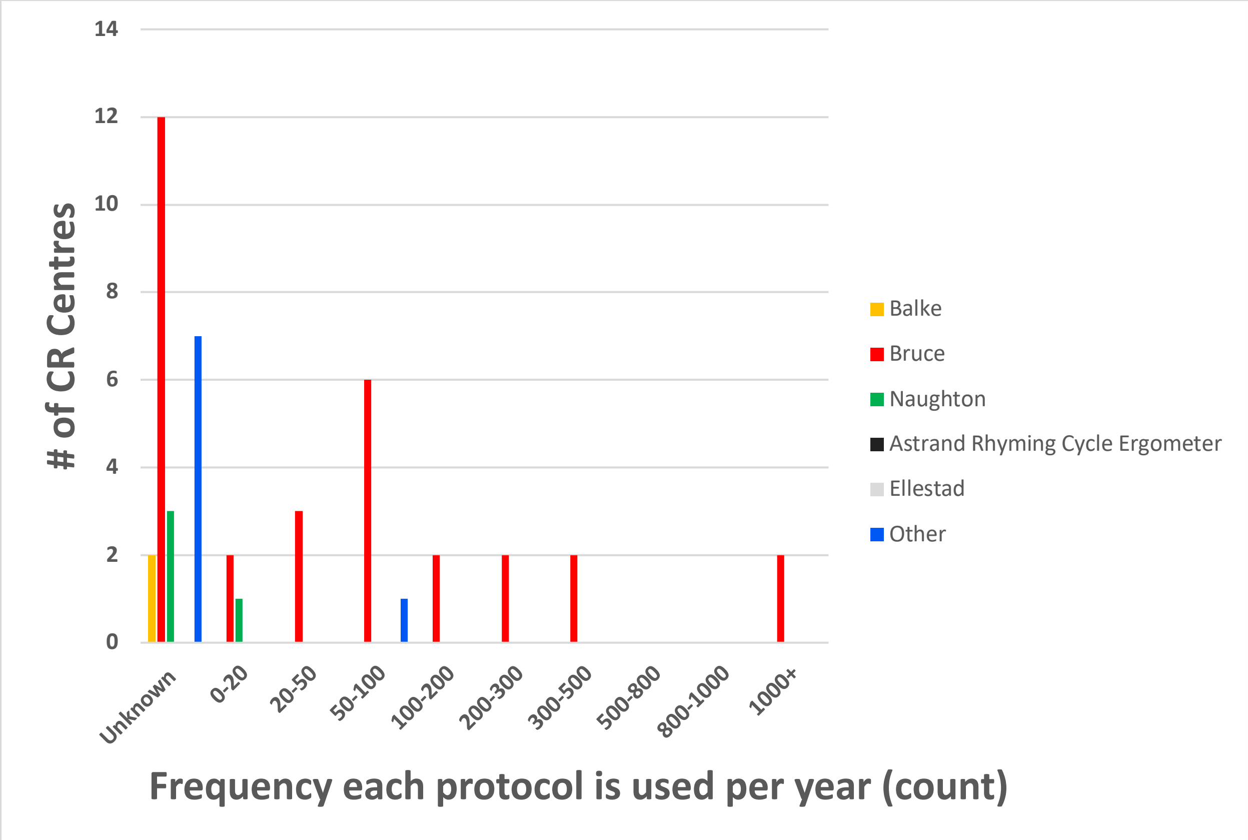

Figure 2.5: Frequency of how often each maximal protocol was used per year.
CR, cardiac rehabilitation.

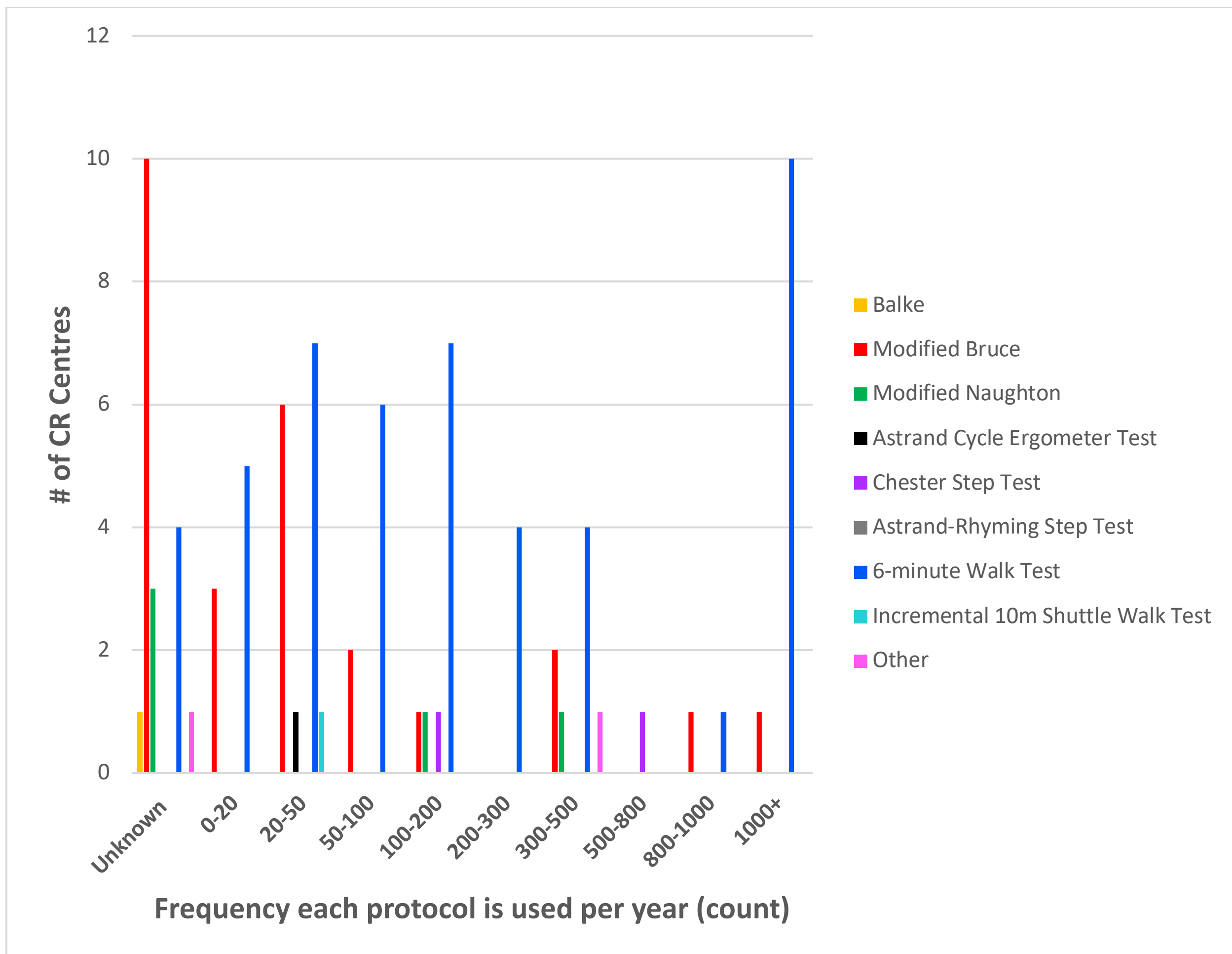

Figure 2.6**:** Frequency of how often each submaximal protocol was used per year.
CR, cardiac rehabilitation.

It was common for CR programs to perform 1 maximal (n=24) and 1 submaximal (n=37) exercise testing protocol. Few CR programs used multiple protocols for exercise testing (i.e., 1 program used 4 submaximal exercise testing protocols, and 2 programs used 4 maximal exercise testing protocols) (Figure 2.7).

A range of both submaximal and maximal protocols were used across Canadian CR centres. Among submaximal protocols, 37 CR centres used 1 protocol, 20 programs used 2 protocols, 5 programs used 3 protocols, 1 program used 4 protocols, 1 program used 5 programs and 1 program used 6 different protocols. Among maximal protocols, 24 programs used a single

protocol, 6 programs used 2 protocols, 4 programs utilized 3 protocols, and 2 programs used 4 protocols.

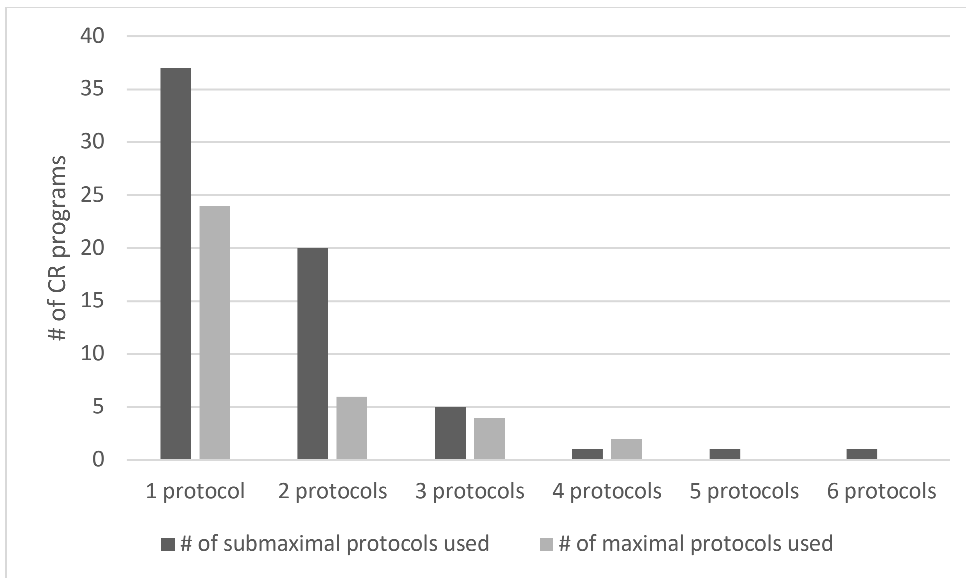

Figure 2.7: Number of submaximal and maximal protocols used at individual CR centres across Canada.
CR, cardiac rehabilitation.

There was a wide range of healthcare professionals across Canada involved in determining the exercise testing protocols used in their CR programs. Physicians were the most frequent decision-makers, overseeing testing protocols in 38 of the 118 programs, followed by nurses (n=15/118), and physiotherapists/kinesiologists (n=13/118) (Figure 2.8).

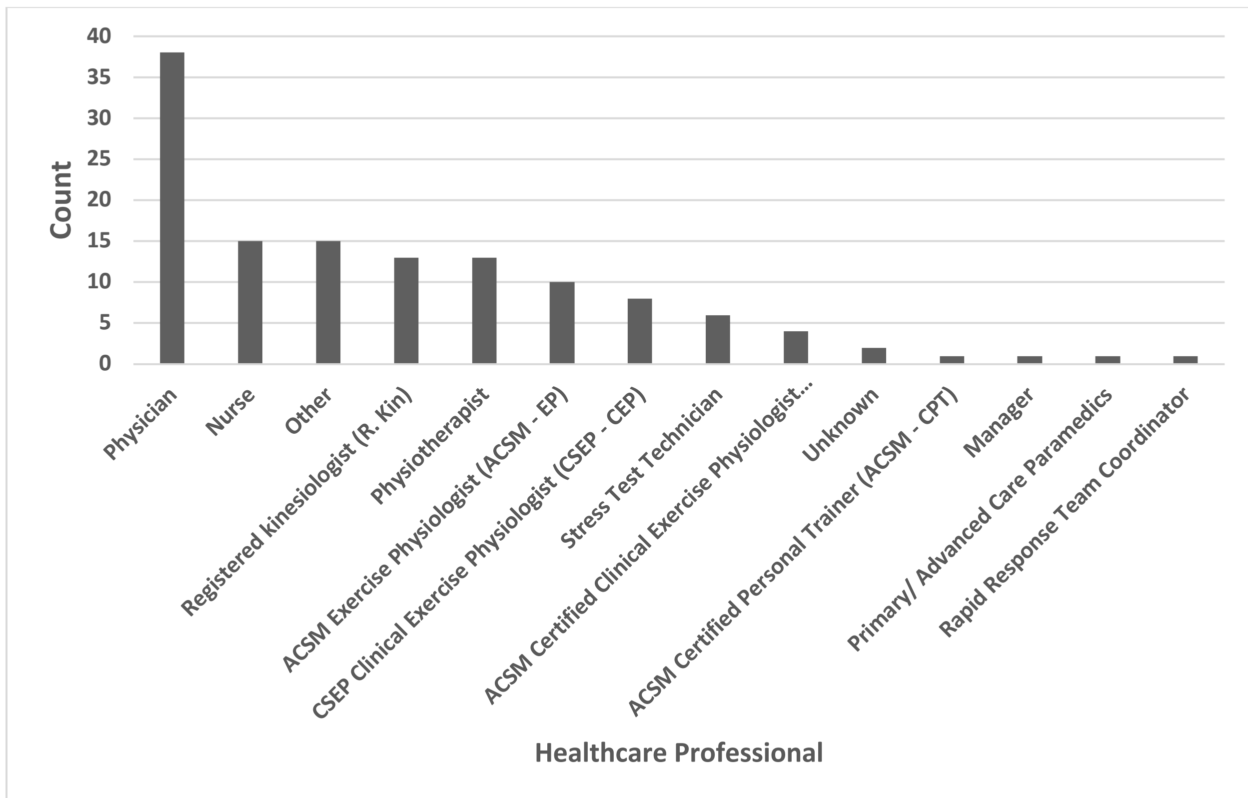

Figure 2.8: Healthcare professionals (e.g., physician, registered kinesiologist, exercise physiologist, cardiovascular technologist, etc.) who most frequently determined the exercise testing protocol.
ACSM-CEP, American College of Sports Medicine Clinical Exercise Physiologist; ACSM-CPT, American College of Sports Medicine Certified Personal Trainer; ACSM-EP, American College of Sports Medicine Exercise Physiologist; CSEP-CEP, Canadian Society for Exercise Physiology Clinical Exercise Physiologist; CR, cardiac rehabilitation; R.Kin, Registered Kinesiologist.

The most common methods for determining exercise test protocols included standard procedures decided upon by management (n = 18), patient medical history, co-morbidities, musculoskeletal (MSK) concerns, exercise tolerance, etc. (n = 17), and physician decision (n = 8) (see Table 2.2).

Table 2.2: Decision making criteria for exercise testing selection at CR centres in Canada

Decision Making Criteria	Total # of CR Centres	# of CR programs that use each criterion			
		Small	Moderate	Large	Unknown
Diagnosis/co-morbidities /MSK concerns, exercise tolerance, etc.	22	8 (36.4%)	7 (31.8%)	7 (31.8%)	0 (0%)
Centre standard procedures	17	5 (29.4%)	1 (5.9%)	11 (64.7%)	0 (0%)
Physician	15	4 (26.7%)	2 (13.3%)	8 (53.3%)	1 (6.7%)
Cardiologist evaluation	5	1 (20%)	1 (20%)	3 (60%)	0 (0%)
Nurse evaluation	2	0 (0%)	1 (50%)	1 (50%)	0 (0%)
Resources available	2	1 (50%)	1 (50%)	0 (0%)	0 (0%)
Team assessment	2	1 (50%)	0 (0%)	1 (50%)	0 (0%)
METs	1	1 (100%)	0 (0%)	0 (0%)	0 (0%)
Cardiology service	1	0 (0%)	1 (100%)	0 (0%)	0 (0%)
Physiotherapist evaluation	1	0 (0%)	0 (0%)	1 (100%)	0 (0%)
Patient preference	1	0 (0%)	1 (100%)	0 (0%)	0 (0%)
6MWT	1	0 (0%)	1 (100%)	0 (0%)	0 (0%)
Demographics and Physical Activity levels	1	0 (0%)	1 (100%)	0 (0%)	0 (0%)
DASI questionnaire	1	0 (0%)	1 (100%)	0 (0%)	0 (0%)
Unknown	1	0 (0%)	1 (100%)	0 (0%)	0 (0%)
Estimated patient capacity	1	1 (100%)	0 (0%)	0 (0%)	0 (0%)
Algorithm	1	0 (0%)	1 (100%)	0 (0%)	0 (0%)

CR, cardiac rehabilitation; DASI, Duke Activity Status Index; MET, metabolic equivalent; MSK, musculoskeletal; RN, registered nurse; 6MWT, 6-minute walk test.

* CR program patient volume was classified into tertiles. Tertile 1, (33rd percentile) – “small”: ≤ 119.2 patients; tertile 2 – “moderate”: between 119.2 and 400.0 patients, tertile 3, (66th percentile) – “Large” > 400.0 patients.

2.4 Discussion and Conclusions

The results of this study provide significant insights into the current exercise testing practices of CR programs across Canada, with data obtained from 118 CR facilities. The findings

show that 73.7% of the participating programs complete some form of exercise testing, which reflects the important role of exercise testing in CR.[85,122]

Maximal Testing

Although CPETs are the gold standard for measuring CRF as indicated by authoritative organizations including the ACSM and CACPR,[42,50] programs often note the requirement of expensive equipment, specialized personnel, training, and cost as reasons for choosing submaximal instead of maximal exercise tests.[54,84,86] A substantial proportion (44.8%) of programs performed maximal exercise tests, with the Bruce Treadmill test being the most used protocol (82.1% of programs performing maximal tests).[25,32] The popularity of the Bruce protocol aligns with its long-established role in clinical exercise testing, where it is widely regarded as the gold standard for assessing peak $\dot{V}O_2$.[52] Serge et al. previously investigated the most commonly used protocols among seven standardized exercise tests (i.e., Bruce, modified Bruce, Cornell 0%, Cornell 5%, Cornell 10%, Naughton, and Modified Naughton) from 1991 to 2015.[144] The Bruce test was found to be the most used test among 120,705 patients who underwent a stress test at the Cleveland Clinic.[144] These patients were referred to stress testing for one of the following reasons: (1) to rule out CAD, (2) symptom evaluation, (3) assess risk factors for CAD, (4) follow-up for known CAD, or (5) other.[144] The findings highlight the Bruce protocol as the primary choice for an exercise testing protocol as it was performed 79,953 times over 24 years. The modified Bruce was the second most frequently used protocol and was performed 8,368 times (between 1991 and 2015).[144]

Furthermore, Mital et al. detailed the use of the Bruce protocol for measuring aerobic fitness in 111 males and 32 females with CVD (i.e., post-MI, angioplasty, CABG) in CR for the

purpose of determining the capacity at which a patient could perform physical work and the physical demands of their jobs in their workplace.[145] In using the Bruce protocol to measure aerobic capacity, the rate of metabolic energy expenditure (from METs) can be calculated for patients.[145] For occupations that require a metabolic energy expenditure ≤ 21% of patients' peak aerobic capacity, these occupations can be completed without overexertion.[145] This can help patients return to work and avoid economic burdens from their cardiovascular events while being able to maintain activities that are less than 2.6 kcal/min and 1.5 kcal/min for males and females, respectively (i.e., sedentary/light activity such as walking [2.0-2.5 mph], weeding or planting flowers, or simple household chores such as dusting or folding laundry).[145] Therefore, although the Bruce protocol is known for measuring CRF in patients with CVD in a clinical setting, it can also play an important role in helping individuals return to work.[145] The results of the exercise test can provide insight into a patient's physical readiness to meet the demands of their occupation and may help vocational counsellors in identifying any limitations or accommodations a patient may need for a successful transition back to work. However, the Bruce protocol is only one of many protocols which can be used to calculate the rate of energy expenditure for occupational assessments. Thus, maximal exercise testing can not only be used to measure CRF in CR, but also to help evaluate a patient's ability to resume occupational activities safely and effectively while promoting recovery and economic stability.

The relatively low use of maximal exercise tests across Canada may reflect the higher cost, the limited availability of resources, the concerns about the safety (0.8 complications per 10,000 tests in healthy adults,[70] and 0.3 to 2.7 and 0.6 to 6.0 events per 10,000 testing hours for men and women, respectively),[42] and feasibility of maximal exertion in high-risk cardiac patients, specifically in community-based CR settings, where patients may not have access to

emergency care or a physician in case of an adverse event.[146] In more rural regions submaximal tests may be more common due to differences in available healthcare infrastructure and clinical training.[146] This practice - supported by the American College of Cardiology and AHA - recommends careful selection of exercise testing protocols based on the patient (i.e., patient's risk factors and functional status).[78] The estimated number of submaximal tests performed annually in Canadian CR programs (18,000 – 22,710) far exceeds the number of maximal tests (3,610 – 4,910). This finding is consistent with other studies showing submaximal tests are favored due to their lower risk of adverse events (i.e., 0.04% or 1 in 2,500 tests),[93] lower cost, and fewer required resources.[80,147] Submaximal tests are particularly valuable in assessing patients with reduced exercise tolerance or those recovering from cardiac events.[80] Therefore, logistically, maximal testing in less frequently performed in CR programs across Canada.

Submaximal Testing Preferences

Submaximal compared to maximal exercise testing was more commonly performed in Canadian CR programs, with 75.2% of the centres performing submaximal tests. The most common submaximal test, the 6MWT, was used in 60.0% of the CR programs. This aligns with previous research which emphasizes the 6MWT's effectiveness in evaluating functional capacity, especially in patients with cardiovascular disease.[134,148–151] The 6MWT's simplicity, safety, and ease of administration make it ideal for large-scale use in CR programs.[90,152] Bierbauer et al. is one of many investigations which have used the 6MWT to examine changes in exercise capacity of both females and males during CR.[149] In 13,612 patients from 2012 to 2018 from six different Swiss CR centres that completed the 6MWT pre and post CR program, the 6MWT was found to be a valid measure of exercise capacity for the majority of patients within their CR programs, including patients who were relatively weak.[149] The 6MWT was chosen as it

is not only a good indicator of exercise capacity but also of activities of daily living (which usually occur at a submaximal workload).[149] Additionally, Fiorina et al. indicated their preference for the 6MWT due to its simplicity and the ability to be performed without expensive equipment or specialized personnel.[150] In 1,370 patients the 6MWT was shown to be a feasible test to conduct for patients in CR with varying levels of complexity of cardiac events (i.e., cardiac surgery [CABG, valve replacement], or post MI).[150] The high use of the 6MWT in Canada aligns with findings from other countries, where this test is commonly used due to its safety and ease of administration.[150,152,153]

The 6MWT is a useful test for facilities with limited resources or for patients with decreased exercise capacity; however, it may not be appropriate for patients with moderate to high functional capacity.[154] As the 6MWT measures the distance a patient can walk (without running or jogging) in 6 minutes; this may not be a sufficient challenge to measure changes from baseline to post-CR for patients who are highly active or fit individuals.[154] This can be due to a "ceiling effect" where patients achieve maximal performance at baseline and, thus, test would not be able to detect improvements if any were to occur.[154] Further, Giannitsi et al. indicated that while there is not a universally defined distance that would indicate that a patient achieved their individual "ceiling", patients who were able to walk 600 m or more within the 6 minutes may not show significant improvements in subsequent tests as they were already near the upper limit of the test's capacity.[155] Other limitations of the 6MWT include the learning effect (i.e., improved distance upon re-testing due to increased familiarity with the test protocol, better pacing, and reduced anxiety[151]) and its inability to reliably estimate peak $\dot{V}O_2$. This learning effect has been reported to account for 2-8% improvement; it is, therefore, recommended to conduct the test twice to ensure accurate assessments.[151,156] Chirico et al. investigated the agreement between the

6MWT and measured peak $\dot{V}O_2$ using a CPET in 54 patients (45 males, 9 females) with heart failure who completed a CR program.[135] The estimated peak $\dot{V}O_2$ from the 6MWT equations had poor agreement with the treadmill CPET, with the authors concluding that the predictive equations using 6MWT distance were not appropriate for monitoring changes in peak $\dot{V}O_2$ in patients with heart failure in CR.[135] Therefore, the use of the 6MWT needs to be carefully assessed before use for patients with higher fitness levels and if using to estimate peak $\dot{V}O_2$.

The Modified Bruce protocol, used by 24% of programs, was the second most used submaximal test. This treadmill protocol is frequently used in clinical settings due to its gradual increase in intensity, which can be beneficial for elderly or deconditioned patients and/or patients with a decreased exercise capacity as is commonly observed in CR.[149] This trend is consistent with findings in the literature that support the popularity of the Modified Bruce test for measuring peak $\dot{V}O_2$ in patients with CVD.[157] El Missiri et al. detailed the use of the Modified Bruce protocol in 60 patients with ischemic heart disease who recovered from a coronary angioplasty or a STEMI managed by a PCI in a CR program in Egypt.[157] The modified Bruce protocol was selected due to its ability to measure peak HR, estimate a target HR range using the Karvonen formula and to measure the change in METs from pre to post CR.[157] Furthermore, Nichols et al. in the United Kingdom also explained their rationale for use of the modified Bruce as the primary assessment tool to measure changes in aerobic fitness in 70 clinically stable patients whom had been diagnosed with angina, MI, CABG surgery or had a PCI.[158] The modified Bruce test was used to measure the effectiveness of an exercise-based CR intervention compared to a routine CR program due to its safety and incremental workloads that can accommodate varying fitness levels.[158] Contrary to our results, the step test is also widely used in the United Kingdom.[89,136,159] Sykes and Roberts indicated a high correlation between the $\dot{V}O_2$

max CPET (using a fast incremental ramp protocol) and a Chester step test ($r = 0.92$, $p < 0.001$) with a standard error of 3.9 mL O_2/kg/min in 68 participants (47 males and 21 females) with a wide range of ages and disabilities, therefore confirming the validity of the Chester step test as a strong predictor for $\dot{V}O_2$ max in rehabilitation settings.[89] The results from my study are, thus, consistent with the extant literature in other countries (i.e., Switzerland, Italy, Egypt, United States of America, and the United Kingdom) identifying the 6MWT and the modified Bruce test as the two most used submaximal exercise tests for measuring CRF in CR.[60]

Implications for Practice

These findings have important implications for the practice of CR in Canada. The variety of exercise testing protocols across CR programs indicates a need for more standardized guidelines to ensure consistency in patient evaluation and care across the country. However, it is important to recognize that the availability of resources (i.e., lack of equipment or trained specialized personnel) can limit exercise testing protocol selection, with programs only being able to perform exercise tests that are feasible and within their means. Establishing national or international guidelines that recommend the most suitable exercise tests for various patient populations – and that consider possible resource constraints could enhance care and outcomes for patients recovering from cardiovascular events or procedures worldwide. Additionally, the strong reliance on physician decision-making in protocol selection, especially in higher-risk populations such as those participating in CR programs, underscores the importance of interdisciplinary collaboration in CR programs.[160] Expanding the role of non-physician healthcare providers in decision-making may improve the efficiency and effectiveness of exercise testing, particularly in programs that may be restricted by limited resources. The decision-making process for selecting exercise testing protocols in CR was predominantly

physician-led with 35 centres (29.7%) indicating that physicians are the primary decision-makers.

Our data also highlights the similarities between the size of the CR program and the deciding professional or criteria used to determine exercise testing protocols. When physicians were identified as the deciding healthcare professionals, the volume of patients performing the exercise tests widely varied from very small (e.g., 40-50 patients per year) to large (e.g., 9,000 patients per year) volumes. When cardiologists were the primary decision-makers, patient volumes tended to be higher (e.g., 1,500 – 8,060 patients per year). This tendency for cardiologists to be the primary decision-makers may reflect that cardiologists are typically associated with larger and more specialized cardiac centres that can manage high patient volumes and have access to exercise testing services.[161,162] Decisions based on centre standard procedures tend to be associated with high patient volumes (e.g., 1,400 – 2,000 patients per year). This suggests that standardized or team-based approaches can be adapted to be efficient for handling large patient volumes.[163,164] Contrarily, programs that use specific criteria such as diagnosis, co-morbidities, or exercise tolerance as deciding factors see all patient volumes (e.g., from small to large CR programs). Resource availability or patient preferences are linked to smaller patient volumes (e.g., 60-70 or <300 patients per year). This highlights a more individualized approach to patient care, which might be present in resource-limited settings or those emphasizing personalized care.[165,166] In summary, higher patient volumes (i.e., greater than 400 patients) were generally associated with standardized procedures, physicians, or cardiologists, suggesting the ability to provide standardized care to a large patient volume. Lower patient volumes (i.e., less than 120 patients) are seen in CR programs where individual patient preferences, assessments and facility resources guide exercise testing decisions, likely

indicating a focus on tailored care and submaximal testing protocols as these tests are a safe, resource efficient alternative to maximal testing and still allow for individualized preferences and exercise programming.[80,132,165,166]

Limitations and Future Research

While this study provides valuable data on exercise testing practices in Canadian CR programs, it is not without limitations. The response rate of 30.2% limits the generalizability of these findings as the practices of non-participating centres (69.8% of Canadian CR programs) are not captured. The results of this study do not contain any sex or gender related data. From discussions with CR leaders in Canada during the development of the survey, it was shared that many CR centres do not track or have easy access to sex and gender related information within their CR programs. Therefore, sex and gender considerations for the primary and secondary research questions were not included in this study. Future studies should seek to investigate how exercise testing in CR may vary between sexes and/or gender. Future research should also aim to examine the outcomes associated with different exercise testing protocols which could provide valuable insights into the most effective methods for improving patients' fitness and reducing cardiovascular disease risk.

Conclusion

In conclusion, this study highlights the variability of exercise testing practice in Canadian CR programs. The diversity in testing protocols and decision-making processes reveals the need for more standardized guidelines to ensure consistent care. Differences in testing may over or underestimate a patient's CRF which can affect exercise prescription including exercise intensity; this may affect a patient's ability to achieve the full benefits of CR and improve their

quality of life.[53,54,122] These findings also suggest a growing trend toward individualized care, with healthcare professionals considering patient-specific factors and preferences when selecting exercise tests. Future research should focus on addressing the limitations identified in this study and exploring ways to optimize exercise testing in CR programs. By refining these practices, patient outcomes can be improved and set a new benchmark for CR standards in Canada.

Chapter 3

Study 2: Comparing Measured and Estimated Peak $\dot{V}O_2$ Values of Maximal and Submaximal Exercise Testing Protocols in Females and Males with Coronary Artery Disease

3.1 Introduction

3.1.1 Maximal vs submaximal exercise testing

Maximal exercise tests that measure peak $\dot{V}O_2$ provide a direct measure of oxygen uptake, a critical predictor of cardiovascular health and mortality risk in patients with CVD.[167] An overview of meta-analyses by Lang et al. including 26 systematic reviews found that for every 1 MET increase in CRF, as measured by peak $\dot{V}O_2$, substantial reductions from 11% to 17% in the risk of CVD and all-cause mortality were identified in apparently healthy and clinical (i.e., with cardiomyopathy, CVD, heart failure, and CAD) adults populations.[168,169] When comparing high to low CRF groups, the hazard ratio for all-cause mortality was 0.47 (95% CI 0.39 to 0.56) indicating that higher CRF is strongly associated with lower risk of mortality in these populations.[168] There is also robust literature showing that patients with higher functional capacity also tend to experience better health care outcomes (i.e., lower rates of re-hospitalization and mortality).[168,170,171]

Although other assessments of CRF including the 6MWT (6-minute walk distance can be used to estimate $\dot{V}O_2$)[135] have demonstrated associations with mortality in patients with CVD,[172–176] the stronger association between measured peak $\dot{V}O_2$ and mortality underscores the importance of using measured values for evaluating CRF.[135,177,178] This approach allows

clinicians to more precisely assess a patient's exercise tolerance and tailor rehabilitation programs and exercise prescription to their individual needs.[67,179] During exercise, $\dot{V}O_2$ increases in response to an increase in energy demands.[96,180] As the exercise intensity and test duration increases, as during maximal exercise testing, skeletal muscles require more oxygen to support increased aerobic metabolism and adenosine triphosphate (ATP) production through oxidative phosphorylation.[91,151] The rise in $\dot{V}O_2$ simultaneously occurs with physiological adaptations which includes increased $\dot{Q}$, blood flow to the muscles, and mitochondrial activity which allows for more efficient oxygen delivery and use at the cellular level.[96] Maximal exercise testing can also identify the workload at which a patient reaches their physiological limit (the point at which a patient can no longer sustain exercise due to maximal exertion of their cardiovascular, respiratory, and muscular systems),[181] helping to create individualized exercise prescriptions for optimal intensity and safety in CR programs.[181] Due to well established anatomical and physiological differences between sexes (i.e., females have a smaller heart size,[95] lower SV,[96] reduced hemoglobin levels,[102] and decreased capillary density[103]), females typically exhibit lower peak $\dot{V}O_2$ values than males.[101] These sex-based differences in cardiovascular function may influence how females compared to males respond to maximal exercise testing.[95,96,101–103] The assessment of an individual's aerobic capacity is critical for the development and implementation of an effective CR program.[179] Maximal exercise testing, typically conducted using a treadmill or cycle ergometer, provides valuable physiological data such as $\dot{V}O_2$, HR, and BP responses as well as blood lactate concentrations during maximal exertion.[60] These outcomes assist healthcare professionals in monitoring the cardiovascular responses to exercise and adapt programs to safely and gradually improve patients' fitness levels.[181]

Despite the clear benefits of maximal exercise testing, it remains underused in many clinical settings due to concerns regarding patient safety, particularly in high-risk populations such as patients with CVD, even though the adverse event rate is low (0.8 complications per 10,000 tests in healthy adults,[70] and 0.3 to 2.7 and 0.6 to 6.0 events per 10,000 testing hours for men and women, respectively[42]). With proper training and adherence to standardized protocols, maximal exercise tests, such as CPETs, can be safely administered to patients with CVD.[182] The ACSM emphasizes the need for thorough pre-testing evaluations to identify individuals at heightened risk for adverse events during maximal testing.[49] In the CAD population, there is a need to balance obtaining clinically relevant data and minimizing the risk of inducing myocardial ischemia or arrhythmias.[183] Maximal exercise testing may lead to cardiac complications, including angina episodes and arrhythmias, in susceptible individuals with CAD.[183] Another challenge with maximal exercise testing in patients with CAD is the potential worsening of symptoms (i.e., exercise induced ischemia, angina, and dyspnea).[87] Fletcher et al. noted that symptom-limited exercise protocols may not be feasible or safe for certain patients.[54] Consequently, the reliance on maximal exercise testing alone may lead to incomplete assessments, indicating that appropriate testing protocols may need to be reconsidered for patients with CAD. These safety considerations have led researchers and healthcare providers to explore alternative testing modalities, such as submaximal exercise testing, to decrease potential risks and improve the overall safety of CRF assessments in patients with CAD. Further, the cost (i.e., for specialized personnel) and specialized equipment (i.e., metabolic cart, ECG equipment, etc.) required to run maximal exercise tests may not be affordable for CR programs.

3.1.2 Introduction to submaximal exercise testing

Submaximal exercise tests estimate a patient's CRF as tests are stopped at a pre-determined time or HR according to testing protocols, particularly in individuals with CVD.[184,185] Submaximal testing often relies on extrapolations or formulas to predict and calculate CRF based on limited data collected during submaximal exercise, providing less accurate evaluations, which can lead to underestimation or overestimation of a patient’s exercise capacity.[181,182,184,185] In patients with CAD, submaximal testing also allows for an evaluation of exercise tolerance without inducing high levels of stress or exacerbating CAD-related symptoms.[80,185] It also allows for a graded and/or controlled assessment of a patient’s response to exercise and involves patients exercising at a workload below their maximal capacity,[186] allowing for a comprehensive assessment of cardiovascular responses while minimizing the risks associated with maximal exertion.[187] This not only increases the overall safety of the testing protocol, but also assists with the integration of exercise testing into routine clinical assessments for the management of CAD.[76,185] Submaximal exercise testing is beneficial for advancing our understanding of cardiovascular health and providing meaningful data on CRF and exercise capacity, particularly in populations where maximal testing may be impractical or contraindicated (i.e., acute MI within 2 days, unstable angina, symptomatic aortic stenosis, uncontrolled cardiac arrythmias, acute pulmonary embolism, pulmonary infarction, deep vein thrombosis, acute myocarditis, acute pericarditis, or decompensated heart failure).[42,80,188] There are many other advantages of submaximal exercise testing. These include but are not limited to feasibility, lower costs (i.e., do not require specialized equipment or personnel), and the ability to predict functional performance (i.e., the ability to stand up from a chair, walk and return to a seated position).[54,84,86,185]

3.1.3 Exercise Testing Protocols

There are many protocols to consider for measuring the physiological responses to maximal exercise testing in patients with CAD. The modified Naughton protocol has become a popular treadmill test for those with CAD as it was the selected protocol in the National Exercise and Heart Disease Project[94] and has since been routinely used in patients with CAD.[189] The modified Bruce protocol is a standard test in cardiology practice that was developed as a clinical tool to estimate CRF in patients with or suspected CAD.[137] The modified Bruce protocol is routinely used in CR programs across Canada and reported in the literature. The Balke treadmill protocol was developed to measure peak $\dot{V}O_2$ in patients with cardiovascular disease, but also to estimate CRF in athletes.[72] Ramp protocols gradually increase speed and grade at increments of 10-60s, rather than in discrete steps.[68,187] Ramp protocols were developed in the 1980s and 1990s as an alternative to the Bruce protocol which has abrupt increases in workload every three minutes.[54,68,190–193] Due to the more gradual increase in workload, CR programs adapted the use of ramp protocols for patients with CVD.[194,195] In fact, the UOHI operates several ramp protocols including a slow, regular, and athletic ramp.

The above protocols descriptions and their routine use in clinical practice are the reasons for which these protocols were selected for this thesis investigation. There are several Balke protocols, but we opted to select one that was different from the modified Naughton, modified Bruce, and the UOHI show ramp protocol. The details of each of these treadmill protocols are provided in the Methods (see section 3.2.6).

3.1.3.1 Sex differences in Exercise Testing

Sex based differences in exercise testing are influenced by anatomical and physiological factors such as heart size,[95] muscle mass,[102] and hemoglobin concentrations (see section 1.4).[102]

However, there are conflicting findings regarding sex differences during exercise testing. Reported $\dot{V}O_2$ values during exercise tests have varied with no differences in $\dot{V}O_2$ at rest between females and males, but that females have a higher $\dot{V}O_2$ at the same workload during moderate and vigorous intensity exercise; these findings suggest a higher cardiometabolic demand is required for females to complete the same type of exercise.[99,101,199] This greater cardiometabolic demand is reported by Butt et al.[200] and Wang et al.[201] who showed that males compared to females demonstrated higher absolute workload and power output as evidenced by greater maximal $\dot{V}O_2$ values and higher peak running speeds during treadmill exercise testing. In addition, studies by Garcin et al.[197] and Deschenes et al.[198] reported no differences in HR during submaximal exercise between females and males, however studies by Wheatley et al.[101] and Laurent et al.[199] reported that females compared to males had a higher HR when exercising at the same absolute workload.

Although there are known sex differences within exercise testing, there is limited literature as to how exercise testing protocol selection may affect peak $\dot{V}O_2$ for females compared to males with CAD. Study 2 of my thesis will therefore examine how different maximal and submaximal exercise testing protocols affects peak $\dot{V}O_2$ within females and within males with CAD.

3.1.4 Research Objectives

3.1.4.1 Maximal Research Questions

Primary research question: Does peak $\dot{V}O_2$ vary between different maximal treadmill exercise testing protocols in females and males with CAD?

Hypothesis: Maximal exercise testing protocols with lower starting speeds/grades and lower incremental magnitudes will yield a higher peak $\dot{V}O_2$ in females and males with CAD.

Secondary research questions: Secondary research questions include:

(1) How do peak cardiometabolic responses (i.e., HR, BP, RPE, and blood lactate concentrations) compare between different maximal treadmill exercise testing protocols for females and males with CAD?

(2) Do different increments of grade/speed affect test duration for females and males?

(3) What is the most common reason for test termination for females and males?

(4) Does higher patient enjoyment of a test protocol yield a higher peak $\dot{V}O_2$ for females and males?

(5) Which test was most frequently ranked as the most enjoyable test by female and male patients?

(6) Which of the tested protocols (i.e., modified Bruce, modified Balke, modified Naughton, and UOHI Slow Ramp) achieves a greater number of ACSM criteria for maximal test termination for females and males with CAD?

3.1.4.2 Submaximal Research Questions

Primary research question: Does estimated peak $\dot{V}O_2$ vary between different submaximal treadmill exercise testing protocols in females and males with CAD?

Hypothesis: Submaximal exercise testing protocols with lower starting grade and or speed and lower incremental magnitudes will yield a higher peak $\dot{V}O_2$ in females and males with CAD.

Secondary research questions: The secondary research questions include:

(1) Does the test duration differ between submaximal exercise testing protocols for males and females with CAD?

(2) Do peak cardiometabolic responses (i.e., BP, HR, and blood lactate concentrations) and rating of perceived exertion (RPE) differ between submaximal exercise testing protocols for males and females with CAD?

3.2 Methods

3.2.1 Design and Setting

This randomized single blind cross-over study was completed at the University of Ottawa Heart Institute (UOHI), a quaternary cardiovascular health centre in Ottawa, Canada. The UOHI has a catchment area of 1.4 million people and provides care to Eastern Ontario and Western Quebec. The approval for this study was obtained from the Ottawa Health Science Network Research Ethics Board (OHSN-REB#: 20230327-01H) and the University of Ottawa Office of Research Ethics and Integrity (H-02-25-11335).

3.2.2 Participants and Recruitment Process

Participant recruitment occurred between March 1st, 2024, and September 1st, 2024, using several methods. Firstly, physicians, nurses, and physiotherapists at the UOHI referred potentially eligible patients to the study. Secondly, posts were made on Instagram, Facebook, and Twitter to reach as many adults with CAD as possible. Thirdly, EPIC (an online medical record system), weekly UOHI CR intake lists, and a database of patients who had previously participated in an Exercise Physiology and Cardiovascular Health Lab (EPCHL) study and consented to being contacted for research purposes were used to identify eligible patients. These patients were then contacted by telephone to determine their interest in participating in the study. Following verbal consent to participate, the patient was sent an email to review the informed consent form (ICF) and schedule their first appointment. The timeline for patient participation and CONSORT flow diagram are shown in Figures 3.1 and Figure 3.2, respectively.

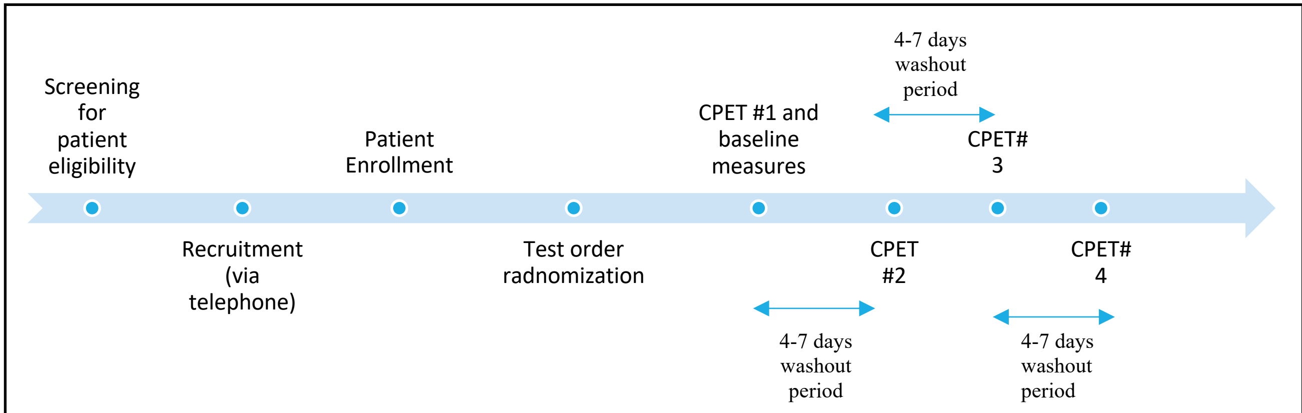

Figure 3.1: Timeline for the involvement of participants in the study.
CPET, cardiopulmonary exercise test.

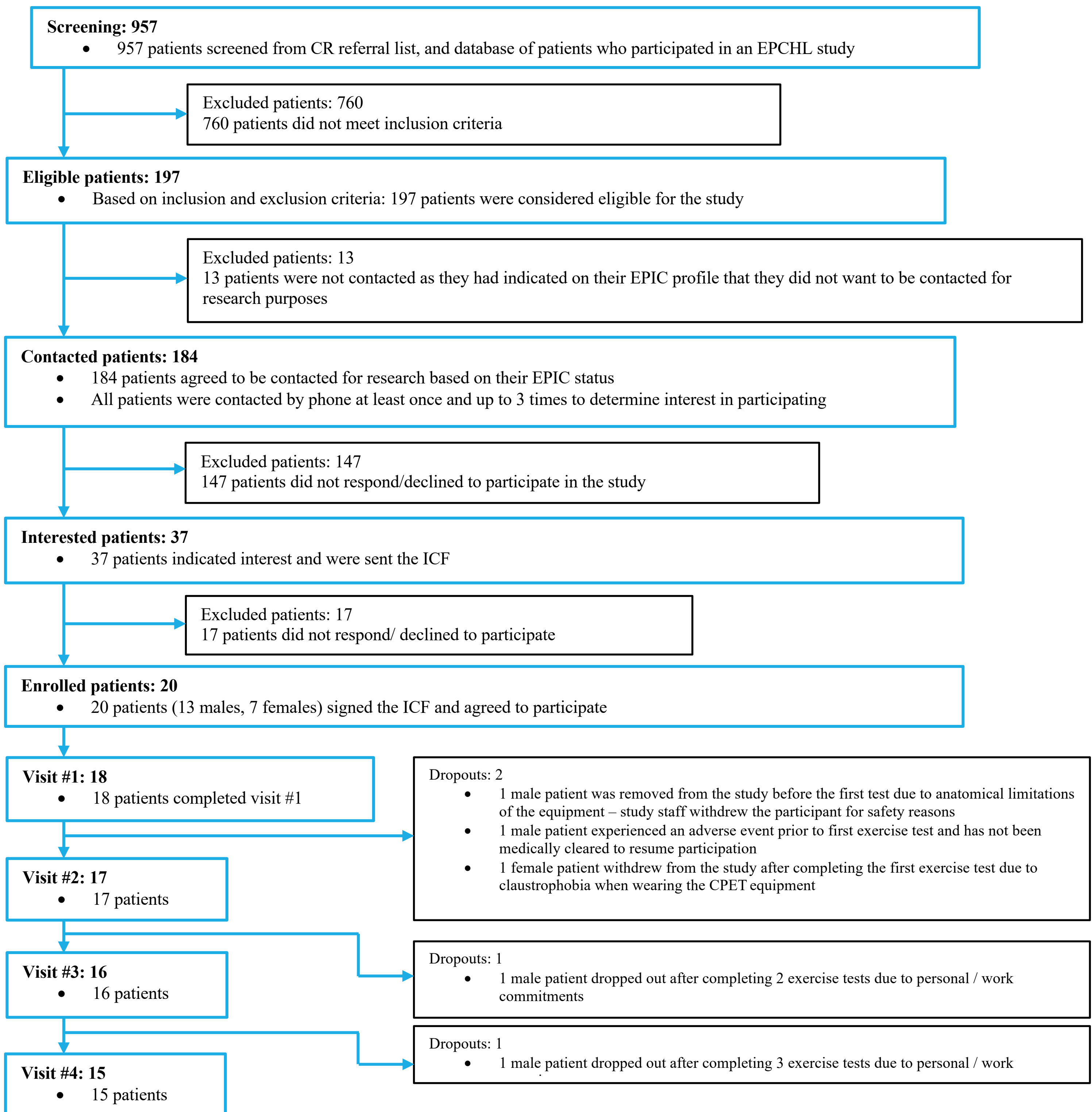

Figure 3.2: CONSORT flow diagram showing the number of patients who were screened and recruited as well as reasons for patient exclusion for the PACED Study.
CR, cardiac rehabilitation; CPET, cardiopulmonary exercise test; EPCHL, Exercise Physiology and Cardiovascular Health Lab; ICF, informed consent form.

Study Staff

Highly trained students (MSc and PhD) and staff (research coordinator, research assistant, research fellow) were involved in conducting the CPETs. These study staff followed standard operating procedures (SOPs) for performing CPETs as well as the use and calibration of the study devices (i.e., metabolic cart [Parvo Medics TrueOne® 2400, Salt Lake City, UT], 12-lead ECG [Nasiff CardioCard®, Central Square, NY], BP measurements [SunTech Tango M2, Morrisville, NC], and blood lactate analyzer [Lactate Plus; Nova Biomedical Corporation, Cheshire, UK]). All study staff participated in training sessions for all devices that were used. In advance of study start, trial CPETs were performed for each of the exercise testing protocols to familiarize study staff with the procedures.

3.2.3 Eligibility Criteria

Participants with CAD who (i) were 18 years and older, (ii) had a previous CAD diagnosis by a physician, (iii) were able to perform a CPET until volitional exhaustion, (iv) had not changed their PA levels within the previous 4 weeks prior to starting the study, (v) were able to self-ambulate on a treadmill, (vi) were at least 8 weeks post cardiovascular event or procedure, and (vii) were able to provide written informed consent were included.

Participants were excluded if they (i) were not able to speak, read, write, or understand English or French, (ii) were actively enrolled in a CR program (as this could impact the ability to compare outcomes between exercise testing protocols), (iii) had heart failure with an ejection fraction <45% (indication of possible cardiomyopathy),[42] (iv) had a diagnosed arrythmia (relative contraindication for exercise testing),[42] peripheral artery disease, severe aortic stenosis, valvular disease, spontaneous coronary artery dissection (SCAD), and/or chronic obstructive

pulmonary disease (COPD) (contraindications for maximal exercise testing), (v) had an implantable cardioverter-defibrillator (ICD), (vi) were pregnant (sustained vigorous exercise in pregnant women may induce fetal bradycardia),[196] or (vii) were unable to complete exercise testing (i.e. treadmill, due to musculoskeletal limitations).

3.2.4 Visit #1 (screening and CPET #1)

During the screening portion of the first visit, the study staff consented the participants before any study measures were collected. After obtaining written consent, the study staff collected participants' sex, age, medical history, and medication regime. They then measured participants' height, body mass, waist circumference, and body composition (% of body fat and body muscle mass) using standardized procedures.[42,197] Questionnaires including demographics and the International Physical Activity Questionnaire (IPAQ) were then completed either using REDCap (a secure web application for building and managing online surveys) or paper copies. After the completion of these measures, participants were randomized for their exercise testing order.

During this first visit, participants also completed a symptom-limited CPET at the UOHI. This test was used to measure the peak aerobic power ($\dot{V}O_2$peak) and peak HR using state-of-the-art metabolic equipment (Parvo Medics TrueOne® 2400, Salt Lake City, UT). After the completion of the exercise test, the participant was asked to fill out a short questionnaire (i.e., enjoyment questionnaire). The participants were allowed to choose not to answer any questions that may upset them or cause distress.

3.2.5 Visits #2, #3, and #4

Subsequent visits had a washout period of 4-7 days between the exercise tests. Clinical guidelines suggest at least 48 hours between maximal exercise tests to allow for recovery between high intensity/maximal exercise sessions,[42,146] with at least 72 hours recommended to prevent delayed onset muscle soreness which may affect testing results.[42,146] A range of 4-7 days was also chosen to allow for flexibility in scheduling the tests. All appointments were conducted at similar times of day (i.e. +/- 1 hour in appointment time) to minimize the potential influences from changes in daily activities that may occur prior to the appointments.

During each visit, the research staff measured participants' height, body mass, waist circumference, and body composition (% of body fat and body muscle mass) using standardized procedures.[42,197] Then, participants completed a symptom-limited CPET at the UOHI as described above. Following the final exercise test during visit #4, participants completed a longer questionnaire which asked them to compare their experience throughout the four different tests (i.e., exercise test feedback questionnaire [Appendix I]).

3.2.6 Cardiopulmonary Exercise Tests

All exercise tests were extended from a submaximal to a maximal exercise test and patients performed the test until volitional exhaustion for the purposes of measured submaximal and maximal values. Gas exchange was continuously monitored; the highest rate of oxygen consumption (i.e., peak $\dot{V}O_2$ in mL/kg/min) represented peak aerobic power. Symptoms that would limit the test include muscle fatigue, exhaustion, extreme shortness of breath and light-headedness. BP was recorded at the end of every 2 stages, blood lactate concentration was measured during the last 30s of every stage, RPE was recorded at the end of every stage, and HR

were continuously measured throughout the tests. To ensure standardization, the following procedures were followed:

Blinding: Patients were blinded to the protocol names, test order, and were not able to see or hear the stage, speed, incline, or test duration.

Encouragement: Despite not using a script, all study staff followed a standardized approach during the tests and did not indicate the test duration or stage level to the participants throughout the tests.

Rail support: Patients were not allowed to use the treadmill handrails for support, except during blood lactate collection when they were allowed to steady themselves using the handrails.

Safety: Participants were instructed on how to communicate any adverse events or to terminate the test if needed. A nurse and other support staff were available to assist, if required. A safety mat was placed behind the treadmill to protect participants in the event of a fall and to minimize injury risk if they were unable to maintain ambulation on the treadmill. Biosafety measures for capillary blood collection included the use of paper towels on the treadmill handrails to minimize risk of contamination and exposure to germs.

For all submaximal tests, HR, BP, and peak $\dot{V}O_2$ were recorded when patients reached 85% of age-predicted maximal HR (i.e., max HR = 220 – age; for patients on β-blockers: max HR = 220 - age - 30bpm).[198] For maximal tests, HR and $\dot{V}O_2$ were continuously recorded throughout the test, BP was measured every 2 stages, RPE was collected at the end of every stage, and blood lactate was collected after the warm-up stage, at test termination, and 2 and 4 minutes into recovery. For all protocols, tests were considered successful if participants were able to complete at least 2 stages of the test and reached 85% of their age-predicted peak HR.[47]

The tests were terminated when the patient requested to stop or the exercise professional (R. Kin or exercise physiologist) felt that the patient could not continue safely.

Protocols

Modified Naughton

Patients walked on a treadmill for 2-minute stages of increasing speeds and grades (see appendix B and F). HR and RPE were collected at the end of each stage. The exercise test duration and age of the patient were used to estimate $\dot{V}O_2$ from the formula by Martin and Acker for patients with CAD:[189]

$$\dot{V}O_{2_{peak}} = 17.66 + (test\ duration\ (min) \times 0.985) - (age(years) \times 0.169)$$

Modified Bruce

Patients walked on a treadmill for 3-minute stages of increasing speeds and grades (see appendix E). HR and RPE were collected at the end of each stage. The speed and grade of the last fully completed stage was used to estimate peak $\dot{V}O_2$ using the ACSM Walking equation (ACSM):[42]

$$\dot{V}O_{2_{peak}} = \left[speed\ \left(\frac{m}{min}\right) \times 0.1\right] + \left[grade\ (decimal) \times speed\ \left(\frac{m}{min}\right) \times 1.8\right] + 3.5$$

Modified Balke

For the first stage of the modified Balke, patients walked on a treadmill at 4 mph for 4 minutes and 0% grade. Each subsequent stage increased in intensity by a 2% grade every minute until 12% grade was reached and speed then increased by 0.5 mph every minute (see Appendix B and D). The speed and grade of the last fully completed stage was used to estimate peak $\dot{V}O_2$ using the ACSM walking equation:[42]

$$\dot{V}O_{2_{peak}} = \left[speed\ \left(\frac{m}{min}\right) \times 0.1\right] + \left[grade\ (decimal) \times speed\ \left(\frac{m}{min}\right) \times 1.8\right] + 3.5$$

UOHI Slow Ramp

For the first stage of the UOHI Slow Ramp, patients walked on a treadmill for 2 minutes at 1.5 mph and 0% grade. For every stage the speed or grade changed by varying amounts (see appendix G). Although no formula exists for predicting $\dot{V}O_2$ for this exact protocol, ramp protocols are commonly used, and the following formula was used to calculate $\dot{V}O_2$:[163]

$$\dot{V}O_{2_{max}} = 45.2 - (0.35 \times Age\ (years)) - (10.9 \times Sex) - (0.15 \times Weight\ (pounds)) + (0.68 \times Height\ (inches)) - (0.46 \times Exercise\ mode)$$

($R = 0.79$, $R^2 = 0.62$, standard error of the estimate = 6.6 ml kg^{-1} min^{-1})

Sex: male= 1; female =2

Exercise mode: treadmill = 1; bike = 2

These aforementioned equations were used to estimate peak $\dot{V}O_2$ at 85% of age-predicted maximal HR for each respective protocol. The following equations[164] were then used to estimate $\dot{V}O_2$ max from the values obtained at 85% of age-predicted maximal HR:

$HR_{max} = 220 - age$ or $HR_{max} = 220 - age - 30bpm$ (for patients taking β-blockers)

$$Slope\ (b) = \frac{(SM_2 - SM_1)}{(HR_2 - HR_1)}$$

$$\dot{V}O_2max = SM_2 + b(HR_{max} - HR_2)$$

SM_2 = VO_2 at last stage
SM_1 = VO_2 at 2nd last stage

HR_2 = HR at last stage
HR_1 = HR at 2nd last stage

Each patient performed each protocol until volitional exhaustion. To attain values at 85% of age-predicted maximal HR, measures (i.e., BP, RPE, and blood lactate concentrations) were taken as closely to 85% of age-predicted maximal HR as possible, but this may not have been at the same time across protocols and it was unlikely at the time participants decided to terminate or exactly at 85.0% of age-predicted maximal HR.

3.2.7 Outcomes

3.2.7.1 Outcomes: Maximal exercise tests

Primary Outcome

The primary outcome was peak $\dot{V}O_2$: defined as the highest $\dot{V}O_2$ value (mL/kg/min) achieved based on the highest 20-second average of sampled measures during the last minute of the test. $\dot{V}O_2$ was measured continuously using a metabolic system with gas analysis (Parvo Medics TrueOne® 2400, Salt Lake City, UT).

Secondary Outcomes

The secondary outcomes included: (i) BP (measured at the end of every stage using a BP cuff [SunTech Tango M2, Morrisville, NC]), (ii) HR (continuously measured using a 12-lead electrocardiogram system [Nasiff CardioCard, Central Square, NY], (iii) HRR (calculated using HRR = Max HR – resting HR)), (iv) RPE (measured at the end of every stage using the Borg 6-20 RPE scale), (v) blood lactate concentrations (measured using a blood lactate analyzer [Lactate Plus; Nova Biomedical Corporation, Cheshire, UK] during the last 30s of every stage), (vi) test duration (measured using the metabolic system [Parvo Medics TrueOne® 2400, Salt Lake City, UT]), (vii) reason for ending the test, (viii) enjoyment (measured using a self-reported enjoyment questionnaire [see appendix H]), (ix) perceived CRF improvement, and (x) the test that was most frequently ranked as the most enjoyable.

3.2.7.2 Outcomes: Submaximal Exercise Testing

Primary Outcome

The primary outcome was estimated peak $\dot{V}O_2$. Estimated $\dot{V}O_2$ was calculated based on the final completed stage and equations provided in section 3.1.3.

Secondary Outcomes

The secondary outcomes included: (i) BP (measured at the end of every stage using a BP cuff [SunTech Tango M2, Morrisville, NC]), (ii) HR (measured at the end of every stage using a 12-lead electrocardiogram system [Nasiff CardioCard, Central Square, NY]), (iii) RPE (measured at the end of every stage using the Borg 6-20 RPE scale), (iv) blood lactate concentrations (measured using a blood lactate analyzer during the last 30s of every stage [Lactate Plus; Nova® Biomedical Corporation, Cheshire, UK]), and (v) test duration and enjoyment (measured using a self-report enjoyment questionnaire [see appendix H]).

Additional Outcomes

Other outcomes included demographics (i.e., age, sex, ethnicity), anthropometrics (i.e., body mass, height, waist circumference), and medical information (i.e., other cardiovascular conditions and medications).

3.2.8 Sample Size

The minimal clinically important difference (MCID) for change in peak $\dot{V}O_2$ is 3.5 mL/kg/min based on evidence that a 3.5 mL/kg/min (1 MET) is associated with a 10-25% decreased risk for all-cause mortality over a 10-year follow-up[58,199] with a standard error of 2.47 mL/kg/min.[200] Using the PASS software for repeated measures sample size calculations, the following information was used to calculate the sample size: MCID = 3.5mL/kg/min (1 MET), SD = 2.47mL/kg/min, alpha = 0.05, power = 0.8, 4 levels (as there were four planned CPET

protocols). Using this information, the calculated sample size was N = 44. To plan for an expected 20% dropout rate, the total target sample size was 52.8 (N = 54). As this thesis is focused on differences within females and within males, an equal number of females and males were to be included in the target sample size. The target sample size was 27 females and 27 males.

3.2.9 Statistical Analysis

All analyses were performed using SPSS for Windows (Version 29.0.1.0 [171]) (IBM Corp., Armonk, NY, USA). All variables were assessed for normality using a combination of the Shapiro-Wilk test, Q-Q plots, and histograms. Demographics and anthropometrics (i.e., age, body mass, height, BMI, and BP) were summarized as means and standard deviation or median and 95% confidence intervals (CI) to describe the baseline characteristics of the participants. For maximal (i.e., measured peak $\dot{V}O_2$) and submaximal (i.e., estimated peak $\dot{V}O_2$), repeated measures analysis of variance (ANOVA), or Friedman tests if variables were not normally distributed, were used to compare measured and estimated peak $\dot{V}O_2$ between the four different exercise testing protocols. Repeated measures ANOVA were also used to compare continuous variables (i.e., HR, BP, test duration, blood lactate concentrations, RPE, and enjoyment), or Friedman tests if variables were not normally distributed. For normally distributed data, post-hoc pairwise comparisons were performed using Bonferroni correction. For non-normally distributed data, post-hoc pairwise comparisons were performed using Wilcoxon signed-rank tests with Bonferroni correction. Effect sizes were calculated using Cohen's f for normally distributed data and Kendall's W for non-normally distributed data. Cohen's f for ANOVA was interpreted as "T" (f <0.10), "S" (f = 0.10 – 0.24), "M" (f = 0.25 – 0.39), or "L" (f ≥ 0.40). Kendall's W for Friedman were interpreted as "T" (f <0.10), "S" (f = 0.10 – 0.19), "M" (f = 0.20 – 0.29), or "L"

(f ≥ 0.30). Chi-square analyses were used to compare categorical variables (i.e., reason for stopping the test). Paired t-tests were used to compare normally distributed continuous variables (i.e., CRF difference between test 1 and test 4 and perceived CRF) or Wilcoxon signed rank tests, if data were not normally distributed. Spearman's rho correlations were used to compare peak $\dot{V}O_2$ and enjoyment and test duration and enjoyment. Paired t-tests were used to compare estimated $\dot{V}O_2$ max (from equations) with measured peak $\dot{V}O_2$, or Wilcoxon signed rank tests if variables were not normally distributed. Paired t-tests were used to compare estimated $\dot{V}O_2$ (from equations) at 85% of age-predicted maximal HR with measured $\dot{V}O_2$ at 85% of age-predicted maximal HR or Wilcoxon signed rank tests if variables were not normally distributed. The above-mentioned analyses were performed separately for females and males, as the research questions focused on examining optimal exercise testing protocols for within women and within males.

3.3 Results

The study included 20 patients (7 females and 13 males) who were diagnosed with CAD and were between the ages of 52 and 82 years of age. Patient demographics including self-reported ethnicity, work status, level of completed education, yearly earnings, medical history, and medication are shown in Table 3.1.

Table 3.1: Patient demographics, anthropometrics, medical history and medications

	Females (n=7, 100%)	**Males (n=13, 100%)**
Age (years)	64 ± 7	64 ± 8
Ethnic Background		
White	7 (100%)	11 (84.6%)
Arab	0 (0%)	1 (7.7%)
Lebanese	0 (0%)	1 (7.7%)
Work Status		
Retired	4 (57.1%)	6 (46.2%)

Employed part-time	3 (42.9%)	0 (0%)
Employed full-time	0 (0%)	7 (53.8%)
Level of Completed Education		
College	3 (42.8%)	4 (30.8%)
University	2 (28.6%)	6 (46.2%)
High school	2 (28.6%)	2 (15.4%)
Trades certificate	0 (0%)	1 (7.6%)
Anthropometrics		
Height (cm)	156.7 ± 7.2	171.5 ± 5.4
Weight (kg)	65.4 ± 12.7	89.9 ± 17.1
Resting HR (bpm)	62 ± 11	62 ± 12
Resting systolic BP (mmHg)	122 ± 10	128 ± 11
Resting diastolic BP (mmHg)	72 ± 8	79 ± 6
Resting blood lactate (mmol/ L)	1.7 ± 1.1	3.7 ± 7.9
Waist circumference (cm)	88.7 ± 15.3	99.1 ± 14.7
Fat mass (%)	38.7 ± 7.5	29.5 ± 7.9
Muscle mass (%)	25.4 ± 2.5	30.8 ± 4.0
Medical History		
Circulatory disorders		
CAD	7 (100%)	13 (100%)
PCI	6 (85.7%)	8 (61.5%)
Hypertension	5 (71.4%)	8 (61.5%)
Cardiac catheterization	5 (71.4%)	6 (46.2%)
CABG	2 (28.6%)	5 (38.5%)
STEMI	2 (28.6%)	0 (0%)
MI	1 (14.3%)	6 (46.2%)
Non-ST-elevation myocardial infarction (NSTEMI)	1 (14.3%)	1 (7.6%)
Endocrine		
Dyslipidemia	3 (42.9%)	6 (46.2%)
Hyperlipidemia	3 (42.9%)	3 (23.1%)
Diabetes	1 (14.3%)	2 (15.4%)
Diabetes mellitus, type 2	1 (14.3%)	1 (7.6%)
Musculoskeletal		
Arthritis	3 (42.9%)	3 (23.1%)
Nervous		
Angina	3 (42.9%)	5 (38.5%)
Respiratory		
Hiatal hernia	1 (14.3%)	1 (7.6%)
Asthma	0 (0%)	2 (15.4%)
Obstructive sleep apnea	0 (0%)	2 (15.4%)
Digestive		

GERD (gastroesophageal reflux disease)	1 (14.3%)	4 (30.8%)
Medications		
Antiplatelet drugs	7 (100%)	12 (92.3%)
Statins	7 (100%)	12 (92.3%)
ACE inhibitors	3 (42.9%)	4 (30.8%)
Cholesterol absorption inhibitor	3 (42.9%)	0 (0%)
Beta blockers	2 (28.6%)	7 (53.8%)
Antidepressants	2 (28.6%)	4 (30.8%)
Nitrates	2 (28.6%)	4 (30.8%)
Steroids & bronchodilators	2 (28.6%)	4 (30.8%)
SGLT2 inhibitors	2 (28.6%)	3 (23.1%)
Biguanides (metformin-based drugs)	2 (28.6%)	2 (15.4%)
GLP-1 receptor agonist	2 (28.6%)	1 (7.7%)
Insulin	2 (28.6%)	0 (0%)
Sulfonylureas	1 (14.3%)	1 (7.7%)
Benzodiazepines (Anxiolytics/sedatives/psychotropics)	1 (14.3%)	0 (0%)
Angiotensin 2 receptor blockers	0 (0%)	4 (30.8%)
Calcium channel blocker	0 (0%)	2 (15.4%)
Anticoagulant	0 (0%)	1 (7.7%)
DPP-4 inhibitors	0 (0%)	1 (7.7%)
Mood stabilizer	0 (0%)	1 (7.7%)

Values are presented as mean ± standard deviation or absolute numbers and percentages. Percentages were calculated within females and within males.

BP, blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; GERD, gastroesophageal reflux disease; HR, heart rate; MI, myocardial infarction; NSTEMI, non-ST-elevated myocardial infarction; STEMI, ST-elevated myocardial infarction; PCI, percutaneous coronary intervention.
* Female patient, PACED-21, although prescribed to take β-blockers, did not take a β-blocker before any of her CPETs due to instructions for set time for taking her pill from her general physician.

3.3.1 Maximal Results

The number of successful tests for females and males per protocol are shown in Tables 3.2 - 3.5. For females, 1 (17%) successfully complete the modified Balke test, 3 (43%) the modified Bruce, 3 (50%) the modified Naughton, and 3 (50%) the UOHI Slow Ramp. For males, 5 (50%) successfully completed the modified Balke test, 7 (64%) the modified Bruce, 5 (56%) the modified Naughton, and 5 (63%) the UOHI Slow Ramp.

Table 3.2: Stage completion and successful modified Balke CPETs

	Female (n = 7) *			Males (n = 11) ♦♣♠		
	Started Stage n (%)	**Completed Stage n (%)**	**Final Stage Completed n (%)**	**Started Stage n (%)**	**Completed Stage n (%)**	**Final Stage Completed n (%)**
Stage 1	6 (100%)	2 (33%)	1 (17%)	10 (100%)	7 (70%)	0 (0%)
Stage 2	2 (33%)	1 (17%)	1 (100%)	7 (70%)	7 (70%)	1 (10%)
Stage 3	1 (17%)	0 (0%)	0 (0%)	7 (70%)	5 (50%)	1 (10%)
Stage 4	0 (0%)	0 (0%)	0 (0%)	5 (50%)	5 (50%)	2 (20%)
Stage 5	0 (0%)	0 (0%)	0 (0%)	5 (50%)	3 (30%)	1 (10%)
Stage 6	0 (0%)	0 (0%)	0 (0%)	3 (30%)	2 (20%)	0 (0%)
Stage 7	0 (0%)	0 (0%)	0 (0%)	2 (20%)	2 (20%)	1 (10%)
Stage 8	0 (0%)	0 (0%)	0 (0%)	2 (20%)	1 (10%)	1 (10%)
Stage 9	0 (0%)	0 (0%)	0 (0%)	1 (10%)	0 (0%)	0 (0%)
Modified Balke, n (%) successful		1 (17%)* n=6			5 (50%)♦ n= 10	

Successful tests were defined as completing 2 stages and reaching 85% of age predicted peak HR.
"Started Stage" was defined as the total number of participants who started the stage, regardless of whether they were able to complete the stage.
"Completed Stage" was defined as the total number of participants who completed the stage in its entirety.
"Final Completed Stage" was defined as the highest stage successfully completed by patients, representing the last stage they were able to complete in its entirety.

* 1 female patient (PACED-15) and 1 male patient (PACED-01) completed only one exercise test, the modified Bruce, before dropping out of the study.
♦ 2 male patients signed informed consents but did not complete any exercise tests (PACED-09: had an adverse event prior to the first exercise test and has not been medically cleared to resume participation; PACED-12: was removed from the study before the first test as equipment was not able to function properly due to the large size of the patient – study staff removed the patient for safety reasons).
♣1 male patient (PACED-03) completed only 2 exercise tests, the Modified Balke and Modified Bruce, before dropping out of the study.
♠1 male patient (PACED-02) completed 3 exercise tests, the modified Balke, modified Bruce and modified Naughton, before dropping out of the study.

Table 3.3: Stage completion and successful modified Bruce CPETs

	Females (n = 7) *			Males (n = 11) ♦♣♠		
	Started Stage n (%)	**Complete d Stage n (%)**	**Final Stage Completed n (%)**	**Started stage n (%)**	**Completed Stage n (%)**	**Final Stage Completed n (%)**
Stage 0	7 (100%)	7 (100%)	0 (0%)	11 (100%)	11 (100%)	0 (0%)
Stage 0.5	7 (100%)	7 (100%)	0 (0%)	11 (100%)	11 (100%)	1 (9%)
Stage 1	7 (100%)	6 (86%)	5 (71%)	11 (100%)	10 (91%)	3 (27%)
Stage 2	6 (86%)	1 (14%)	1 (14%)	10 (91%)	5 (45%)	4 (36%)
Stage 3	1 (14%)	0 (%)	0 (%)	5 (45%)	3 (27%)	2 (18%)

Stage 4	0 (%)	0 (%)	0 (%)	3 (27%)	1 (9%)	0 (0%)
Stage 5	0 (%)	0 (%)	0 (%)	1 (9%)	0 (0%)	1 (9%)
Modified Bruce, n (%) successful		3 (43%) n=7			7 (64%)♦ n=11	

Successful tests were defined as completing 2 stages and reaching 85% of age predicted peak HR.
“Started Stage” was defined as the total number of participants who started the stage, regardless of whether they were able to complete the stage.
“Completed Stage” was defined as the total number of participants who completed the stage in its entirety.
"Final Completed Stage" was defined as the highest stage successfully completed by patients, representing the last stage they were able to complete in its entirety.

* 1 female patient (PACED-15) and 1 male patient (PACED-01) completed only one exercise test, the modified Bruce, before dropping out of the study.
♦ 2 male patients signed informed consents but did not complete any exercise tests (PACED-09- had an adverse event prior to the first exercise test and has not been medically cleared to resume participation; PACED-12: was removed from the study before the first test as equipment was not able to function properly due to the large size of the patient – study staff removed the patient for safety reasons).
♣1 male patient (PACED-03) completed only 2 exercise tests, the Modified Balke and Modified Bruce, before dropping out of the study.
♠1 male patient (PACED-02) completed 3 exercise tests, the modified Balke, modified Bruce, and modified Naughton, before dropping out of the study.

Table 3.4: Stage completion and successful modified Naughton CPETs

	Female n=7 *			Males (n=11) ♦♣♠		
	Started Stage n (%)	**Completed Stage n (%)**	**Final Stage Completed n (%)**	**Started stage n (%)**	**Completed Stage n (%)**	**Final Stage Completed n (%)**
Stage 1	6 (100%)	6 (100%)	0 (0%)	9 (100%)	9 (100%)	0 (0%)
Stage 2	6 (100%)	6 (100%)	1 (17%)	9 (100%)	9 (100%)	0 (0%)
Stage 3	6 (100%)	5 (83%)	0 (0%)	9 (100%)	9 (100%)	2 (22%)
Stage 4	5 (83%)	5 (83%)	3 (50%)	9 (100%)	7 (78%)	2 (22%)
Stage 5	5 (83%)	2 (33%)	1 (17%)	7 (78%)	4 (44%)	1 (11%)
Stage 6	2 (33%)	1 (17%)	1 (17%)	4 (44%)	4 (44%)	0 (0%)
Stage 7	1 (17%)	0 (0%)	0 (0%)	4 (44%)	4 (44%)	2 (22%)
Stage 8	0 (0%)	0 (0%)	0 (0%)	4 (44%)	2 (22%)	2 (22%)
Stage 9	0 (0%)	0 (0%)	0 (0%)	2 (22%)	0 (0%)	0 (0%)
Modified Naughton, n (%) successful		3 (50%) * n=6			5 (56%)♦♣ n= 9	

Successful tests were defined as completing 2 stages and reaching 85% of age predicted peak HR.
“Started Stage” was defined as the total number of participants who started the stage, regardless of whether they were able to complete the stage.
“Completed Stage” was defined as the total number of participants who completed the stage in its entirety.

"Final Completed Stage" was defined as the highest stage successfully completed by patients, representing the last stage they were able to complete in its entirety.

* 1 female patient (PACED-15) and 1 male patient (PACED-01) completed only one exercise test, the modified Bruce, before dropping out of the study

♦ 2 male patients signed informed consents but did not complete any exercise tests (PACED-09- had an adverse event prior to the first exercise test and has not been medically cleared to resume participation; PACED-12: was removed from the study before the first test as equipment was not able to function properly due to the large size of the patient – study staff removed the participant for safety reasons).

♣1 male patient (PACED-03) completed only 2 exercise tests, the Modified Balke and Modified Bruce, before dropping out of the study.

♠1 male patient (PACED-02) completed 3 exercise tests, the modified Balke, modified Bruce, and modified Naughton, before dropping out of the study.

Table 3.5: Stage completion and successful UOHI Slow Ramp CPETs

	Female n=7 *			Males (n=11) ♦♣♠		
	Started Stage n (%)	**Completed Stage n (%)**	**Final Stage Completed n (%)**	**Started stage n (%)**	**Completed Stage n (%)**	**Final Stage Completed n (%)**
Stage 1	6 (100%)	6 (100%)	0 (0%)	8 (100%)	8 (100%)	0 (0%)
Stage 2	6 (100%)	6 (100%)	0 (0%)	8 (100%)	8 (100%)	0 (0%)
Stage 3	6 (100%)	6 (100%)	0 (0%)	8 (100%)	8 (100%)	0 (0%)
Stage 4	6 (100%)	6 (100%)	1 (17%)	8 (100%)	8 (100%)	0 (0%)
Stage 5	6 (100%)	5 (83%)	0 (0%)	8 (100%)	8 (100%)	0 (0%)
Stage 6	5 (83%)	5 (83%)	0 (0%)	8 (100%)	8 (100%)	2 (25%)
Stage 7	5 (83%)	5 (83%)	1 (17%)	8 (100%)	6 (75%)	0 (0%)
Stage 8	5 (83%)	4 (67%)	2 (33%)	6 (75%)	6 (75%)	2 (25%)
Stage 9	4 (67%)	2 (33%)	0 (0%)	6 (75%)	4 (50%)	0 (0%)
Stage 10	2 (33%)	2 (33%)	1 (17%)	4 (50%)	4 (50%)	1 (13%)
Stage 11	2 (33%)	1 (17%)	1 (17%)	4 (50%)	3 (38%)	0 (0%)
Stage 12	1 (17%)	0 (0%)	0 (0%)	3 (38%)	3 (38%)	0 (0%)
Stage 13	0 (0%)	0 (0%)	0 (0%)	3 (38%)	3 (38%)	1 (13%)
Stage 14	0 (0%)	0 (0%)	0 (0%)	3 (38%)	1 (13%)	2 (25%)
Stage 15	0 (0%)	0 (0%)	0 (0%)	1 (13%)	0 (0%)	0 (0%)
UOHI Slow Ramp, n (%) successful		3 (50%)* n=6			5 (63%)♦♣♠ n= 8	

Successful tests were defined as completing 2 stages and reaching 85% of age predicted peak HR.
"Started Stage" was defined as the total number of participants who started the stage, regardless of whether they were able to complete the stage.
"Completed Stage" was defined as the total number of participants who completed the stage in its entirety.
"Final Completed Stage" was defined as the highest stage successfully completed by patients, representing the last stage they were able to complete in its entirety.

* 1 female patient (PACED-15) and 1 male patient (PACED-01) completed only one exercise test, the modified Bruce, before dropping out of the study.
♦ 2 male patients signed informed consents but did not complete any exercise tests (PACED-09- had an adverse event prior to the first exercise test and has not been medically cleared to resume participation; PACED-12: was removed from the study before the first test as equipment was not able to function properly due to the large size of the patient – study staff removed the patient for safety reasons).
♣1 male patient (PACED-03) completed only 2 exercise tests, the Modified Balke and Modified Bruce, before dropping out of the study.
♠1 male patient (PACED-02) completed 3 exercise tests, the modified Balke, modified Bruce, and modified Naughton, before dropping out of the study.

Peak $\dot{V}O_2$

The $\dot{V}O_2$ values for females and males across the exercise testing protocols are shown in Figure 3.3. For females, there was a significant difference for $\dot{V}O_2$ between the protocols ($F = 9.222$, $p = 0.001$). The location of the differences in peak $\dot{V}O_2$ could not be identified, likely due to insufficient power as few females completed the modified Balke protocol. When only comparing the modified Bruce, modified Naughton, and UOHI Slow Ramp, no significant difference in peak $\dot{V}O_2$ was observed across the protocols ($F = 0.891$, $p = 0.44$). For males, no difference in peak $\dot{V}O_2$ was observed across the protocols ($F = 0.189$, $p = 0.75$).

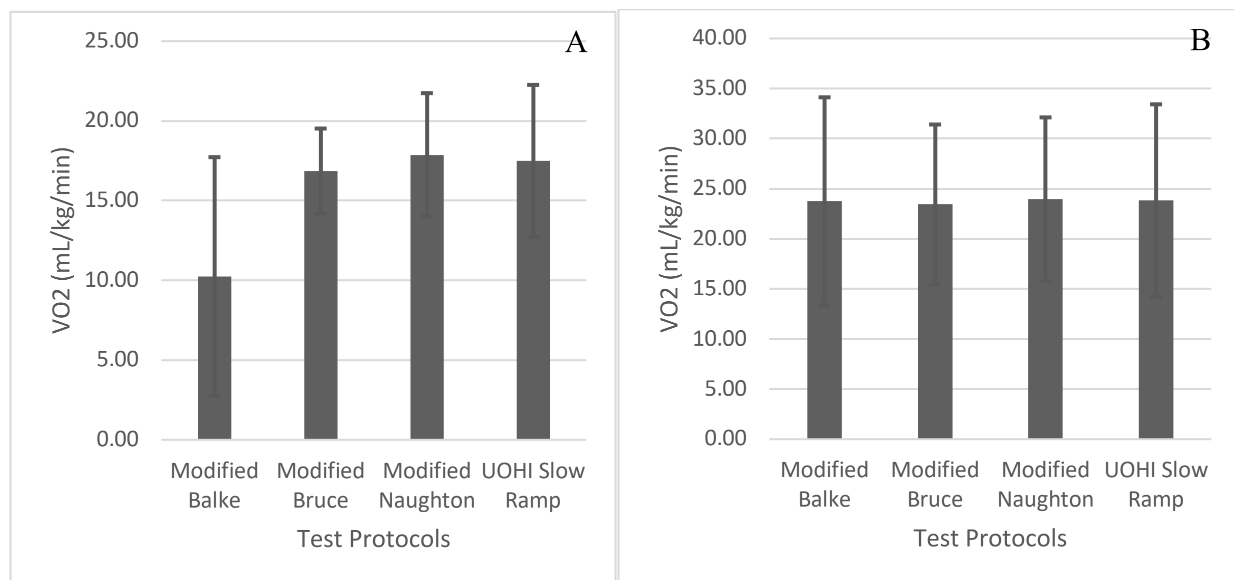

Figure 3.3: Peak $\dot{V}O_2$ of females (A) and males (B) with coronary artery disease across the four maximal cardiopulmonary exercise testing protocols.
$\dot{V}O_2$, oxygen consumption.

Peak Heart Rate

The HR values for females and males across the exercise testing protocols are shown in Tables 3.6 and 3.7. For females, no significant difference in peak HR was observed across the protocols (F = 3.079 p = 0.425). When excluding the modified Balke (given how few successful tests were performed), no significant difference in peak HR was observed (F = 0.017, p = 0.945). For males, no significant difference in peak HR was observed across the protocols (F = 0.203, p = 0.649).

Table 3.6: Maximal values (exercise test results) for female patients

	Modified Balke	Modified Bruce	Modified Naughton	UOHI Slow Ramp	p-value (ES)
Peak HR (bpm)	105 ± 35	121 ± 13	122 ± 22	121 ± 24	0.425 (0.44) L
Peak BP Systolic (mmHg)	190 ± 21	165 ± 25	177 ± 30	172 ± 32	N/A
Peak BP Diastolic (mmHg)	108 ±10	73 ± 15	72 ± 15	76 ± 17	N/A
RPE	13 ± 5	17 ± 3	17 ± 3	18 ± 3	0.033 (1.37) L
Blood Lactate (mmol/L)	5.2 ± 1.1	3.9 ± 1.0	4.2 ± 0.9	3.7 ± 0.9	N/A
Test Duration (min)	1.82 ± 2.33	9.99 ± 1.79	9.00 ± 2.40	9.31 ± 2.40	0.028 (5.26) L
Enjoyment	6.5 ± 2.4	7.7 ± 1.6	7.3 ± 2.1	7.7 ± 1.6	0.34 (0.39) M

BP, blood pressure; ES, effect size (Cohen's *f*); HR, heart rate; RPE, rating of perceived exertion.
N/A indicates that a p-value was not able to be calculated due to the small sample size / missing data.

Table 3.7: Maximal values (exercise test results) for male patients

	Modified Balke	Modified Bruce	Modified Naughton	UOHI Slow Ramp	p-value (ES)
Peak HR (bpm)	143 ± 30	139 ± 27	136 ± 26	135 ± 26	0.649 (0.28) M
Peak BP Systolic (mmHg)	197 ± 27	189 ± 33	197 ± 26	174 ± 18	0.420 (0.50) L

Peak BP Diastolic (mmHg)	83 ± 14	72 ± 10	78 ± 12	79 ± 10	0.524 (0.44) L
RPE	16 ± 4	17 ± 2	18 ± 2	18 ± 2	0.197 (0.49) L
Blood Lactate (mmol/L)	7.1 ± 2.5	6.5 ± 2.6	6.3 ± 3.6	5.1 ± 2.2	0.409 (0.41) L
Test Duration (min)	6.01 ± 4.03	12.14 ± 2.48	10.75 ± 5.60	10.94 ± 3.31	0.005 (0.89) L
Enjoyment	8.2 ± 1.7	8.3 ± 2.0	8.4 ± 2.1	8.5 ± 2.3	0.478 (0.29) M

BP, blood pressure; ES, effect size (Cohen's f); HR, heart rate; RPE, rating of perceived exertion.

Blood Pressure

The BP values for females and males across the exercise testing protocols are shown in Tables 3.6 and 3.7. Females appeared to achieve a higher systolic BP using the modified Balke (F = 0.40, p = N/A); however, there was insufficient power for this analysis due to the few females who completed the modified Balke protocol. When only comparing the modified Bruce, modified Naughton, and UOHI Slow Ramp protocols, there was no significant difference in systolic BP (F = 0.33, p = 0.62). Females appeared to achieve a higher diastolic BP using the modified Balke protocol (F = 5.270, p = N/A); however, as noted above, there was insufficient power for this analysis. When excluding the modified Balke, no significant difference in peak diastolic BP was observed (F = 0.586, p = 0.62). For males, no significant differences in systolic BP (F = 1.015, p = 0.420) or diastolic BP (F = 0.786, p = 0.524) were observed across the protocols.

Blood Lactate

The blood lactate values for females and males across the exercise testing protocols are shown in Tables 3.6 and 3.7. Females appeared to achieve a higher peak lactate using the Modified Balke protocol (F = 1.395, p = N/A); however, there was insufficient power for the

analysis due to the few females who completed the modified Balke protocol. When excluding the modified Balke, no significant difference in blood lactate was observed ($F = 0.594$, $p = 0.575$). For males, no significant difference in peak lactate was observed across the protocols ($F = 1.015$, $p = 0.409$).

Rating of Perceived Exertion (RPE)

The RPE values for females and males across the exercise testing protocols are shown in Tables 3.6 and 3.7. For females, there was a statistical difference in RPE across the protocols ($F = 7.510$, $p < 0.05$). Post-hoc analysis did not reveal differences between protocols as there was likely insufficient power for the analysis due to the few females who completed the modified Balke protocol. When only comparing the modified Bruce, modified Naughton, and UOHI Slow Ramp, no statistical difference was observed ($F = 2.416$, $p = 0.177$). For males, no significant difference in RPE was observed across the protocols ($F = 1.701$, $p = 0.197$).

Test Duration

The test durations for females and males across the exercise testing protocols are shown in Tables 3.6 and 3.7. For females, there was a difference in test duration across the protocols ($F = 138.169$, $p = 0.028$). The test duration for the modified Balke was significantly shorter than the modified Bruce, modified Naughton, and UOHI Slow Ramp protocols (all p values < 0.001). When only comparing the modified Bruce, modified Naughton, and UOHI Slow Ramp, a statistically significant difference in test duration was observed ($F = 20.783$, $p < 0.001$). The test duration of the modified Bruce protocol was significantly longer than the modified Naughton ($p < 0.001$). For males, there was a difference in test duration across the protocols ($F = 7.132$, $p <$

0.005). The test duration of the modified Balke protocol was significantly shorter than the modified Bruce, modified Naughton, and the UOHI Slow Ramp ($p < 0.001$).

For females, there was no significant association between test duration and enjoyment (modified Balke: ρ = 0.314, ρ = 0.544; modified Bruce: ρ = 0.491, p = 0.263; modified Naughton: ρ = 0.638, p = 0.173; and UOHI Slow Ramp: ρ = 0.213, p = 0.686). Similarly for males, there was no significant association between test duration and enjoyment (0 (Figure 3.4).

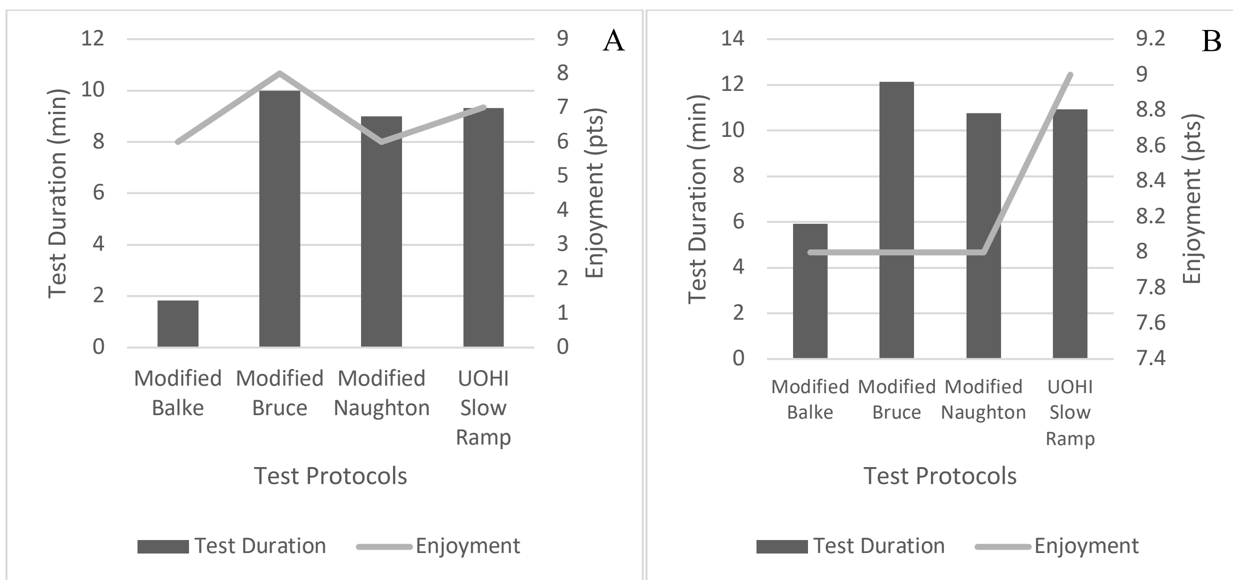

Figure 3.4: Exercise test duration vs. enjoyment for female (A) and male (B) patients with coronary artery disease across the four maximal cardiopulmonary exercise testing protocols. UOHI, University of Ottawa Heart Institute.

Reasons for Test Termination

The primary reason for test termination for females and males across the exercise testing protocols are shown in Figures 3.5 and 3.6. For females, 67% cited speed as the main reason for test termination for the modified Balke, 29% and 50% cited shortness of breath for the modified Bruce and UOHI Slow Ramp, respectively, and 33% cited musculoskeletal fatigue for the modified Naughton.

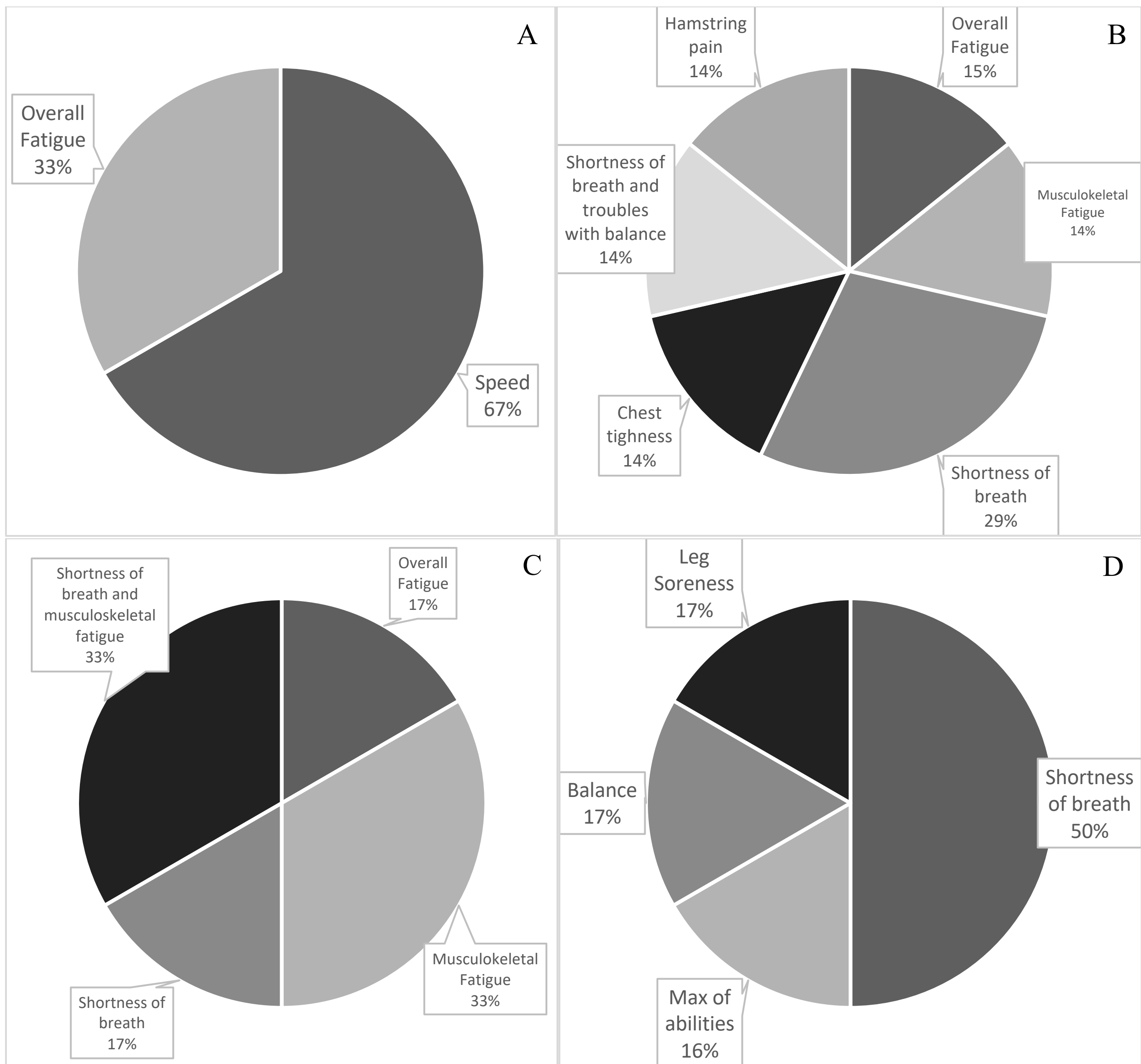

Figure 3.5: Reason for test termination for females with coronary artery disease for the four different cardiopulmonary exercise test protocols.
A: Modified Balke, B: Modified Bruce, C: Modified Naughton, D: UOHI Slow Ramp

For males, 20% cited speed as the primary reason for test termination for the modified Balke, while 28% cited muscuolskeletal fatigue for the modified Bruce, and 23% and 50% cited shortness of breath for the modifed Naughton and UOHI Slow Ramp, respectively.

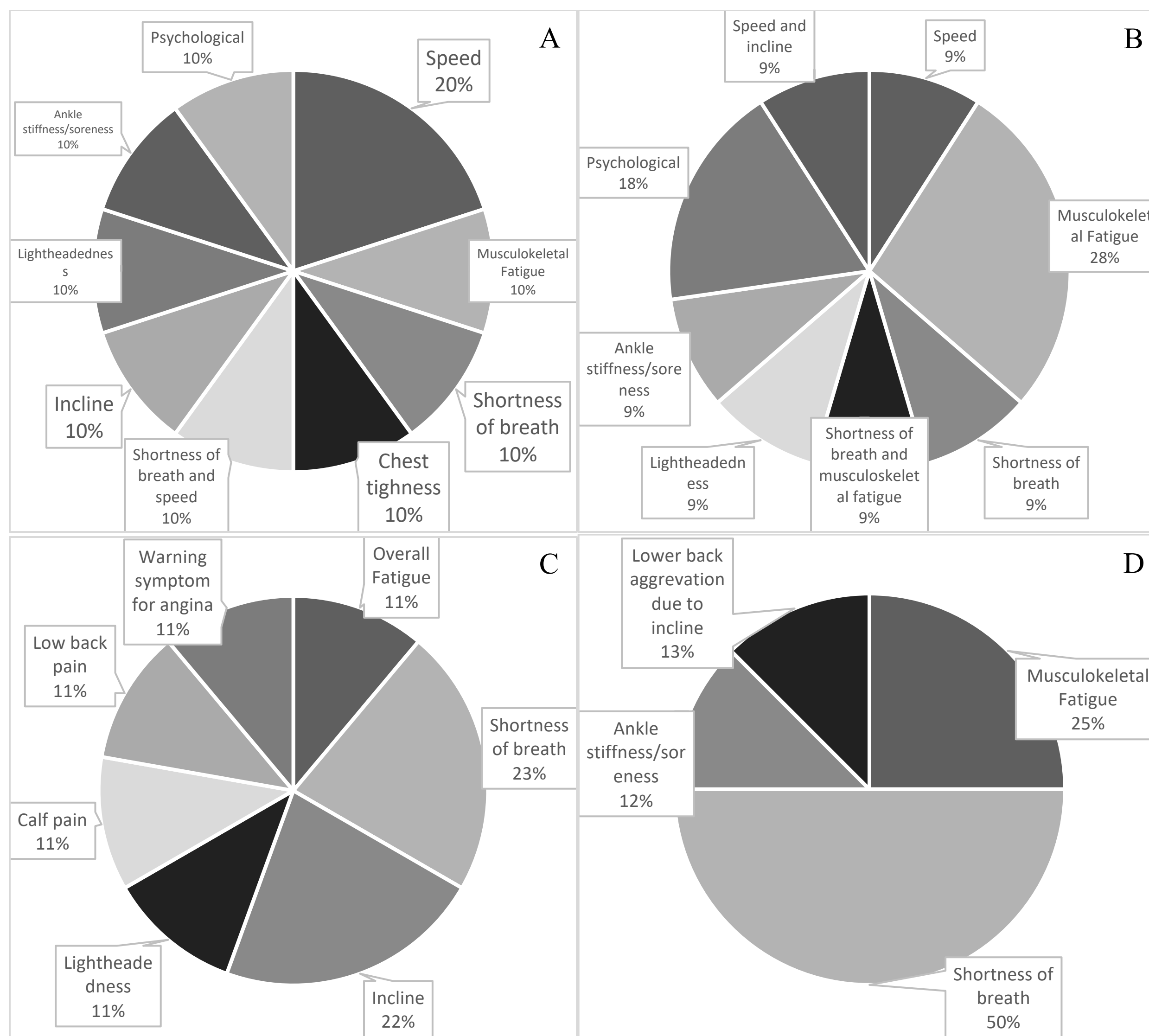

Figure 3.6: Reason for test termination for males with coronary artery disease for the four different cardiopulmonary exercise test protocols.
A: Modified Balke, B: Modified Bruce, C: Modified Naughton, D: UOHI Slow Ramp

The ACSM criteria achieved by females and males across the exercise testing protocols are shown in Tables 3.8 and 3.9. Few participants achieved at least 3 of the 5 ACSM criteria to determine if they reached their physiological maximum. No females achieved at least 3 of the 5 criteria for any of the protocols and only 2 males achieved at least 3 of the 5 criteria for the modified Balke and the UOHI Slow Ramp.

Table 3.8: Number of ACSM criteria achieved by females for determining if physiological maximum was attained

	Modified Balke (n = 6)	Modified Bruce (n = 7)	Modified Naughton (n = 6)	UOHI Slow Ramp (n = 6)
Visual plateau in $\dot{V}O2$ (≤150mL/min) with increased workload	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Respiratory exchange ratio (RER) ≥ 1.10	1 (16.7%)	0 (0%)	1 (16.7%)	0 (0%)
Failure of HR to increase with increasing workload	0 (0%)	0 (0%)	0 (0%)	2 (33.3%)
Post-exercise venous lactate concentration >8.0mmol/L	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Rating of perceived exertion (RPE) at peak exercise >17 on the 6-20 RPE scale	2 (33.3%)	3 (42.9%)	4 (66.7%)	4 (66.7%)
3/5 maximal criteria achieved	0 (0%)	0 (0%)	0 (0%)	0 (0%)

ACSM, American College of Sports Medicine; HR, heart rate; RER, respiratory exchange ratio; RPE, rating of perceived exertion; UOHI, University of Ottawa Heart Institute; $\dot{V}O_2$, oxygen consumption.
A minimum of three criteria must be met for physiological maximum to be achieved.

Table 3.9: Number of ACSM criteria achieved by males for determining if physiological maximum was attained

	Modified Balke (n = 10)	Modified Bruce (n = 11)	Modified Naughton (n = 9)	UOHI Slow Ramp (n = 8)
Visual plateau in $\dot{V}O2$ (≤150mL/min) with increased workload	0 (0%)	1 (9.1%)	0 (0%)	0 (0%)
Respiratory exchange ratio (RER) ≥ 1.10	3 (30%)	4 (36.4%)	1 (11.1%)	4 (50%)
Failure of HR to increase with increasing workload	1 (10%)	0 (0%)	1 (11.1%)	1 (12.5%)
Post-exercise venous lactate concentration >8.0mmol/L	4 (40%)	3 (27.3%)	3 (33.3%)	3 (37.5%)
Rating of perceived exertion (RPE) at peak exercise >17 on the 6-20 RPE scale	8 (80%)	5 (45.5%)	7 (77.8%)	7 (87.5%)

3/5 maximal criteria achieved	2 (20%)	1 (9.1%)	0 (0%)	2 (25%)

ACSM, American College of Sports Medicine HR, heart rate; RER, respiratory exchange ratio; RPE, rating of perceived exertion; UOHI, University of Ottawa Heart Institute; $\dot{V}O_2$, oxygen consumption.
A minimum of three criteria must be met for physiological maximum to be achieved.

The most enjoyed testing protocols for females and males are shown in Figure 3.7. For females, the exercise testing protocol females enjoyed the most varied, with 1 participant citing each protocol as their most enjoyed (i.e., modified Balke: n = 1 [16.7%], modified Bruce: n = 1[16.7%], modified Naughton: n = 1[16.7%], and UOHI Slow Ramp: n = 1[16.7%]), and two participants indicating there was no difference in enjoyment amongst the four protocols. For males, the modified Naughton (n = 3, 37.5%) and UOHI Slow Ramp protocols (n = 3, 37.5%) were ranked highest for enjoyment, while two males (25%) indicated that there was no difference in their enjoyment for the test in which they most enjoyed.

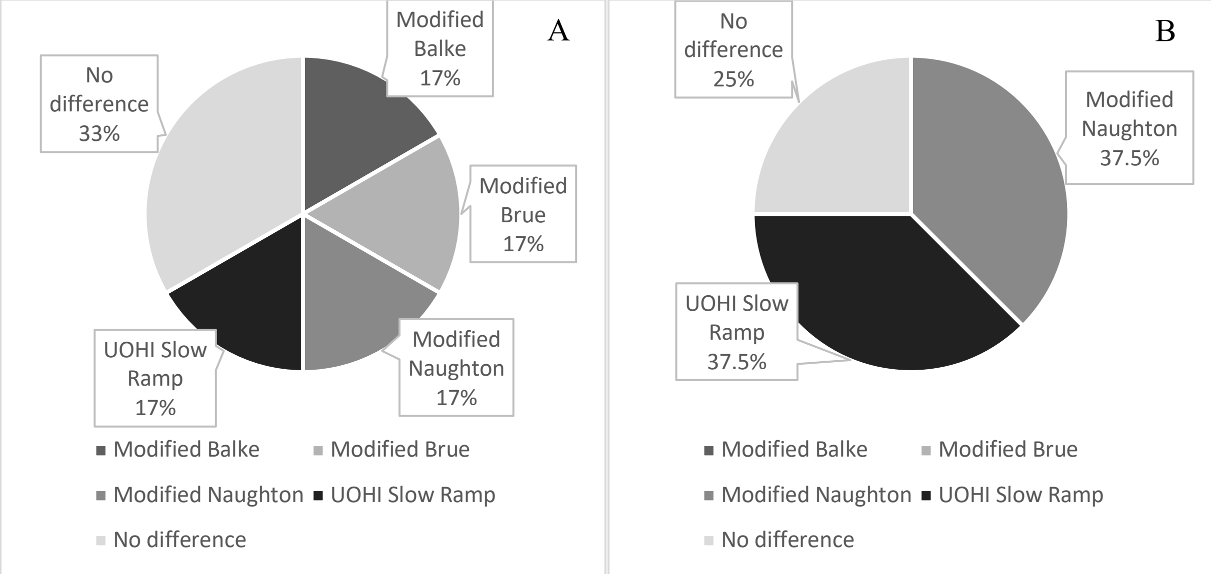

Figure 3.7: Most enjoyed cardiopulmonary exercise testing protocol for females (A) and males (B) with coronary artery disease.
UOHI, University of Ottawa Heart Institute.

Correlations between peak $\dot{V}O_2$ and enjoyment are shown in Tables 3.10 and 3.11. No differences were observed between peak $\dot{V}O_2$ and enjoyment for females or males.

Table 3.10: Peak $\dot{V}O_2$ and enjoyment spearman correlation coefficients for females

	Spearman's Rho Correlation Coefficient	p-value
Modified Balke (n = 6)	0.657	0.156
Modified Bruce (n = 7)	0.30	0.5
Modified Naughton (n = 6)	0.516	0.295
UOHI Slow Ramp (n = 6)	0.273	0.6

Table 3.11: Peak $\dot{V}O_2$ and enjoyment spearman correlation coefficients for males

	Spearman's Rho Correlation Coefficient	p-value
Modified Balke (n = 10)	0.241	0.503
Modified Bruce (n = 11)	0.109	0.751
Modified Naughton (n = 9)	-0.055	0.888
UOHI Slow Ramp (n = 8)	0.041	0.923

No difference in peak $\dot{V}O_2$ was observed between the first and last CPET for females ($p = 0.301$) or males ($p = 0.997$). Additionally, no difference in perceived CRF was observed between the first and last CPET for females ($p = 0.1398$) or males ($p = 0.3466$).

The magnitude of change in intensity for the modified Balke, modified Bruce, modified Naughton, and UOHI Slow Ramp is shown in Appendix L. The modified Balke had an average change in intensity of 7.8% per stage, with a range of 5.6% to 11.3%. The modified Bruce had an average increase in intensity of 30.2%, with a range from 4.5% to 50.9%. The modified Naughton had an average change of 18.0% in intensity per stage, with a range from 8.0% to 38.1%. The UOHI Slow Ramp had an average increase of 8.7% per stage, with a range of 3.6% to 39.6%.

3.3.2 Submaximal Results

Predicted versus measured $\dot{V}O_2$ at 85% of age-predicted maximal HR is shown for females and males in Figure 3.8. For females, both the predictive equations for the modified Balke ($p = 0.028$) and modified Naughton ($p = 0.013$) for estimating $\dot{V}O_2$ at 85% of age-predicted maximal HR estimated a significantly lower $\dot{V}O_2$ than the measured $\dot{V}O_2$ at 85% of age-predicted maximal HR (Figure 3.8). No differences were observed using the predictive equations for estimating $\dot{V}O_2$ at 85% of age-predicted maximal HR and the measured $\dot{V}O_2$ at 85% of age-predicted max HR using the modified Bruce ($p = 1.00$) or the UOHI Slow Ramp ($p = 0.052$) protocols. For males, both the predictive equations for the modified Balke ($p = 0.007$) and modified Naughton ($p = 0.005$) for estimating $\dot{V}O_2$ at 85% of age-predicted max HR estimated a significantly lower $\dot{V}O_2$ than the measured $\dot{V}O_2$ at 85% of age-predicted maximal HR (Figure 3.8). The predictive equations for the UOHI Slow Ramp ($p = 0.006$) for estimating $\dot{V}O_2$ at 85% of age-predicted maximal HR estimated a significantly higher $\dot{V}O_2$ than the measured $\dot{V}O_2$ at 85% of age-predicted maximal HR. No differences were observed using the predictive equations for estimating $\dot{V}O_2$ at 85% of age-predicted maximal HR and the measured $\dot{V}O_2$ at 85% of age-predicted maximal HR using the modified Bruce protocol ($p = 0.778$).

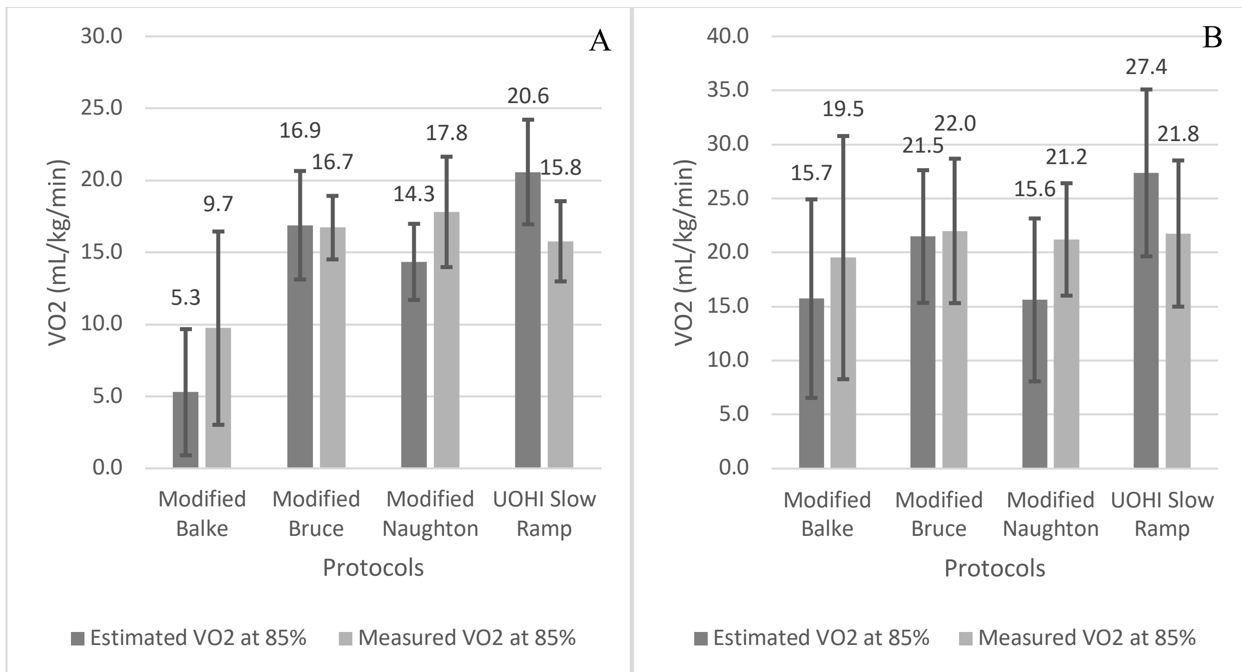

Figure 3.8: Estimated $\dot{V}O_2$ at 85% of age predicted maximal heart rate vs. measured $\dot{V}O_2$ at 85% of age-predicted maximal heart rate of females (A) and males (B) with coronary artery disease during submaximal treadmill protocols. $\dot{V}O_2$, oxygen consumption.

The predicted maximal $\dot{V}O_2$ versus measured peak $\dot{V}O_2$ values are shown for females and males in Figure 3.9. The equations for estimating maximal $\dot{V}O_2$ led to a higher $\dot{V}O_2$ than the measured peak $\dot{V}O_2$ for females and males across the four protocols.

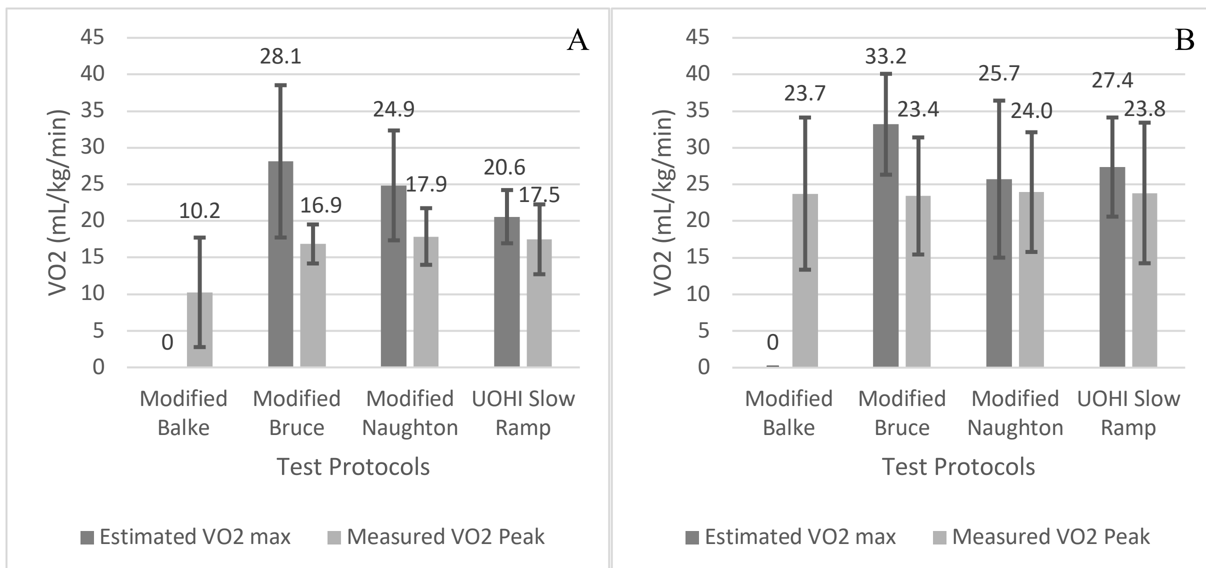

Figure 3.9: Estimated maximal $\dot{V}O_2$ vs. measured peak $\dot{V}O_2$ of females (A) and males (B) with coronary artery disease during four treadmill protocols.
Not enough female participants were able to successfully complete at least 1 stage of the modified Balke protocol to calculate an average peak $\dot{V}O_2$ for males.
$\dot{V}O_2$, oxygen consumption.

Peak Heart Rate

The peak submaximal HR values for females and males across the exercise testing protocols are shown in Tables 3.12 and 3.13. A difference in submaximal peak HR was observed across the protocols ($\chi^2 = 8.76$, p = 0.033, df = 3). For females, the peak submaximal HR observed during the modified Balke was significantly lower than the peak HR observed during the modified Bruce, modified Naughton, and UOHI Slow Ramp protocols (all p values < 0.05). When comparing the modified Bruce, modified Naughton, and UOHI Slow Ramp, no significant difference in peak HR was observed (F = 1.649, p = 0.255). For males, no difference in peak HR was observed across the protocols (F = 0.385, p = 0.839).

Table 3.12: Cardiometabolic responses at 85% of age-predicted maximal HR for females during treadmill exercise tests

	Modified Balke	Modified Bruce	Modified Naughton	UOHI Slow Ramp	p-value (ES)
HR (bpm)	101 ± 29	121 ± 13	120 ± 20	119 ± 22	0.033 (0.88) L
Systolic BP (mmHg)	190 ± 21	168 ± 28	177 ± 30	165 ± 31	0.419 (1.29) L
Diastolic BP	108 ± 10	71 ± 34	72 ± 15	62 ± 27	0.241 (0.7) L
RPE	14 ± 6	16 ± 3	15 ± 3	17 ± 3	0.300 (0.41) L
Test Duration (minutes)	1.33± 1.68	9.95 ± 1.87	8.79 ± 2.34	8.94 ± 2.11	<0.001 (0.92) L

BP, blood pressure; ES, effect size (Cohen's *F for parametric results, Kendall's W for non-parametric results* - T, Trivial; S, Small; M, Moderate; L, Large); HR, heart rate; RPE, rating of perceived exertion.

Blood lactate was only taken at the end of the test, therefore blood lactate concentration at 85% of age predicted HR cannot be predicted as it was not taken throughout the test, only at resting, immediately following warm-up, immediately after test termination, 2 minutes into recovery, and 4 minutes into recovery.

Table 3.13: Cardiometabolic responses at 85% of age-predicted maximal HR for males during the treadmill exercise tests

	Modified Balke	Modified Bruce	Modified Naughton	UOHI Slow Ramp	p-value (ES)
HR (bpm)	123 ± 15	125 ± 14	125 ± 14	124 ± 15	0.839 (0.04) T
Systolic BP (mmHg)	197 ± 25	172 ± 32	186 ± 30	170 ± 20	0.095 (0.71) L
Diastolic BP (mmHg)	80 ± 18	89 ± 55	70 ± 27	77 ± 11	0.771 (0.27) M
RPE	14 ± 3	13 ± 2	14 ± 4	15 ± 2	0.465 (0.34) M
Test Duration (seconds)	4.30 ± 2.78	10.20 ± 1.87	8.17 ± 3.30	9.20 ± 2.18	<0.001 (2.16) L

BP, blood pressure; ES, effect size (Cohen's *F for parametric results, Kendall's W for non-parametric results* - T, Trivial; S, Small; M, Moderate; L, Large); HR, heart rate; RPE, rating of perceived exertion.

Note: Blood lactate was only taken at the end of the test, therefore blood lactate concentration at 85% of age predicted HR cannot be predicted as it was not taken throughout the test, only at resting, immediately following warm-up, immediately after test termination, 2 minutes into recovery, and 4 minutes into recovery.

Blood Pressure

The peak submaximal BP values for females and males across the exercise testing protocols are shown in Tables 3.12 and 3.13. For females, no significant difference in systolic BP at 85% of age-predicted maximal HR was observed across the protocols (F =1.674, p = 0.419). When comparing the modified Bruce, modified Naughton, and UOHI Slow Ramp, no significant difference in systolic BP was observed (F = 0.506, p = 0.419). Similarly, no significant difference in diastolic BP at 85% of age-predicted maximal HR was observed across the protocols ($\chi^2 = 4.2$, p = 0.241, df = 3). When comparing the modified Bruce, modified Naughton, and UOHI Slow Ramp, no significant difference in diastolic BP was observed ($\chi^2 =$ 0.087, p = 0.241, df = 2). For males, no significant difference in systolic BP at 85% of age-predicted maximal HR was observed across the protocols (F = 2.547, p = 0.095). Similarly, no

significant differences in diastolic BP at 85% of age-predicted maximal HR was observed (F = 0.376, p = 0.771).

Rating of Perceived Exertion (RPE)

The peak RPE values for females and males across the exercise testing protocols are shown in Tables 3.12 and 3.13. For females, no significant difference in RPE at 85% of age-predicted maximal HR was observed across the protocols ($\chi^2 = 3.667$, p = 0.300, df = 3). When comparing the modified Bruce, modified Naughton, and UOHI Slow Ramp, no significant difference in RPE at 85% of age-predicted maximal HR was observed ($\chi^2 = 6.7$, p = 0.067, df = 2). For males, no significant difference in RPE was observed across the protocols (F = 0.706, p = 0.465).

Test Duration (min)

The submaximal test duration for females and males across the exercise testing protocols are shown in Tables 3.12 and 3.13. For females, a significant difference in test duration was observed among the protocols at 85% of age-predicted maximal HR (c). Females achieved a longer submaximal test duration using the modified Bruce protocol than the modified Balke (p = 0.027), modified Naughton (p = 0.027) and UOHI Slow Ramp (p = 0.042) protocols. Females achieved a shorter submaximal test duration using the modified Balke than the modified Bruce (p = 0.027), modified Naughton (p = 0.027) and UOHI Slow Ramp protocols (p = 0.028). No difference in test duration between the modified Naughton and UOHI ramp was observed (p = 0.345). When comparing the modified Bruce, modified Naughton, and UOHI Slow Ramp, a significant difference in test duration was observed across the protocols (F = 11.942, p= 0.002).

Females achieved a longer submaximal test duration using the modified Bruce than the modified Naughton ($p = 0.027$) and the UOHI Slow Ramp ($p = 0.042$) protocols.

For males, a significant difference in test duration was observed among the protocols at 85% of age-predicted maximal HR ($F = 44.805$, $p < 0.001$). Males achieved a shorter submaximal test duration using the modified Balke protocol than the modified Bruce ($p = 0.005$), the modified Naughton ($p = 0.008$) and the UOHI Slow Ramp ($p = 0.012$) protocols. No differences in test duration were observed between the other protocols for males with CAD.

3.4 Discussion

The extant literature shows there has been an under-representation of females included in the development and validation of exercise testing protocols.[71–76] Given the anatomical and physiological differences between sexes (females vs. males), the response to different exercise testing protocols may vary and provide inaccurate measures or estimates (i.e., overestimation or underestimation) of peak $\dot{V}O_2$.[98,100] The findings from this study showed that females achieved the highest peak $\dot{V}O_2$ during the modified Naughton protocol, but no differences in HR, SBP, DBP or enjoyment were observed among the maximal protocols (i.e., modified Balke, modified Bruce, and UOHI Slow Ramp). A difference in RPE was observed among the maximal protocols, but the protocol responsible for this difference could not be identified, likely due to insufficient power as few females completed the modified Balke protocol. Among the four protocols, females achieved the shortest test duration with the modified Balke, but a longer test duration with the modified Bruce for both the maximal and submaximal protocols. For males, no differences in peak $\dot{V}O_2$, HR, SBP, DBP, RPE, blood lactate concentrations, or enjoyment were observed across the maximal or submaximal protocols. Both females and males achieved the shortest test duration with the modified Balke. However, no difference in test duration was

observed when comparing the modified Bruce, modified Naughton, and UOHI Slow Ramp. The results of this study provide key insights into how females and males with CAD may respond to different CPET protocols, with variation across the measured physiological markers.

Maximal Exercise Testing

The modified Naughton protocol yielded the highest peak $\dot{V}O_2$ values for females, while no differences in peak $\dot{V}O_2$ were observed across the protocols for males. Our findings are inconsistent with previous research demonstrating that the Bruce treadmill protocols are typically better suited for eliciting higher peak $\dot{V}O_2$ values, as these protocols allow the physiological responses of patients to stabilize throughout the longer stages (i.e., 3 minutes per stage),[57] and should be used for measuring CRF in patients with CAD.[146,201–203] Myers et al. investigated the gas exchange and hemodynamic responses of three treadmill (Bruce, Balke, and individualized ramp) exercise testing protocols using 10 patients with chronic heart failure, 21 patients with CAD (either asymptomatic or limited by angina during exercise), and 10 age-matched apparently healthy participants.[201] The Bruce protocol yielded a slightly but significantly higher peak $\dot{V}O_2$ (22.3 ± 8 ml/kg/min) than the Balke (21.1 ± 8 mL/kg/min) and ramp (21.0 ± 8 mL/kg/min) protocols ($p < 0.05$).[201] Furthermore, the sensitivity, specificity, and accuracy of the Bruce and ramp treadmill protocols were investigated using 43 participants (11 females and 32 males) with CAD, previous MI, and/or a previous angioplasty.[202] Within both protocols, patients were able to attain the recommended 8-12 minute test duration; however, no difference in peak $\dot{V}O_2$ was observed.[202] Furthermore, in 24 patients (14 females and 10 males) with CAD over 60 years of age whom performed exercise tests (ramp and modified Bruce protocols), Bader et al. showed there was no significant difference in peak $\dot{V}O_2$ (19.3 ± 6.3 vs. 19.1± 6.4 ml/kg/min) between the protocols when appropriately selected based on pre-test activity questionnaires.[203] It was also

reported that the mean test duration was significantly greater for the ramp than Bruce protocols (9.0 ± 6.3 vs. 7.1 ± 3.1 minutes, $p < 0.0001$) allowing the ramp protocol to achieve a mean test duration of 8-12 minutes.[203]

While many studies have focused on commonly used CPET protocols (i.e., Bruce, Naughton, ramp, etc.), none have examined the effect of sex differences on CPET protocols for prescribing exercise intensity.[131] Keir challenges the use of traditional methods for using peak $\dot{V}O_2$ from CPETs for prescribing exercise intensity for several reasons:[131] (i) the first ventilatory threshold (VT1) and second ventilatory threshold (VT2) is not considered.[131] Exercise prescriptions based off ventilatory thresholds improves aerobic exercise training interventions compared to the traditional use of percentage of peak $\dot{V}O_2$;[131,204] (ii) percentage of peak $\dot{V}O_2$ used for exercise intensity prescription assumes that maximal $\dot{V}O_2$ has been measured and that peak $\dot{V}O_2$ can approximate $\dot{V}O_2$ max.[131] This indicates that if peak $\dot{V}O_2$ were used for exercise prescription instead of $\dot{V}O_2$ max, the exercise intensity prescription given to the patient would be a fraction of a fraction of $\dot{V}O_2$ max and patients may be exercising at suboptimal exercise intensities;[131] (iii) main predictors for not achieving VT1 or $\dot{V}O_2$ max were being a female, > 60 years of age, and being tested on a treadmill instead of a cycle ergometer. Among 7227 patients, 91% and 92% of females and males, respectively, those < 51 years of age were able to attain VT1 or $\dot{V}O_2$ max, however in patients ≥ 80 years of age, 47% and 70% of females and males, respectively, were able to attain VT1 or $\dot{V}O_2$ max, indicating the inability to use % of peak $\dot{V}O_2$ for accurate exercise prescription for females and older adults, and inevitably leading to underestimating exercise intensity to improve physiological performance and CRF.[131] Keir suggested that to mitigate the effects of sex and age, incremental protocols should be adjusted to a lower baseline workload and reduced rate of increase per stage for females relative to males of

the same age.[131] Therefore, although the Bruce protocol is commonly used for patients with CAD,[205,206] further studies should continue to investigate the use of ramp protocols for clinical populations when $\dot{V}O_2$ and CRF are the primary outcome measures, especially as these peak values are then used for exercise prescription in CR programs.[194,207]

Submaximal Exercise Testing - Equations for predicting $\dot{V}O_2$ *max*

Our findings revealed that the equations used to estimate $\dot{V}O_2$ at 85% of age-predicted maximal HR provided similar predictions of $\dot{V}O_2$ using the modified Bruce protocol for both females and males. However, the modified Balke and modified Naughton underestimated peak $\dot{V}O_2$ and the UOHI Slow Ramp overestimated peak $\dot{V}O_2$. Submaximal test results are routinely used in CR and clinical settings for determining or predicting exercise capacity and prescribing individualized exercise intensity prescriptions as many patients are not able to attain or sustain exercise intensities above 85% of age-predicted maximal HR.[54,187]

Our findings align with the literature demonstrating that estimates of $\dot{V}O_2$ max which are calculated using equations are often overestimated among a variety of populations. Dugas et al. investigated the accuracy of estimating $\dot{V}O_2$ max using the ACSM running equation during both maximal and submaximal treadmill tests in 99 apparently healthy adult runners (41 females and 58 males).[208] Although the ACSM equation overestimated $\dot{V}O_2$ max for the maximal and submaximal treadmills tests, the submaximal tests provided more accurate estimations of $\dot{V}O_2$ max when compared to the maximal treadmill tests.[184] Koutilanos et al. also observed a significant overestimation of $\dot{V}O_2$ of 14.6% using the ACSM equation in 55 elite male athletes performing the Bruce protocol.[169] Similarly, studies investigating ramp protocols in healthy males observed an overestimation of 10%[187] and 18%[209,210] using the ACSM equation, however

the effect on females is unknown as it was not investigated.[206] Jang et al. compared direct measures of $\dot{V}O_2$ to the ACSM walking and running equations in 293 patients (229 males, 64 females) with CAD completing the Bruce protocol.[211] The direct measurement of $\dot{V}O_2$ was overestimated by 16% in females and 20% in males.[211] Several factors should be considered when using the ACSM equation for predicting $\dot{V}O_2$ which may explain the inaccurate estimates of $\dot{V}O_2$ during submaximal exercise tests. Firstly, the equation was developed for steady state exercise, yet this equation is frequently used in exercise tests with incremental speeds and grades.[210,212,213] Secondly, the equation was developed using a small sample of young, apparently healthy college aged males which may render this equation inaccurate for its use within clinical populations.[88,213,214] The ACSM equation for predicting $\dot{V}O_2$ should, therefore, be used with careful consideration for submaximal exercise tests. Future studies should explore the validity of all available equations for predicting $\dot{V}O_2$ from submaximal treadmill tests for patients with CAD.

Heart Rate and Blood Pressure

Our study findings did now show any differences in peak HR among the four CPET protocols in females or males. These results are somewhat conflicting with those in the literature. Machado et al. investigated the response to different stage durations (1-, 2 -and 3-minute stages) on maximal HR[215] in 34 male, recreationally trained endurance runners who completed 3 maximal treadmill exercise tests.[215] The 2- compared to 1-minute stage test led to a significantly higher maximal HR ($p < 0.001$), but this was not different from the maximal HR of the 3-minute stage test.[215] These results are consistent with Kuipers et al. who also found no difference in peak HR between 1- and 3-minute stage durations in well trained runners.[216] HR drift (the gradual increase in HR over a prolonged period of time during steady state aerobic exercise),[217,218]

coupled with a decrease in SV but a continued maintenance of $\dot{Q}$ contributes to higher maximal HR in protocols with longer stage durations;[217,218] however, this does not explain why protocols with brief 2-minute stage durations may be producing higher maximal HRs. Exercise intensity can also affect HR. Machado et al. suggested that speed at exhaustion was significantly higher in the 2-minute compared to 3-minute stage protocols and that after 10-15 minutes, speed may contribute more to maximal HR than the HR drift.[215] We also observed that systolic and diastolic BP increased throughout the protocols for females and males, as would be expected of these physiological parameters with increasing workloads.[42,219,220] SBP increased throughout the duration of the CPET with no change or a slight drop in DBP as the test progressed.[42,219,220] No general BP indications for stopping the CPET occurred (i.e., drop in SBP of ≥10 mm Hg with an increase in work rate, an excessive rise in systolic pressure > 250mmHg, or diastolic pressure > 115mmHg).[42] Future studies should continue to explore how stage duration and different exercise intensities can affect $\dot{V}O_2$, HR, and other physiological responses for females and males with CAD during exercise tests.

Stage Duration and Stage Intensity

Many studies have investigated the effect different stage durations and intensities on $\dot{V}O_2$ and HR, but gaps remain in determining the optimal stage durations for females and males with CVD.[216,221,222] The modified Bruce (3-minute stages) yielded the longest test duration for females, while the modified Balke (1-minute stages) yielded the shortest test duration. The same finding was observed for males. Females and males were able to attain the recommended test duration of 8-12 minutes for the modified Bruce, modified Naughton and UOHI Slow Ramp protocols. Our results are inconsistent with Machado et al. who investigated the effects of 1-, 2- and 3-minute treadmill stages on maximal HR and post-exercise blood lactate concentrations in

34 male recreational endurance runners.[215] Maximal HR was higher with the 2-minute when compared to the 1-minute ($p < 0.001$) and 3-minute stage protocols ($p < 0.05$), but there was no statistical difference in maximal HR between the 1-minute and 3-minute stage protocols,[215] indicating that the longer stage durations may have caused premature fatigue and yielded a lower maximal HR.[215]

Kuipers et al. investigated the effect of 1-, 3- and 6-minute treadmill stages on several physiological outcomes in 10 (4 female and 6 male) well-trained competitive middle-distance runners.[215] Maximal running speed (power output) was significantly lower using the 3- and 6-minute when compared to 1-minute stage protocols.[215] Mean peak $\dot{V}O_2$ and mean peak HR were not different among protocols of different stage durations.[215] Bishop et al. investigated the influence of 1- and 3-minute stage durations on peak $\dot{V}O_2$ and lactate threshold using a cycle ergometer maximal exercise test in 8 moderately active females.[221] Peak $\dot{V}O_2$ was not statistically significantly different between the 1- and 3-minute stage durations; however, the maximal HR achieved using the 1-minute stage protocol was significantly lower than the 3 minute-stage protocol.[221] It was also shown that power output at exhaustion was significantly greater with the 1- vs. 3-minute stage protocols.[221]

Using shorter stage durations of 1-minute has been shown to improve the accuracy of determining $\dot{V}O_2$ max and VT in patients with CAD.[60] Given the smaller increases in workload between stages are less abrupt,[194] muscle fatigue is thought to be minimized allowing for a more accurate assessment of CRF without the cofounding effects of peripheral muscle fatigue.[60] However, these short stages may not provide sufficient time for $\dot{V}O_2$ or HR to reach steady state. This has led to the frequent use of 3-minute stage durations which allow for $\dot{V}O_2$ and HR

responses to stabilize and reflect metabolic demand rather than the responses to rapid transitions.[86,223] Two-minute stages do not allow the advantages from both the 1-minute and 3-minute stages to be acquired. Examining every stage duration, including single stage exercise testing protocols, affords an opportunity to thoroughly evaluate physiological markers of CRF while considering the clinical practicality and feasibility for CR programs to evaluate CRF of their patients.[79,187,224] The goal of using CPETs is to administer a test that can provide physiological information to clinicians and healthcare professionals in a timely and safe manner within the capacity of individuals with CVD.[79,187]

Research on 2- minute stages is limited and highlights the need for further studies on the effect of 2-minute stage durations on peak $\dot{V}O_2$. The 3-minute stage protocol may allow for the determination of the lactate threshold without compromising peak $\dot{V}O_2$, but maximal HR and peak power output may be lower. This may result in more conservative exercise intensity prescription which can lead to smaller clinical improvements for both physical and mental health.[53,122,221] These findings suggests that 2-minute stages, such as those in the modified Naughton, will elicit a higher peak $\dot{V}O_2$ than 1- or 3-minute stages and could be used when completing maximal exercise testing as the stage duration will not cause premature fatigue and may have better effects on peak power output compared to 3-minute stage protocols.[221]

Our hypothesis that lower starting speeds/grades and lower incremental magnitudes will yield a higher peak $\dot{V}O_2$ in females and males with CAD was partially supported. We observed that the protocol with the highest starting speed yielded the lowest peak $\dot{V}O_2$ in female with CAD, however this was not observed in males. The aggressive starting speed (4 mph) in the modified Balke protocol made it difficult for patients with lower levels of CRF to maintain the

speed for any length of time while feeling safe throughout the test. Patients reported concerns including falling off the back of the treadmill and/or stumbling and hurting themselves due to the inability to self-ambulate at that speed. The risk of falls during maximal exercise tests is not well documented,[225] with primary complications including risk of MI, angina, and arrythmias.[70,93,187] This is consistent with literature that suggests that continuous protocols with aggressive workloads, such as the Balke, tend to result in lower peak $\dot{V}O_2$ due to higher metabolic stress and shorter time to exhaustion.[167,226] Incremental magnitudes did not appear to influence peak $\dot{V}O_2$. The modified Balke, the modified Bruce, modified Naughton, and UOHI Slow Ramp had an average increase in workload per stage of +7.80%, +30.17%, +18.04%, and +8.66%, respectively. However there was no difference in peak $\dot{V}O_2$ within females or within males using these protocols, suggesting that variations in workload increases do not significantly affect peak $\dot{V}O_2$ for females or males participating in exercise tests.[216,227] However, no studies have investigated the optimal magnitude increase per stage and how this may affect test duration and peak $\dot{V}O_2$ within the CAD population.

Test Duration

It is widely recommended that the duration of CPETs should fall within 8 to 12 minutes to optimize the likelihood of reaching peak $\dot{V}O_2$ for patients with CVD.[77,202,226,228] We observed these recommended test durations for the modified Bruce, modified Naughton, and UOHI Slow Ramp protocols for both females and males. It is recommended that work rate increments should be selected to lead to test durations of approximately 10 minutes.[77] The literature indicating that exercise testing protocols should lead to test durations between 8 and 12 minutes because (i) it is ideal for detecting $\dot{V}O_2$ plateau,[226] (ii) shorter test durations may not provide adequate time for participants to reach a $\dot{V}O_2$ plateau,[226] (iii) test durations exceeding 12 minutes may lead to

earlier fatigue,[226] and (iv) test durations within this range have been shown to achieve a $\dot{V}O_2$ max that is significantly higher than durations outside of this range.[77]

Enjoyment

Many studies have shown that intrinsic motivation and enjoyment significantly influence exercise behaviour and duration of physical activity.[229–233] Although our results did not identify differences in enjoyment, or relations between enjoyment and peak $\dot{V}O_2$, for females and males performing the four different maximal exercise testing protocols, Mikkelson et al. found that individuals with higher motivation and enjoyment had a significant increase in peak $\dot{V}O_2$ ($p < 0.001$) from CPETs in 203 elderly cardiac patients (64 years and older) pre and post CR.[234] In addition, Teixeira et al.[232] found that higher levels of exercise enjoyment was positively correlated with stronger intentions to continue exercising in 273 apparently healthy participants (146 females and 127 males, mean age = 36.21 ± 11.29 years).[233] Additionally, enjoyment was amplified when there was an agreement between a patient's preferred and experienced exercise intensity.[233] These findings indicate that tailoring exercise programs or testing to align with personal intensity preferences can improve enjoyment.[233] An approach where practitioners modify exercise tests to intensities at which patients enjoy may potentially lead to longer exercise test durations (but within desired 8 to 12 minutes) and result in a higher achieved peak $\dot{V}O_2$. This may consequently lead to exercise prescriptions with higher target exercise intensities which could enhance the physical and mental benefits gained from CR.[53,122,235]

ACSM Criteria

The use of ACSM criteria for determining if a patient has reached their physiological maximum during an exercise test has long been used.[64,68,236] However, the application of these

criteria has been the subject of debate within the field of exercise physiology as many criteria may not be achieved during 'maximal' exercise testing. The primary criteria, a plateau in $\dot{V}O_2$, is supposed to be indicative of a maximal effort test.[237] However, many individuals may not exhibit a $\dot{V}O_2$ plateau during an exercise test,[237–239] and, consequently, this criterion is now no longer included in the most recent ACSM guidelines for exercise testing.[211,212] In place of using $\dot{V}O_2$ plateau as a means for determining maximal exertion, ventilatory thresholds (VT) could be used.[122,240] The VT, particularly the VT2, indicates the point at which ventilation increases disproportionately to oxygen consumption, thus reflecting a shift towards anaerobic metabolism and the point at which exercise intensity transitions from sustainable to unsustainable.[240] In 301 females and 791 males who performed an incremental treadmill test, Benítez-Muñoz et al.[241] found that physiological determinants of an individual's maximum are more related to VT1 and VT2 than to $\dot{V}O_2$ max.[241] Due to the higher percentages of maximum HR and $\dot{V}O_2$ at which VT1 and VT2 (i.e., $\dot{V}O_2$: males 66.0% and 90.6%; females: 69.4% and 92.2% of VT1 and VT2, respectively. HR: males: 80.8% and 94.6%; females: 82.9% and 95.6% of max HR at VT1 and VT2, respectively)[241] occur in individuals with higher training age (defined as the amount of time accumulated from both periodic and longitudinal participation in structured training programs and/or sport related activities that help with the development of musculoskeletal health, movement patterns and fitness),[242] the typical strategy for establishing exercise intensity as a fixed percentage of the maximum HR or $\dot{V}O_2$ might not be effective for individuals with different training ages.[241] Further investigations should continue to examine the use of VT for exercise intensity prescription within cardiovascular and clinical settings. Furthermore, based on low the incidence of $\dot{V}O_2$ plateau, some researchers have suggested the use of $\dot{V}O_2$ max verification phases.[237,243,244] This methodology suggests that a constant load test should be

performed after an incremental exercise test and a recovery phase.[237,243] If there is no difference between the $\dot{V}O_2$ peak of the incremental phase and the verification phase, a $\dot{V}O_2$ plateau occurs and the $\dot{V}O_2$ max of the incremental test is verified.[243] The minimum duration of verification phases to raise $\dot{V}O_2$ to maximal value using cycle ergometers range between 2.3 ± 0.3 and 3.5 ± 0.5 minutes,[237,245,246] however, despite many published articles about verification phases in untrained,[247,248] specific trained,[249] or non-specific trained[250–252] individuals on cycle ergometers, and specific trained[249,253–255] or non-specific trained[256–258] individuals on a treadmill, there is currently no research on the duration of verification phases for untrained individuals on treadmill tests. Such research would be highly applicable to patients with CAD who typically present to CR with low physical activity levels and CRF. Faricier et al. found, on average, that the $\dot{V}O_2$ predicted from the step-ramp-step protocol (incremental cycling exercise is preceded and followed by bouts of constant- power output exercise within the moderate [below lactate threshold] and heavy-intensity domains [between lactate threshold and respiratory compensation point], respectively) was not different from the $\dot{V}O_2$ measured during the domain-specific constant power output at a moderate intensity or heavy intensity exercise on a cycle ergometer in 4 patients (3 female and 11 male, age: 65 ± 12 years) with CAD.[259] These findings suggests that the step-ramp-step protocol may be an option for prescribing constant power output for exercise training programs for patients with CAD.[259] Future studies should identify verification protocols for females and males with CVD and to determine if verification phases (i.e., performed at the same time as an initial baseline CPET with a typical break of 5-20 minutes between the CPET and the verification phase)[260] would be beneficial for determining peak $\dot{V}O_2$ and how this might affect exercise intensity prescriptions within cardiovascular and clinical populations.

Study Strengths and Limitations

This study had several strengths. Firstly, patients were asked to not change their exercise or daily regime (except for asking patients not to perform any moderate to vigorous exercise 12 hours prior to their appointment) throughout the study. Ensuring patients' CRF remained stable was crucial to being able to measure and maintain the validity of our comparisons of peak $\dot{V}O_2$ among the four protocols. Performing four exercise tests could serve as an exercise intervention and lead to improvements in $\dot{V}O_2$ over the course of the study duration instead of changes in peak $\dot{V}O_2$ occurring because of the protocol that was used to measure CRF. Our objectively measured peak $\dot{V}O_2$ and subjective measures of fitness indicated no significant change in CRF for females and males with CAD. Secondly, patients were blinded to the protocol names, test order, and were not able to see or hear the stage, speed, incline, or test duration to prevent performance and expectation bias. Thirdly, the study staff followed SOPs for performing CPETs as well as the use and calibration of the study devices (i.e., metabolic cart [Parvo Medics TrueOne® 2400, Salt Lake City, UT], 12-lead ECG (Nasiff CardioCard®, Central Square, NY), BP measurements [SunTech Tango M2, Morrisville, NC], and blood lactate analyzer [Lactate Plus; Nova Biomedical Corporation, Cheshire, UK]). All study staff participated in training sessions for all devices that were used. In addition, in advance of the study start, trial CPETs were performed for each of the exercise testing protocols to familiarize study staff with the procedures.

There were several limitations to this master's project. Firstly, there were several delays that occurred throughout the study conduct (see Appendix M, Table M.1). The longest delay was 7 months in duration for obtaining approval of the ethics application. The second prolonged delay occurred with attaining the approved blood lactate device due to the company's delay in

processing our order and low stock of the device. Secondly, a smaller than desired sample size was recruited. The lower than required number of female participants affects the generalizability of our findings to females with CAD. However, recruitment is ongoing, and a final publication will include, hopefully, the target sample size (n = 54). Therefore, results should be interpreted with caution when applying them to the CAD population due to the small sample size and small number of female patients. Thirdly, the EPCHL treadmill used for this study has a maximum grade of 15%, thus requiring protocol adjustments to maintain the same workload at each stage which potentially could have altered physiological responses to the exercise protocol. Fourthly, the size of the testing equipment (i.e., BP cuff and Polar HR chest strap) restricted participation for larger individuals (i.e., a patient with a BMI of 56.7 kg/m^2) which limits the study's inclusivity and generalizability of findings for patients with higher body mass indexes. Fifthly, the use of β-blockers posed some challenges for the collection of blood lactate as these medications affect blood flow consistency which sometimes led to insufficient blood concentrations being able to be collected in a timely manner leading to missing lactate data.[261–264] Lastly, the data collection for the submaximal component of the exercise tests should be interpreted with caution. Although intended for submaximal data to be collected at 85% of age-predicted maximal HR, because the test was not terminated at this point, but extended to a maximal test, data used for the submaximal results had a cutoff of 83.9 – 85.9% of age-predicted maximal HR.

In conclusion, the findings from this study demonstrated that no difference in peak $\dot{V}O_2$, BP, or blood lactate was observed among the modified Balke, modified Bruce, modified Naughton, or UOHI Slow Ramp protocols within females or within males for both maximal and submaximal exercise testing protocols. The equations for estimating $\dot{V}O_2$ max elicited a higher

$\dot{V}O_2$ than the measured peak $\dot{V}O_2$ within females and within males across all four protocols. Future research should investigate the use of VT thresholds and verification phases for exercise tests for patients with CAD and more broadly CVD and how this might affect exercise intensity prescription for patients in CR.

Chapter 4: Conclusion

The overall aim of my thesis was to investigate the exercise testing practices in CR programs across Canada and the optimal maximal and submaximal exercise testing protocols for achieving peak $\dot{V}O_2$ in females and males with CAD. A summary of findings for both the TRADE and PACED studies are shown in Table 4.1

Table 4.1 Summary of results

Research Question	Chapter	Findings
Which maximal and submaximal exercise testing protocols are the most frequently used to measure or estimate peak $\dot{V}O_2$, respectively, in patients with CVD at CR centres across Canada?	Chapter 2	• The 6MWT and the Modified Bruce protocol were the most frequently used submaximal and maximal exercise testing protocols, respectively, in CR across Canada.
How many maximal and submaximal exercise testing protocols does each CR centre use?	Chapter 2	• A total of 24 and 37 programs used 1 maximal and 1 submaximal protocol, respectively. Other programs used a range of 2 to 4 maximal protocols, and 2 to 6 submaximal protocols.
How many maximal and submaximal exercise tests are completed per year?	Chapter 2	• It was estimated that 3,610 – 4,910 maximal exercise tests and 18,000 – 22,710 submaximal exercise tests were performed annually at CR centres across Canada.
How many times is each maximal and submaximal exercise testing protocol used per year?	Chapter 2	Approximate # of times each maximal protocol was used annually: • Balke: unknown; Bruce: 3,560 – 4,790; Naughton: 0 – 20; Astrand Rhyming Cycle Ergometer: 0; Ellestad: 0; Other: 50 – 100. Approximate # of times each submaximal protocol was used annually: • Balke: unknown; Modified Bruce: 2,720 – 3,760; Modified Naughton: 400 – 700; Astrand Cycle Ergometer Test: 20 – 50; Chester Step Test: 600 – 1,000; 6MWT: 13,940 – 16,650; Incremental 10m Shuttle Walk Test: 20 – 50; Other: 300 – 500; Balke-Ware: 0; Astrand-Rhyming Step Test: 0.
Which healthcare professional (e.g., physician, registered kinesiologist, exercise physiologist, cardiovascular technologist, etc.) is most often	Chapter 2	Physicians were the most frequent decision-makers, overseeing testing protocols in 38 of the 118 programs, followed by nurses (n = 15/118), and physiotherapists/kinesiologists (n = 13/118).

deciding the exercise testing protocol?		
What is the decision-making process and criteria used for selecting an exercise testing protocol for patients with CVD to reach their peak $\dot{V}O_2$?	Chapter 2	The most common methods for determining test protocols included standard procedures decided upon by management (n = 18), patient medical history, co-morbidities, musculoskeletal concerns, exercise tolerance, etc. (n = 17), and physician decision for test protocol (n = 8).
Does peak $\dot{V}O_2$ vary between different maximal treadmill exercise testing protocols in females and males with CAD?	Chapter 3 – Maximal exercise testing	**Females** • A significant difference in $\dot{V}O_2$ was observed across the protocols ($F = 9.222$, $p = 0.001$); yet which protocols differed could not be identified due to insufficient power (few females completed the modified Balke protocol). • When only comparing the modified Bruce, modified Naughton, and UOHI Slow Ramp, no significant difference in peak $\dot{V}O_2$ was observed across the protocols ($F = 0.891$, $p = 0.44$). **Males** • No differences in peak $\dot{V}O_2$ were observed across the protocols ($F = 0.189$, $p = 0.75$).
How do peak cardiometabolic responses (i.e., HR, BP, RPE, and blood lactate) compare between different maximal treadmill exercise testing protocol for females and males with CAD?	Chapter 3 – Maximal exercise testing	**Females** **HR**: no difference in peak HR was observed across the protocols. **SBP**: Females appeared to achieve a higher SBP using the modified Balke (190 ± 21 mmHg, $F = 0.40$, p = N/A); however, there was insufficient power for this analysis. **DBP**: Females appeared to achieve a higher DBP using the modified Balke protocol (108 ± 10 mmHg, $F = 5.270$, p = N/A); however, there was insufficient power for this analysis. **RPE**: A significant difference in RPE was observed across the protocols ($F = 7.510$, $p < 0.05$); yet there was insufficient power for this analysis. **Blood lactate**: Females appeared to achieve a higher peak lactate using the Modified Balke protocol (5.2 ± 1.1 mmol/L, $F = 1.395$, p = N/A); however, there was insufficient power for this analysis. **Males**

		• No significant differences in peak HR, systolic or diastolic BP, RPE, or blood lactate were observed across the protocols.
Do different increments of grade/speed affect test duration for females and males?	Chapter 3 – Maximal exercise testing	• The modified Balke, Bruce, Naughton, and UOHI Slow Ramp had an average change in intensity of 7.80% per stage (range: 5.6-11.3%), 30.2% (range: 4.5-50.9%), 18.0% (range: 8.0-38.1%), 8.7% (range: 3.6-39.6%), respectively. **<u>Females</u>** • The test duration for the modified Balke was significantly shorter than the modified Bruce, modified Naughton, and UOHI Slow Ramp protocols ($p < 0.001$). • The modified Bruce test duration was significantly longer than the modified Naughton protocol ($p < 0.001$). **<u>Males</u>** • The test duration for the modified Balke was significantly shorter than the modified Bruce, modified Naughton and the UOHI Slow Ramp ($p < 0.001$). • No difference in test duration for males was observed between the modified Bruce and modified Naughton, the modified Bruce and UOHI Slow Ramp or the modified Naughton and UOHI Slow Ramp.
What is the most common reason for test termination for females and males?	Chapter 3 – Maximal exercise testing	• Females: 67% cited speed as the main reason for test termination for the modified Balke, 29% and 50% cited shortness of breath for the modified Bruce and UOHI Slow Ramp, respectively, and 33% cited musculoskeletal fatigue for the modified Naughton. • Males: 20% cited speed as the primary reason for test termination for the modified Balke, while 28% cited muscuolskeletal fatigue for the modified Bruce, and 23% and 50% cited shortness of breath for the modifed Naughton and UOHI Slow Ramp, respectively.
Does higher patient enjoyment of a test protocol yield a higher peak $\dot{V}O_2$ for females and males?	Chapter 3 – Maximal exercise testing	• No differences were observed between peak $\dot{V}O_2$ and enjoyment for females or males.

Which test was most frequently ranked as the most enjoyable test by female and male patients?	Chapter 3 – Maximal exercise testing	• Females: one participant cited each protocol as their most enjoyed (i.e., modified Balke: n = 1 [16.7%], modified Bruce: n = 1 [16.7%], modified Naughton: n = 1 [16.7%], and UOHI Slow Ramp: n = 1 [16.7%]), and two participants reported no difference in enjoyment among the four protocols. • Males: the modified Naughton (n = 3 [37.5%]) and UOHI Slow Ramp protocols (n = 3 [37.5%]) were ranked highest for enjoyment, while two participants (25%) indicated that there was no difference in their enjoyment.
Which of the tested protocols (i.e., modified Bruce, modified Balke, modified Naughton and UOHI ramp) achieves a greater number of ACSM criteria for maximal test termination for females and males with CAD?	Chapter 3 – Maximal exercise testing	• No females achieved at least 3 of the 5 criteria for any of the protocols. • Two males achieved at least 3 of the 5 criteria for the modified Balke and the UOHI Slow Ramp.
Does estimated peak $\dot{V}O_2$ vary between different submaximal treadmill exercise testing protocols in females and males with CAD?	Chapter 3 – Submaximal exercise testing	**Females** • Predictive equations for estimating peak $\dot{V}O_2$ at 85% of age-predicted max HR was significantly underestimated compared to the measured $\dot{V}O_2$ using the modified Balke ($p = 0.028$) and modified Naughton ($p = 0.013$). • No differences were observed using the predictive equations for estimating $\dot{V}O_2$ at 85% of age-predicted max HR and the measured $\dot{V}O_2$ at 85% of age-predicted max using the modified Bruce ($p = 1.00$) or the UOHI Slow Ramp ($p = 0.052$) protocols. **Males** • Predictive equations for estimating peak $\dot{V}O_2$ at 85% of age-predicted max HR was significantly underestimated compared to the measured $\dot{V}O_2$ using the modified Balke ($p = 0.007$) and modified Naughton ($p = 0.005$). • Predictive equations for estimating peak $\dot{V}O_2$ at 85% of age-predicted max HR was significantly overestimated compared to the measured $\dot{V}O_2$ using the UOHI Slow Ramp ($p = 0.006$). • No differences were observed using the predictive equations for estimating $\dot{V}O_2$ at 85% of age-predicted max HR and the measured $\dot{V}O_2$ at 85% of age-predicted max using the modified Bruce protocol ($p = 0.778$).

Does the test duration differ between submaximal exercise testing protocols for males and females with CAD?	Chapter 3 – Submaximal exercise testing	**Females** • The test duration of the modified Bruce protocol was significantly longer than the modified Balke ($p = 0.027$), modified Naughton ($p = 0.027$), and UOHI Slow Ramp ($p = 0.042$) protocols. • The test duration of the modified Balke protocol was significantly shorter than the modified Bruce ($p = 0.027$), modified Naughton ($p = 0.027$), and UOHI Slow Ramp ($p = 0.028$) protocols. **Males** • The test duration of the modified Balke protocol was significantly shorter than the modified Bruce ($p = 0.005$), the modified Naughton ($p = 0.008$) and the UOHI Slow Ramp ($p = 0.012$) protocols. No differences in test duration were observed among the other protocols.
Do peak cardiometabolic responses (i.e., BP, HR and blood lactate) and rating of perceived exertion (RPE) differ between submaximal exercise testing protocols for males and females with CAD?	Chapter 3 – Submaximal exercise testing	**Females** • **HR**: Females achieved a higher peak HR with the modified Bruce protocol (121 ± 13 bpm, $\chi^2 = 8.76$, $p = 0.033$, $df = 3$). Peak HR was significantly lower during the modified Balke than the modified Bruce, modified Naughton, and UOHI Slow Ramp protocols ($p < 0.05$). • No significant difference in systolic or diastolic BP or RPE at 85% of age-predicted max HR was observed across the protocols. **Males** • No differences in peak HR, SBP, DBP, or RPE were observed across the protocols.

The two studies included in this thesis, TRADE and PACED, investigated the landscape of maximal and submaximal exercise testing in CR in Canada. Findings from TRADE revealed that although a wide variety of exercise testing protocols are used nationwide, the 6MWT and the modified Bruce protocol are the most applied maximal and submaximal testing protocols, respectively. Despite the frequent use of the modified Bruce protocol, findings from PACED showed that this protocol did not yield superior physiological responses (i.e., higher peak $\dot{V}O_2$, HR, SBP, RPE, or blood lactate concentrations), achieve a greater number of ACSM criteria for determining physiological maximum, achieve a longer test duration, or demonstrate superior patient-centred outcomes such as patient enjoyment. The PACED study also highlighted the physiological and perceptual differences elicited by four commonly used maximal exercise testing protocols. The modified Naughton yielded the highest peak $\dot{V}O_2$ for females, yet it is underutilized nationally according to TRADE (10.2% of CR centres used the modified Naughton protocol). For patients with CAD, improving CRF is critical as even modest increases are associated with substantial reductions in cardiovascular morbidity and mortality.[52] A 1 MET increase in CRF has been shown to be associated with a 15% decrease in CVD and a 13% decrease in risk of all-cause mortality.[58] Differences in the selection of exercise testing protocols may over- or under-estimate a patient's CRF which can affect exercise prescription, including exercise intensity. This may influence patients' ability to achieve the full physical and mental health and quality of life benefits of CR.[53,54,122] The Bruce protocol, which was the most frequently used among Canadian CR programs, did not produce the highest peak $\dot{V}O_2$ or other cardiometabolic responses (i.e., HR, SBP, RPE, or blood lactate concentrations) within females or males and was more often terminated due to musculoskeletal fatigue. The modified Balke, despite producing the highest blood lactate concentrations in females, yielded the shortest test

duration for both females and males. The modified Balke was most often terminated due to treadmill speed, particularly among female patients. Compared to the remaining three protocols (i.e., modified Bruce, modified Naughton, and UOHI Slow Ramp), the modified Balke was the only protocol whereby patients were unable to attain the recommended 8-to-12-minute test duration as per the ACSM. These findings suggest that the modified Balke protocol should not be preferred in clinical settings as there is a limitation in measuring physiological outcomes when using this protocol due to reduced tolerability (as measured by test duration) for patients with CAD. The above findings and interpretation must, however, be interpreted with caution as only three of the six females were able to complete at least one minute of the test (with only 2 females completing the first stage of the protocol), and eight of the ten males were able to complete at least one minute of the test (with 6 males completing the first stage of the protocol). Additional efforts are underway to reach the target sample size for more definitive conclusions.

For both females and males, the predictive equations significantly underestimated peak $\dot{V}O_2$ at 85% of age-predicted max HR compared to the measured $\dot{V}O_2$ using the modified Balke and modified Naughton. For males alone, the predictive equations overestimated peak $\dot{V}O_2$ at 85% of age-predicted max HR compared to the measured $\dot{V}O_2$ using the UOHI Slow Ramp. However, no differences were observed within females or males when comparing the predictive equations to the measured $\dot{V}O_2$ at 85% of age-predicted max HR using the modified Bruce and within females when comparing the predictive equations to the measured $\dot{V}O_2$ at 85% of age-predicted max HR using the UOHI Slow. These findings are important for CR programs to note as they frequently rely on submaximal exercise testing to estimate CRF when programs have limited resources (i.e. staff and/ or expensive and specialized equipment). If predictive equations

are consistently over or underestimating peak $\dot{V}O_2$, healthcare providers may resultantly over-or under prescribe exercise intensities, which may affect the efficacy and safety of a patient's training program,[54,265] and the patient's ability to achieve the full benefits of CR and improve their quality of life.[53,54,122]

This thesis bridges the gap between nationwide exercise testing practice and protocol performance in clinical testing, notably, the discrepancy between protocol popularity and physiological responses. The results of this thesis suggest the need for standardization (based on patient data and patient-centred outcomes) and updated national guidelines. Once the PACED trial is completed (estimated completed date: December 2025), the data will be shared with CACPR and possibly support a re-assessment of current exercise testing standards in CR and consideration of sex-specific differences in exercise testing. The integration of the TRADE survey and PACED trial data affords an opportunity to refine current exercise testing practices with empirical evidence. CR programs may benefit from standardized, evidence-based guidelines that account for physiological performance (i.e., $\dot{V}O_2$, HR, BP, blood lactate concentrations), test duration, patient safety, and enjoyment separately for females and males. This approach could improve both the quality and personalization of care for patients with CVD and possibly other chronic conditions. A collaborative approach that includes kinesiologists, exercise physiologists, physiotherapists, nurses, physicians, and patients may support the delivery of a more personalized and effective testing experience for patients in CR. This thesis thus contributes to the growing literature examining differences in testing protocols and physiological measurements of CRF within CR for females and males.[204] It also provides a foundation upon which future research, clinical guidelines, and pragmatic decision making can be built, with

growing literature suggesting that the use of old protocols should be used with caution as it has limits for creating tailored and personalized exercise prescription intensities for patient in CR.[131]

From this thesis it still remains unclear (i) if exercise testing in CR may vary between sexes and/or gender (as this thesis did not include a gender-based evaluation), (ii) validity of other available equations for predicting $\dot{V}O_2$ from submaximal treadmill tests separately for females and males with CAD (as it was beyond the feasibility of the thesis to test more than those included), (iii) how stage duration and different exercise intensities can affect $\dot{V}O_2$ and HR for females and males with CAD during exercise tests, (iv) if the use of VT for exercise intensity prescription within cardiovascular and clinical settings would be appropriate for patients with CVD,[122] (v) if a verification phase would be beneficial for determining peak $\dot{V}O_2$ for females and males and how this might affect exercise intensity prescriptions within cardiovascular and clinical populations.

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Appendix

Appendix A: TRADE Survey

Page 1

Submaximal and Maximal Exercise Test Protocol Selection Process (TRADE)

Please complete the survey below. You can contact the study lead at jennwong@ottawaheart.ca for any questions, or problems related to the survey. If the options provided in the questions are not suitable responses for your facilities, please contact me directly and we can set up a call to collect your responses.

Thank you!

Question	Response
Name of the cardiac rehabilitation centre	______________________
Date	______________________
Province	______________________
City	______________________
Full name of person completing the survey	______________________
What is your position/ title/ role at the hospital/ in cardiac rehabilitation centre:	______________________
Phone number and email (if needed to clarify answers)	______________________
What is the typical patient volume on average per year for cardiac rehabilitation program?	______________________
What is the cost of your cardiac rehab program?	______________________
What are the types of cardiac rehabilitation programs offered? Please check all that apply.	☐ In person exercise ☐ Virtual exercise (home exercise programs) ☐ Hybrid (in person and virtual exercise) ☐ Education only, virtual ☐ Education only, in person ☐ Hybrid (in person exercise with virtual education) ☐ Hybrid (virtual exercise with person education) ☐ Other
If you selected "other" in the previous question, please specify the type(s) of cardiac rehabilitation you offer.	______________________
What is the length of your cardiac rehab program (i.e. 6 weeks, 12 weeks, 3 months, etc.)? If program lengths differ, please specify for all programs.	______________________

How many education sessions in total are included per cardiac rehab program?

- ◯ 0
- ◯ 1
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5
- ◯ 6
- ◯ 7
- ◯ 8
- ◯ 9
- ◯ 10
- ◯ 11
- ◯ 12
- ◯ 13
- ◯ 14
- ◯ 15
- ◯ 16
- ◯ 17
- ◯ 18
- ◯ 19
- ◯ 20
- ◯ 21
- ◯ 22
- ◯ 23
- ◯ 24
- ◯ 25+
- ◯ Range

If you do not provide education sessions, do you provide resources or other educational materials to the patients? (i.e., brochures, videos, referrals to other resources, etc.)

____

If you selected "range", please indicate the range for the number of education sessions with a brief explanation of why the range is used.

____

Who leads the education sessions?

- ☐ Physiotherapist
- ☐ Registered kinesiologist
- ☐ Exercise Physiologist
- ☐ Personal trainer
- ☐ Occupational therapist
- ☐ Nurse
- ☐ Physician
- ☐ Dietician
- ☐ Nutritionist
- ☐ Social worker
- ☐ Psychotherapist
- ☐ Psychiatrist
- ☐ Clinical psychologist
- ☐ Other

If "Other", please indicate who leads the education sessions.

____

How many exercises sessions in total are included per cardiac rehab program?	◯ 0 ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 ◯ 8 ◯ 9 ◯ 10 ◯ 11 ◯ 12 ◯ 13 ◯ 14 ◯ 15 ◯ 16 ◯ 17 ◯ 18 ◯ 19 ◯ 20 ◯ 21 ◯ 22 ◯ 23 ◯ 24 ◯ 25+ ◯ Range
If you do not provide exercise sessions, do you provide resources or other exercise related materials to the patients? (i.e., brochures, videos, referrals to other resources, etc.)	________________________________
If you selected "range", please indicate the range for the number of exercise sessions in the program with a brief explanation of why the range is used.	________________________________
Who leads the exercise sessions?	☐ Physiotherapist ☐ Registered kinesiologist ☐ Exercise Physiologist ☐ Personal trainer ☐ Occupational therapist ☐ Nurse ☐ Physician ☐ Dietician ☐ Nutritionist ☐ Social worker ☐ Psychotherapist ☐ Psychiatrist ☐ Clinical psychologist ☐ Other
If "Other", please indicate who leads the exercise sessions.	__________________________

How many nutritional counselling sessions in total are included per cardiac rehab program?	◯ 0 ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 ◯ 8 ◯ 9 ◯ 10 ◯ 11 ◯ 12 ◯ 13 ◯ 14 ◯ 15 ◯ 16 ◯ 17 ◯ 18 ◯ 19 ◯ 20 ◯ 21 ◯ 22 ◯ 23 ◯ 24 ◯ 25+ ◯ Range
If you do not provide nutrition counselling sessions, do you provide resources or other nutrition related materials to the patients? (i.e., brochures, videos, referrals to other resources, etc.)	____________________________________
If you selected "range", please indicate the range for the number of nutrition counselling sessions in the program with a brief explanation of why the range is used.	____________________________________
Who leads the nutrition counselling sessions?	☐ Physiotherapist ☐ Registered kinesiologist ☐ Exercise Physiologist ☐ Personal trainer ☐ Occupational therapist ☐ Nurse ☐ Physician ☐ Dietician ☐ Nutritionist ☐ Social worker ☐ Psychotherapist ☐ Psychiatrist ☐ Clinical psychologist ☐ Other
If you selected "other", please indicate who leads the nutrition counselling sessions	______________________________

How many psychosocial counselling sessions in total are included per cardiac rehab program?	◯ 0 ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 ◯ 8 ◯ 9 ◯ 10 ◯ 11 ◯ 12 ◯ 13 ◯ 14 ◯ 15 ◯ 16 ◯ 17 ◯ 18 ◯ 19 ◯ 20 ◯ 21 ◯ 22 ◯ 23 ◯ 24 ◯ 25+ ◯ Range
If you do not provide psychosocial counselling sessions, do you provide resources or other related materials to the patients? (i.e., brochures, videos, referrals to other resources, etc.)	________________________________
If you selected "range", please indicate the range for the number of psychosocial counselling sessions in the program with a brief explanation of why the range is used.	________________________________
Who leads the psychosocial counselling sessions?	☐ Physiotherapist ☐ Registered kinesiologist ☐ Exercise Physiologist ☐ Personal trainer ☐ Occupational therapist ☐ Nurse ☐ Physician ☐ Dietician ☐ Nutritionist ☐ Social worker ☐ Psychotherapist ☐ Psychiatrist ☐ Clinical psychologist ☐ Other
If "Other", please indicate who leads the psychosocial counselling sessions.	__________________________

How many social work sessions in total are included per cardiac rehab program?	◯ 0 ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 ◯ 8 ◯ 9 ◯ 10 ◯ 11 ◯ 12 ◯ 13 ◯ 14 ◯ 15 ◯ 16 ◯ 17 ◯ 18 ◯ 19 ◯ 20 ◯ 21 ◯ 22 ◯ 23 ◯ 24 ◯ 25+ ◯ Range
If you do not provide social work sessions, do you provide resources or other related materials to the patients? (i.e., brochures, videos, referrals to other resources, etc.)	________________________________
If you selected "range", please indicate the range for the number of social work sessions in the program with a brief explanation of why the range is used.	________________________________
Who leads the social work sessions?	☐ Physiotherapist ☐ Registered kinesiologist ☐ Exercise Physiologist ☐ Personal trainer ☐ Occupational therapist ☐ Nurse ☐ Physician ☐ Dietician ☐ Nutritionist ☐ Social worker ☐ Psychotherapist ☐ Psychiatrist ☐ Clinical psychologist ☐ Other
If "Other", please indicate who leads the social work sessions	__________________________

How many risk factor awareness/ modification sessions in total are included per cardiac rehab program?	◯ 0 ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 ◯ 8 ◯ 9 ◯ 10 ◯ 11 ◯ 12 ◯ 13 ◯ 14 ◯ 15 ◯ 16 ◯ 17 ◯ 18 ◯ 19 ◯ 20 ◯ 21 ◯ 22 ◯ 23 ◯ 24 ◯ 25+ ◯ Range
If you do not provide risk factor awareness/modification sessions, do you provide resources about risk factor modification or other related materials to the patients? (i.e., brochures, videos, referrals to other resources, etc.)	________________________________
If you selected "range", please indicate the range for the number of risk factor modification sessions in the program with a brief explanation of why the range is used.	________________________________
Who leads the risk factor awareness/modification sessions?	☐ Physiotherapist ☐ Registered kinesiologist ☐ Exercise Physiologist ☐ Personal trainer ☐ Occupational therapist ☐ Nurse ☐ Physician ☐ Dietician ☐ Nutritionist ☐ Social worker ☐ Psychotherapist ☐ Psychiatrist ☐ Clinical psychologist ☐ Other
If "Other", please indicate who leads the risk factor modification sessions.	__________________________
Does your cardiac rehab program include exercise testing?	◯ Yes ◯ No

If you do not complete submaximal or maximal testing, what methods/ tests/ criteria do you use to determine cardiorespiratory fitness? ________________________________

Submaximal Testing

Do you complete submaximal exercise testing at your cardiac rehabilitation centre?

- ◯ Yes
- ◯ No

How many submaximal exercise tests (tests that are completed to 80-85% of age-predicted heart rate max) are performed per year (i.e., Modified Balke, Modified Bruce, Modified Naughton, Astrand Cycle Ergometer Test, Chester Step Test, 6-minute Walk Test, Incremental 10m Shuttle Walk Test)? __________________________

If you know the exact total number of tests, please specify, if not, please approximate. Please indicate if it's an approximation. (i.e., approx. xxx).

Which modalities do you use for submaximal exercise tests? (Check all that apply)

- ☐ Cycler ergometer
- ☐ Treadmill
- ☐ Track/ hallway
- ☐ Step
- ☐ Other

If you selected "other", please specify which other tests that you use at your cardiac rehabilitation centre ________________________________

Which submaximal protocol(s) are used at your cardiac rehabilitation centre? (Check all that apply)

- ☐ Modified Balke
- ☐ Balke-Ware
- ☐ Modified Bruce
- ☐ Modified Naughton
- ☐ Astrand Cycle Ergometer Test
- ☐ Chester Step Test
- ☐ Astrand-Rhyming Step Test
- ☐ 6-minute Walk Test
- ☐ Incremental 10m Shuttle Walk Test
- ☐ Other

How many times has modified Balke protocol been performed in the last year?

- ◯ 0-20
- ◯ 20-50
- ◯ 50-100
- ◯ 100-200
- ◯ 200-300
- ◯ 300-500
- ◯ 500-800
- ◯ 800-1000
- ◯ 1000+
- ◯ Unknown

(If you know the specific number, please answer the following question)

How many times has the Balke-Ware protocol been performed in the last year?	◯ 0-20 ◯ 20-50 ◯ 50-100 ◯ 100-200 ◯ 200-300 ◯ 300-500 ◯ 500-800 ◯ 800-1000 ◯ 1000+ ◯ Unknown (If you know the specific number, please answer the following question)
How many times has the modified Bruce protocol been performed in the last year?	◯ 0-20 ◯ 20-50 ◯ 50-100 ◯ 100-200 ◯ 200-300 ◯ 300-500 ◯ 500-800 ◯ 800-1000 ◯ 1000+ ◯ Unknown (If you know the specific number, please answer the following question)
How many times has the modified Naughton protocol been performed in the last year?	◯ 0-20 ◯ 20-50 ◯ 50-100 ◯ 100-200 ◯ 200-300 ◯ 300-500 ◯ 500-800 ◯ 800-1000 ◯ 1000+ ◯ Unknown (If you know the specific number, please answer the following question)
How many times has the Astrand cycle ergometer protocol been performed in the last year?	◯ 0-20 ◯ 20-50 ◯ 50-100 ◯ 100-200 ◯ 200-300 ◯ 300-500 ◯ 500-800 ◯ 800-1000 ◯ 1000+ ◯ Unknown (If you know the specific number, please answer the following question)

How many times has the Chester Step Test been performed in the last year?	◯ 0-20 ◯ 20-50 ◯ 50-100 ◯ 100-200 ◯ 200-300 ◯ 300-500 ◯ 500-800 ◯ 800-1000 ◯ 1000+ ◯ Unknown (If you know the specific number, please answer the following question)
How many times has the Astrand Rhyming Step Test been performed in the last year?	◯ 0-20 ◯ 20-50 ◯ 50-100 ◯ 100-200 ◯ 200-300 ◯ 300-500 ◯ 500-800 ◯ 800-1000 ◯ 1000+ ◯ Unknown (If you know the specific number, please answer the following question)
How many times has the 6-minute Walk Test been performed in the last year?	◯ 0-20 ◯ 20-50 ◯ 50-100 ◯ 100-200 ◯ 200-300 ◯ 300-500 ◯ 500-800 ◯ 800-1000 ◯ 1000+ ◯ Unknown (If you know the specific number, please answer the following question)
How many times has the Incremental Shuttle Walk Test been performed in the last year?	◯ 0-20 ◯ 20-50 ◯ 50-100 ◯ 100-200 ◯ 200-300 ◯ 300-500 ◯ 500-800 ◯ 800-1000 ◯ 1000+ ◯ Unknown (If you know the specific number, please answer the following question)
If you know the specific number of times each submaximal protocol has been used in the last year, please indicate here.	________________________________
If you selected "other" for the previous question, please specify all other submaximal tests that you use at your cardiac rehabilitation facility.	________________________________

If you know the number of times each "other" protocol has been used in the last year, please indicate here (please indicate if the number provided is an estimate or exact number).

____

Which submaximal protocol(s) is/are the most frequently used at your cardiac rehabilitation centre?

- ☐ Modified Balke
- ☐ Balke-Ware
- ☐ Modified Bruce
- ☐ Modified Naughton
- ☐ Astrand Cycle Ergometer Test
- ☐ Chester Step Test
- ☐ Astrand-Rhyming Step Test
- ☐ 6-minute Walk Test
- ☐ Incremental 10m Shuttle Walk Test
- ☐ Other

If you selected other for the previous question, please specifiy the protocol that is the most frequently used at your cardiac rehabilitation facility.

____

Maximal Testing

Do you complete maximal exercise testing at your cardiac rehabilitation centre?

- ○ Yes
- ○ No

How many maximal exercise tests (tests that are completed until volitional exhaustion) are performed per year (i.e., Balke, Bruce, Naughton, Astrand Rhyming Cycle Ergometer Test, Ellestad, etc.)?

If you know the exact total number of tests, please specify, if not please approximate. Please indicate if it's an approximation (i.e., approx. xxx).

____

Which modalities do you use for maximal exercise tests? (Check all that apply)

- ☐ Cycler ergometer
- ☐ Treadmill
- ☐ Track/ hallway
- ☐ Step
- ☐ Other

If you selected "other", please specify which other maximal tests that you use at your cardiac rehabilitation centre

____

Which maximal protocol(s) are used at your cardiac rehabilitation centre? (check all that apply).

- ☐ Balke
- ☐ Bruce
- ☐ Naughton
- ☐ Astrand Rhyming Cycle Ergometer Test
- ☐ Ellestad
- ☐ Other
- ☐ Do not administer maximal exercise testing at our facility

How many times has the Balke protocol been performed in the last year?	◯ 0-20 ◯ 20-50 ◯ 50-100 ◯ 100-200 ◯ 200-300 ◯ 300-500 ◯ 500-800 ◯ 800-1000 ◯ 1000+ ◯ Unknown (if you know the exact number, please answer the following question)
How many times has the Bruce protocol been performed in the last year?	◯ 0-20 ◯ 20-50 ◯ 50-100 ◯ 100-200 ◯ 200-300 ◯ 300-500 ◯ 500-800 ◯ 800-1000 ◯ 1000+ ◯ Unknown (if you know the exact number, please answer the following question)
How many times has the Naughton protocol been performed in the last year?	◯ 0-20 ◯ 20-50 ◯ 50-100 ◯ 100-200 ◯ 200-300 ◯ 300-500 ◯ 500-800 ◯ 800-1000 ◯ 1000+ ◯ Unknown (if you know the exact number, please answer the following question)
How many times has the Astrand Rhyming Cycle ergometer protocol been performed in the last year?	◯ 0-20 ◯ 20-50 ◯ 50-100 ◯ 100-200 ◯ 200-300 ◯ 300-500 ◯ 500-800 ◯ 800-1000 ◯ 1000+ ◯ Unknown (if you know the exact number, please answer the following question)

How many times has the Ellestad protocol been performed in the last year?	◯ 0-20 ◯ 20-50 ◯ 50-100 ◯ 100-200 ◯ 200-300 ◯ 300-500 ◯ 500-800 ◯ 800-1000 ◯ 1000+ ◯ Unknown (if you know the exact number, please answer the following question)
If you know the specific number of times each maximal protocol has been used in the last year, please indicate here.	________________________
If you selected "other" for the previous question, please specify all other maximal tests that you use at your cardiac rehabilitation facility.	________________________
If you know the exact number of times each "other" protocol has been used, please indicate here (please indicate if the number provided is an estimate or the exact number).	________________________

Testing Protocol Selection - Submaximal and Maximal Protocols

Who decides which test/protocol is used for exercise testing at your cardiac rehabilitation centre?	☐ Registered kinesiologist (R. Kin) ☐ CSEP Clinical Exercise Physiologist (CSEP - CEP) ☐ CSEP Personal Trainer (CSEP - PT) ☐ ACSM Certified Clinical Exercise Physiologist (ACSM - CEP) ☐ ACSM Exercise Physiologist (ACSM - EP) ☐ ACSM Certified Personal Trainer (ACSM - CPT) ☐ Personal Trainer ☐ Physician ☐ Physiotherapist ☐ Nurse ☐ Stress Test Technician ☐ Other ☐ Unknown
If other, please specify.	________________________
What are the qualifications of the individuals conducting the test?	☐ Registered kinesiologist (R. Kin) ☐ CSEP Clinical Exercise Physiologist (CSEP - CEP) ☐ CSEP Personal Trainer (CSEP - PT) ☐ ACSM Certified Clinical Exercise Physiologist (ACSM - CEP) ☐ ACSM Exercise Physiologist (ACSM - EP) ☐ ACSM Certified Personal Trainer (ACSM - CPT) ☐ Personal Trainer ☐ Nurse ☐ Stress Test Technician ☐ Other ☐ Unknown

Question	Response
If other, please specify the qualifications, certifications or education an individual must possess to administer an exercise test?	________________
How is it decided which protocol is run?	________________
Is there a decision tree or criteria that is used to determine which protocol will be administered? If yes, please specify.	________________
Do all exercise tests used include a warm-up?	◯ Yes ◯ No
Why is a warm-up not performed? Please provide a reason (i.e., time, lack of space, lack of qualified personnel to supervise, etc.)	________________
If yes, is it only the warm-up that is already embedded in the testing protocol or is another warm-up performed?	◯ Warm-up within the protocol ◯ Additional warm-up not included in the exercise testing protocol
If additional warm-up, please indicate duration, incline, grade, speed and or/wattage and/or any other info about warm-ups (i.e. dynamic movements, static stretching, myofascial release, etc.)	________________

Appendix B: Protocol Tables

Table 5.B.1: Bloom et al., 2020 – Modified Balke protocol[266]

Stage	Speed (mph)	Grade (%)	Stage duration (min)	Total duration (min)
1	4.0	0	4	4
2	4.0	2	1	5
3	4.0	4	1	6
4	4.0	6	1	7
5	4.0	8	1	8
6	4.0	10	1	9
7	4.0	12	1	10
8	4.5	12	1	11
9	5	12	1	12
10	5.5	12	1	13
11	6	12	1	14
12	6.5	12	1	15

Table 5.B.2: Modified Bruce protocol

Stage	Speed (mph)	Grade (%)	Stage Duration	Total Time (min)
0	1.7	0	3	3
1/2	1.7	5	3	6
1	1.7	10	3	9
2	2.5	12	3	12
3	3.4	14	3	15
4	4.2	16	3	18
5	5	18	3	21
6	5.5	20	3	24
7	5.5	22	3	27

Table 5.B.3: Modified Naughton protocol

Stage	Speed (mph)	Grade (%)	Stage Duration (min)	Total Time (min)	METS*
1	2	0	2	2	2
2	2	3.5	2	4	3
3	2	7	2	6	4
4	2	10.5	2	8	5
5	2	14	2	10	6
6	2	17.5	2	12	7

7	2.6	14	2	14	8
8	3	14	2	16	9
9	3.4	14	2	18	10
10	3.7	14	2	20	11

Metabolic equivalents (METs): 1 MET = 3.5mL O2/kg/min

Table 5.B.4: UOHI Slow Ramp protocol

Stage	Speed (mph)	Grade (%)	Stage duration (min)	Total duration (min)
1	1.5	0.0	2	2
2	2.0	1.7	1	3
3	3.4	3.4	1	4
4	5.1	5.1	1	5
5	2.0	6.8	1	6
6	2.0	8.5	1	7
7	2.0	10.2	1	8
8	2.0	11.9	1	9
9	2.0	13.6	1	10
10	2.0	15.3	1	11
11	2.0	17.0	1	12
12	2.0	18.7	1	13
13	2.0	20.4	1	14
14	2.0	22.1	1	15
15	2.0	23.8	1	16
16	2.0	25.0	1	17
17	2.5	25.0	1	18
18	2.5	25.0	1	19
19	2.5	25.0	1	20
20	2.5	25.0	1	21
21	2.5	25.0	1	22
22	2.5	25.0	99.99	-

Appendix C: Protocols with estimated $\dot{V}O_2$ and % estimated improvement and workload

Table 5.C.1: Modified Balke Protocol

Stage	Stage duration (min)	Speed (mph)	Grade (%)	Estimated $\dot{V}O_2$ (mL/kg/min)	METs	% estimated improvement in $\dot{V}O_2$
1	0:00 - 3:59	4	0	14.22	4.06	
2	4:00 - 4:59	4	2	18.80	5.17	27.14
3	5:00 - 5:59	4	4	21.94	6.27	21.35
4	6:00 - 6:59	4	6	25.80	7.37	17.59
5	7:00 - 7:59	4	8	29.66	8.47	14.96
6	8:00 - 8:59	4	10	33.52	9.58	13.01
7	9:00 - 9:59	4	12	37.38	10.68	11.51
8	10:00 - 10:59	4.5	12	40.64	11.61	8.75
9	11:00 - 11:59	5	12	44.77	12.79	10.15
10	12:00 - 12:59	5.5	12	48.90	13.97	9.23

Metabolic equivalents (METs): 1 MET = 3.5mL O2/kg/min

Table 5.C.2: Modified Bruce protocol

Stage	Stage duration (min)	Speed (mph)	Grade (%)	Estimated $\dot{V}O_2$ (mL/kg/min)	METs	% estimated improvement in $\dot{V}O_2$
0	0:00 - 2:59	1.7	0	8.06	2.30	
0.5	3:00 - 5:59	1.7	5	12.16	3.47	50.90
1	6:00 - 8:59	1.7	10	16.26	4.64	33.73
2	9:00 - 11:59	2.5	12	24.67	7.05	51.76
3	12:00 - 14:59	3.4	14	35.57	10.16	44.19
4*	15:00 - 17:59	4.2	16	42.22	12.06	18.68
5	18:00 - 20:59	5	18	52.01	14.86	23.18
6	21:00 - 23:59	5.5	20	59.51	17.00	14.43
7	24:00 - 26:59	5.5	22	62.17	17.76	4.46

Switched to running equation at stage 4. Metabolic equivalents (METs): 1 MET = 3.5mL

O2/kg/min

Table 5.C.3: Modified Naughton protocol

Stage	Stage duration (min)	Speed (mph)	Grade (%)	Estimated $\dot{V}O_2$ (mL/kg/min)	METs	% estimated improvement in $\dot{V}O_2$
1	0:00 - 1:59	2	0	8.86	2.53	
2	2:00 - 3:59	2	3.5	12.24	3.50	38.11
3	4:00 - 5:59	2	7	15.61	4.46	27.60
4	6:00 - 7:59	2	10.5	18.99	5.43	21.63
5	8:00 - 9:59	2	14	22.37	6.39	17.78
6	10:00 - 11:59	2	17.5	25.74	7.36	15.10
7	12:00 - 13:59	2.6	14	28.03	8.01	8.87
8	14:00 - 15:59	3	14	31.80	9.09	13.46
9	16:00 - 17:59	3.4	14	35.57	10.16	11.87
10	18:00 - 19:59	3.7	14	38.40	10.97	7.80

Metabolic equivalents (METs): 1 MET = 3.5mL O2/kg/min

Table 5.C.4: UOHI Slow Ramp protocol

Stage	Stage duration (min)	Speed (mph)	Grade (%)	Estimated $\dot{V}O_2$ (mL/kg/min)	METs	% estimated improvement in $\dot{V}O_2$
1	0:00 - 1:59	1.5	0	7.52	2.15	
2	2:00 - 2:59	2	1.7	10.50	3.00	39.63
3	3:00 - 3:59	2	3.4	12.14	3.47	15.62
4	4:00 - 4:59	2	5.1	13.78	3.94	13.51
5	5:00 - 5:59	2	6.8	15.42	4.41	11.90
6	6:00 - 6:59	2	8.5	17.06	4.87	10.64
7	7:00 - 7:59	2	10.2	18.70	5.34	9.61
8	8:00 - 8:59	2	11.9	20.34	5.81	8.77
9	9:00 - 9:59	2	13.6	21.98	6.28	8.06
10	10:00 - 10:59	2	15.3	23.62	6.75	7.46
11	11:00 - 11:59	2	17	25.26	7.22	6.94
12	12:00 - 12:59	2	18.7	26.90	7.69	6.49

13	13:00 - 13:59	2	20.4	28.54	8.15	6.10
14	14:00 - 14:59	2	22.1	30.18	8.62	5.75
15	15:00 - 15:59	2	23.8	31.82	9.09	5.43
16	16:00 - 16:59	2	25	32.98	9.42	3.64
17	17:00 - 17:59	2.5	25	40.35	11.53	22.35
18	18:00 - 18:59	2.5	25	40.35	11.53	0
19	19:00 - 19:59	2.5	25	40.35	11.53	0
20	20:00 - 20:59	2.5	25	40.35	11.53	0
21	21:00 - 21:59	2.5	25	40.35	11.53	0
22	22:00 - 22:59	2.5	25	40.35	11.53	0

Metabolic equivalents (METs): 1 MET = 3.5mL O2/kg/min

Appendix D: Modified Balke Exercise Test Data Sheet

Protocol Used: **Modified Balke**

Participant ID: _______________ Date of test: _____________ Staff: _______

Birth Month & Year: _____________ Age: ________

Weight: __________kg (to 0.1kg) Height: ___________

Pre-test BP: ____________mmHg HR: ________bpm

Waist circumference: _________ cm Body composition: _________________

Participant sex: male or female (source: medical chart) *Beta-blocker this morning*?: Yes or No

Estimated HR max (207 – [0.7 x age]): _______bpm (subtract 30 from HRmax if β-blockers)

Pre-test Borg RPE Calibration done (6-20): Yes / No Rating: __________

Exercise:

Stage	Stage duration (min)	Speed (mph)	Grade (%)	Heart rate (bpm)	SBP/DBP (mmHg)	RPE (Borg 6 -20)
1	0:00 - 3:59	4.0	0			
2	4:00 - 4:59	4.0	2			
3	5:00 - 5:59	4.0	4			
4	6:00 - 6:59	4.0	6			
5	7:00 - 7:59	4.0	8			
6	8:00 - 8:59	4.0	10			
7	9:00 - 9:59	4.0	12			
8	10:00 - 10:59	4.5	12			
9	11:00 - 11:59	5	12			
10	12:00 - 12:59	5.5	12			
11	13:00 - 13:59	6	12			
12	14:00 - 14:59	6.5	12			

Recovery:

Stage	Stage duration (min)	Speed (mph)	Grade (%)	Heart rate (bpm)	SBP/DBP (mmHg)	RPE (Borg 6 -20)
Recovery	0:00 - 0:59		0			
Recovery	1:00 - 1:59		0			
Recovery	2:00 - 2:59		0			

Reason for stopping the test:
____
____
____
____

Total Test time (exact): __________
Maximal heart rate: _________________________
Final rating of perceived exertion: ______________
Post-test blood pressure: ____________mmHg HR: ________bpm

Notes:
____
____
____
____

Borg Calibration Script:

While doing physical activity, we want you to rate your perception of exertion. This feeling should reflect how heavy and strenuous the exercise feels to you, combining all sensations and feelings of physical stress, effort and fatigue. Do not concern yourself with any one factor such as leg pain or shortness of breath but try to focus on your total feeling of exertion.

Look at the rating scale while you are engaging in an activity; it ranges from 6 to 20, where 6 means "no exertion at all" and 20 means "maximal exertion." Choose the number that best describes your level of exertion. This will give you a good idea of the intensity level of your activity and you can use this information to speed up or slow down your movements to reach your desired range.

Try to appraise your feeling of exertion as honestly as possible, without thinking about what the actual physical load is. Your own feeling of effort and exertion is important, not how it compares to other people's. Look at the scales and the expressions and then give a number.

Appendix E: Modified Bruce Exercise Test Data Sheet

Protocol Used: **Modified Bruce**

Participant ID: _______________ Date of test: _____________ Staff: _______

Birth Month & Year: _____________ Age: ________

Weight: __________kg (to 0.1kg) Height: ___________

Pre-test BP: ____________mmHg HR: ________bpm

Waist circumference: _________ cm Body composition: _________________

Participant sex: male or female (source medical chart) *Beta-blocker this morning*?: Yes or No

Estimated HR max (207 – [0.7 x age]): _______bpm (subtract 30 from HRmax if β-blockers)

Pre-test Borg RPE Calibration done (6-20): Yes / No Rating: __________

Exercise:

Stage	Stage duration (min)	Speed (mph)	Grade (%)	Heart rate (bpm)	SBP/DBP (mmHg)	RPE (Borg 6 - 20)
0	0:00 - 2:59	1.7	0			
1/2	3:00 - 5:59	1.7	5			
1	6:00 - 8:59	1.7	10			
2	9:00 - 11:59	2.5	12			
3	12:00 - 14:59	3.4	14			
4	15:00 - 17:59	4.2	16			
5	18:00 - 20:59	5	18			
6	21:00 - 23:59	5.5	20			
7	24:00 - 26:59	5.5	22			

Recovery:

Stage	Stage duration (min)	Speed (mph)	Grade (%)	Heart rate (bpm)	SBP/DBP (mmHg)	RPE (Borg 6 - 20)
Recovery	0:00 - 0:59		0			
Recovery	1:00 - 1:59		0			
Recovery	2:00 - 2:59		0			

Reason for stopping the test:

____

____
____
Total Test time (exact): ___________
Maximal heart rate: ___________________________
Final rating of perceived exertion: _______________
Post-test blood pressure: _____________mmHg HR: _________bpm

Notes:
____
____
____
____

Borg Calibration Script:

While doing physical activity, we want you to rate your perception of exertion. This feeling should reflect how heavy and strenuous the exercise feels to you, combining all sensations and feelings of physical stress, effort and fatigue. Do not concern yourself with any one factor such as leg pain or shortness of breath but try to focus on your total feeling of exertion.

Look at the rating scale while you are engaging in an activity; it ranges from 6 to 20, where 6 means "no exertion at all" and 20 means "maximal exertion." Choose the number that best describes your level of exertion. This will give you a good idea of the intensity level of your activity and you can use this information to speed up or slow down your movements to reach your desired range.

Try to appraise your feeling of exertion as honestly as possible, without thinking about what the actual physical load is. Your own feeling of effort and exertion is important, not how it compares to other people's. Look at the scales and the expressions and then give a number.

Appendix F: Modified Naughton Exercise Test Data Sheet

Protocol Used: **Modified Naughton**

Participant ID: _______________ Date of test: _____________ Staff: _______

Birth Month & Year: _____________ Age: ________

Weight: __________kg (to 0.1kg) Height: ___________

Pre-test BP: ____________mmHg HR: ________bpm

Waist circumference: _________ cm Body composition: _________________

Participant sex: male or female (source: medical chart) *Beta-blocker this morning*?: Yes or No

Estimated HR max (207 – [0.7 x age]): _______bpm (subtract 30 from HRmax if β-blockers)

Pre-test Borg RPE Calibration done (6-20): Yes / No Rating: __________

Exercise:

Stage	Stage duration (min)	Speed (mph)	Grade (%)	Heart rate (bpm)	SBP/DBP (mmHg)	RPE (Borg 6 - 20)
1	0:00 - 1:59	2	0			
2	2:00 - 3:59	2	3.5			
3	4:00 - 5:59	2	7			
4	6:00 - 7:59	2	10.5			
5	8:00 - 9:59	2	14			
6	10:00 - 11:59	2	17.5			
7	12:00 - 13:59	2.6	14			
8	14:00 - 15:59	3	14			
9	16:00 - 17:59	3.4	14			
10	18:00 - 19:59	3.7	14			

Recovery:

Stage	Stage duration (min)	Speed (mph)	Grade (%)	Heart rate (bpm)	SBP/DBP (mmHg)	RPE (Borg 6 - 20)
Recovery	0:00 - 0:59		0			
Recovery	1:00 - 1:59		0			
Recovery	2:00 - 2:59		0			

Reason for stopping the test:

____

____
____

Total Test time (exact): __________
Maximal heart rate: _________________________
Final rating of perceived exertion: ______________
Post-test blood pressure: ____________mmHg HR: ________bpm

Notes:
____
____
____
____

Borg Calibration Script:

While doing physical activity, we want you to rate your perception of exertion. This feeling should reflect how heavy and strenuous the exercise feels to you, combining all sensations and feelings of physical stress, effort and fatigue. Do not concern yourself with any one factor such as leg pain or shortness of breath but try to focus on your total feeling of exertion.

Look at the rating scale while you are engaging in an activity; it ranges from 6 to 20, where 6 means "no exertion at all" and 20 means "maximal exertion." Choose the number that best describes your level of exertion. This will give you a good idea of the intensity level of your activity and you can use this information to speed up or slow down your movements to reach your desired range.

Try to appraise your feeling of exertion as honestly as possible, without thinking about what the actual physical load is. Your own feeling of effort and exertion is important, not how it compares to other people's. Look at the scales and the expressions and then give a number.

Appendix G: UOHI Slow Ramp Exercise Test Data Sheet

Protocol Used: **UOHI Slow Ramp**

Participant ID: _______________ Date of test: _____________ Staff: _______

Birth Month & Year: _____________ Age: ________

Weight: __________kg (to 0.1kg) Height: ___________

Pre-test BP: ____________mmHg HR: ________bpm

Waist circumference: _________ cm Body composition: _________________

Participant sex: male or female (source: medical chart) *Beta-blocker this morning*? Yes or No

Estimated HR max (207 – [0.7 x age]): _______bpm (subtract 30 from HRmax if β-blockers)

Pre-test Borg RPE Calibration done (6-20): Yes / No Rating: __________

Exercise:

Stage	Stage duration (min)	Speed (mph)	Grade (%)	Heart rate (bpm)	SBP/DBP (mmHg)	RPE (Borg 6 -20)
1	0:00 - 1:59	1.5	0.0			
2	2:00 - 2:59	2.0	1.7			
3	3:00 - 3:59	2.0	3.4			
4	4:00 - 4:59	2.0	5.1			
5	5:00 - 5:59	2.0	6.8			
6	6:00 - 6:59	2.0	8.5			
7	7:00 - 7:59	2.0	10.2			
8	8:00 - 8:59	2.0	11.9			
9	9:00 - 9:59	2.0	13.6			
10	10:00 - 10:59	2.0	15.3			
11	11:00 - 11:59	2.0	17.0			
12	12:00 - 12:59	2.0	18.7			
13	13:00 - 13:59	2.0	20.4			
14	14:00 - 14:59	2.0	22.1			
15	15:00 - 15:59	2.0	23.8			
16	16:00 - 16:59	2.0	25.0			
17	17:00 - 17:59	2.5	25.0			
18	18:00 - 18:59	2.5	25.0			
19	19:00 - 19:59	2.5	25.0			
20	20:00 - 20:59	2.5	25.0			
21	21:00 - 21:59	2.5	25.0			
22	22:00 - 22:59	2.5	25.0			

Recovery:

Stage	Stage duration (min)	Speed (mph)	Grade (%)	Heart rate (bpm)	SBP/DBP (mmHg)	RPE (Borg 6 -20)
Recovery	0:00 - 0:59		0			
Recovery	1:00 - 1:59		0			
Recovery	2:00 - 2:59		0			

Reason for stopping the test:

____
____
____

Total Test time (exact): ___________
Maximal heart rate: ___________________________
Final rating of perceived exertion: _______________
Post-test blood pressure: _____________mmHg HR: _________bpm

Notes:

____
____
____

Borg Calibration Script:

While doing physical activity, we want you to rate your perception of exertion. This feeling should reflect how heavy and strenuous the exercise feels to you, combining all sensations and feelings of physical stress, effort and fatigue. Do not concern yourself with any one factor such as leg pain or shortness of breath but try to focus on your total feeling of exertion.

Look at the rating scale while you are engaging in an activity; it ranges from 6 to 20, where 6 means "no exertion at all" and 20 means "maximal exertion." Choose the number that best describes your level of exertion. This will give you a good idea of the intensity level of your activity and you can use this information to speed up or slow down your movements to reach your desired range.

Try to appraise your feeling of exertion as honestly as possible, without thinking about what the actual physical load is. Your own feeling of effort and exertion is important, not how it compares to other people's. Look at the scales and the expressions and then give a number.

Appendix H: Enjoyment Questionnaires

Enjoyment Questionnaire: Post Max-Submaximal Exercise Test Participant Feedback

FOR ADMIN ONLY

Participant ID: ________________________
Date: ______________________________
Tester: _____________________________
Test completed: _______________________
Of tests completed to date: _____________

FOR PARITICPANT

To be completed after every exercise test:

Perception

1. Did you feel safe at all times during the exercise test? Yes No
   If no, please explain why: ____
   ____
   ____

Cardiac Intensity

2. Please rate on the following scale **how physically challenging the intensity of the test you completed today was**. (For this question, 0 = not difficult and 10 = extremely difficult.)

1 2 3 4 5 6 7 8 9 10

Very easy **Very difficult**

Enjoyment

3.a) Please rate on the following scale **how much you enjoyed the test you completed today**. (For this question, 0 = did not enjoy the test at all (never want to do it again) and 10 = loved participating in the test, would gladly repeat the test in the future and would recommend to others.)

1 2 3 4 5 6 7 8 9 10

Hate it **Loved it, would do again**

3.b) Why did you give this rating of enjoyment? (i.e., what factors led to this task being more/less enjoyable?

____
____
____

Appendix I: Participant Exercise Test Feedback

UNIVERSITY OF OTTAWA
HEART INSTITUTE
INSTITUT DE CARDIOLOGIE
DE L'UNIVERSITÉ D'OTTAWA

Post Max-Submaximal Exercise Test Participant Feedback

Participant ID: ________________________
Date: ______________________________
Tester: _____________________________
Of tests completed to date: _____________

To be completed after all 4 exercise tests have been performed

1. Please rate your cardiorespiratory fitness **prior** to the exercise tests. (For this question, 0 = no cardiorespiratory fitness (i.e., difficulty walking for 5 minutes) and 10 = extremely high (could run for 20-30 minutes without any problems).

   1 2 3 4 5 6 7 8 9 10

No fitness **Extremely high**

2. Please rate your cardiorespiratory fitness **after** the exercise tests. (For this question, 0 = no cardiorespiratory fitness (i.e., difficulty walking for 5 minutes) and 10 = extremely high (could run for 20-30 minutes without any problems).

   1 2 3 4 5 6 7 8 9 10

No fitness **Extremely high**

3. Describe what factors you think may have contributed to the change, if any.

   Please explain why:
   ____
   ____
   ____
   ____

4.a) Which test did you find the most challenging? Please rank from easiest to hardest (1 being the easiest to 4 being the hardest)

- ❑ Test 1
- ❑ Test 2
- ❑ Test 3
- ❑ Test 4
- ❑ Same
- ❑ No difference

4.b) Why did you find this test the most challenging?

____

5.a) Which test did you enjoy the most? Please rank from favourite to least favourite (1 being your favourite, 4 being your least favourite)

- ❑ Test 1
- ❑ Test 2
- ❑ Test 3
- ❑ Test 4
- ❑ No difference

5.b) Why did you find this test the most enjoyable?

4. Overall, I was satisfied with the exercise tests. Yes No

   Comments:

5. Overall, I would recommend them to other patients. Yes No

   Comments:

6. We are always looking at ways to improve our exercise testing, so please provide any recommendations, additional comments, or concerns.

   Comments:

Appendix J: Protocol Selection Survey

Maximal - Submaximal Exercise Test Protocol Selection Process

Cardiac Rehabilitation centre name: ________________________

Date: ____

City: ____

Province: ____

Name of person completing the survey: ____

Position/ role at the hospital/ in CR centre: ____

Typical patient volume on average per year for cardiac rehab: __________________________

Number of submaximal exercise tests performed per year: _____________________________

Number of maximal exercise tests performed per year: ________________________________

Which submaximal protocol(s) are used at your cardiac rehab centre?

- ❑ Modified Balke
- ❑ Balke-Ware
- ❑ Modified Bruce
- ❑ Modified Naughton
- ❑ Astrand Cycle ergometer test
- ❑ Chester Step Test
- ❑ Astrand-Rhyming Step Test
- ❑ 6 Minute Walk Test
- ❑ Incremental 10m Shuttle Walk test
- ❑ Other ____

Which submaximal protocol(s) is used the most frequently at your cardiac rehab centre?

- ❑ Modified Balke
- ❑ Balke-Ware
- ❑ Modified Bruce
- ❑ Modified Naughton
- ❑ Astrand Cycle ergometer test
- ❑ Chester Step Test
- ❑ Astrand-Rhyming Step Test
- ❑ 6 Minute Walk Test
- ❑ Incremental 10m Shuttle Walk test

Other ____

How many times has each submaximal protocol been performed in the last year?

- ❑ 0-20
- ❑ 20-50
- ❑ 50-100
- ❑ 100-200
- ❑ 200-300
- ❑ 300-500
- ❑ 500-800
- ❑ 800-1000
- ❑ 1000+
- ❑ If you have the specific number for each test, please indicate here:

____
____
____

Which maximal protocol(s) are used at your cardiac rehab centre?

- ❑ Balke
- ❑ Bruce
- ❑ Naughton
- ❑ Astrand Rhyming Cycle ergometer
- ❑ Ellestad
- ❑ Other ____

Which maximal protocol(s) is used the most frequently at your cardiac rehab centre?

- ❑ Balke
- ❑ Bruce
- ❑ Naughton
- ❑ Astrand Rhyming Cycle ergometer
- ❑ Ellestad
- ❑ Other ____

How many times has each maximal protocol been performed in the last year?

- ❑ 0-20
- ❑ 20-50
- ❑ 50-100
- ❑ 100-200
- ❑ 200-300
- ❑ 300-500
- ❑ 500-800
- ❑ 800-1000
- ❑ 1000+
- ❑ If you have the specific number for each test, please indicate here:

____
____
____

Who decides which test/ protocol is used for exercise testing at your centre?

____
____

How do you decide which protocol to run?

____
____
____

Is there a decision tree or criteria that your centre uses to determine which protocol will be administered?

____
____
____

Do all exercise tests used include a warm-up? If yes, please indicate duration, incline, grade, speed and/or wattage.

____
____
____

Appendix K: Exercise test protocols that were not selected

Table 5.K.1: Bruce protocol[73]

Stage	Speed (mph)	Grade (%)	Stage duration (min)	Total duration (min)
1	1.7	10	3	3
2	2.5	12	3	6
3	3.4	14	3	9
4	4.2	16	3	12
5	5.0	18	3	15
6	5.5	20	3	18
7	6.0	22	3	21

Table 5.K.2: Naughton protocol[133]

Stage	Speed (mph)	Grade (%)	Stage duration (min)	Total duration (min)
1	1.0	0	3	3
2	1.5	0	3	6
3	2.0	3.5	3	9
4	2.0	7	3	12
5	2.0	10.5	3	15
6	2.0	14.0	3	18
7	2.0	17.5	3	21
8	3.0	12.5	3	24
9	3.0	15	3	27
10	3.0	17.6	3	30

Table 5.K.3: Balke protocol[71]

Stage	Speed (mph)	Grade (%)	Stage duration (min)	Total duration (min)
1	3.0	0	3	3
2	3.0	2.5	3	6
3	3.0	5	3	9
4	3.0	7.5	3	12
5	3.0	10	3	15
6	3.0	12.5	3	18
7	3.0	15	3	21
8	3.0	17.5	3	24
9	3.0	20	3	27
10	3.0	22.5	3	30

Table 5.K.4: Modified Balke-Ware protocol

Stage	Speed (mph)	Grade (%)	Stage duration (min)	Total duration (min)
1	2.0	0	3	3
2	3.3	0	3	6
3	3.3	5	3	9
4	3.3	10	3	12
5	3.3	15	3	15
6	3.3	20	3	18
7	3.3	25	3	21

Table 5.K.5: Aadlan et al. 2016 - Modified Balke protocol[267]

Stage	Speed (kph)		Grade (%)	Stage duration (min)	Total duration (min)
	≥55 years old	< 55 years old			
1	3.8	4.8	1.4	4	4
2	3.8	4.8	3.4	1	5
3	3.8	4.8	5.4	1	6
4	3.8	4.8	7.4	1	7
5	3.8	4.8	9.4	1	8
6	3.8	4.8	11.4	1	9
7	3.8	4.8	13.4	1	10
8	3.8	4.8	15.4	1	11
9	3.8	4.8	17.4	1	12
10	4.3	5.3	17.4	1	13
11	4.8	5.8	17.4	1	14

*Continue to increase speed by 0.5kph every minute until the participant can no longer continue

Table 5.K.6: Graded exercise protocol[268]

Stage	Speed (mph)	Grade (%)	Stage duration (min)	Total duration (min)
1	4.3-7.5	0	3	3
2	4.3-7.5	0	3	6
3	4.3-7.5	2.5	1	7
4	4.3-7.5	5	1	8
5	4.3-7.5	7.5	1	9
6	4.3-7.5	10	1	10
7	4.3-7.5	12.5	1	11
8	4.3-7.5	15	1	12

Table 5.K.7: Asymptomatic cardiac ischemia pilot (ACIP) protocol[269]

Stage	Speed (mph)	Grade (%)	Stage duration (min)	Total duration (min)
1	2.0	0	3	3
2	2.5	2	3	6
3	3.0	3	3	9
4	3.0	7	3	12
5	3.0	10.5	3	15
6	3.0	14	3	18
7	3.0	17.5	3	21
8	3.0	21	3	24
9	3.1	24	3	27
10	3.4	24	3	30

Note: protocol was developed to test patients with CVD.

Table 5.K.8: Ellestad protocol[74]

Stage	Speed (mph)	Grade (%)	Stage duration (min)	Total duration (min)
1	1.7	10	3	3
2	3.0	10	2	5
3	4.0	10	2	7
4	5.0	10	2	9
5	6.0	15	2	11
6	7.0	15	2	13
7	8.0	15	2	15

Table 5.K.9: Gerkin protocol[270]

Stage	Speed (mph)	Grade (%)	Stage duration (min)	Total duration (min)
0	3.5	0	3	4
1	4.5	0	1	4
2	4.5	2	1	5
3	5	4	1	6
4	5	4	1	7
5	5.5	6	1	8
6	5.5	6	1	9
7	6	8	1	10
8	6	8	1	11
9	6.5	10	1	12
10	6.5	10	1	13
11	7	12	1	14
12	7	12	1	15

13	7.5	14	1	16
14	7.5	14	1	17

Note: this protocol is mainly used to assess CRF in the firefighter profession

Table 5.K.10: Healthy active living and obesity research group protocol (HALO – protocol)[271]

Stage	Speed (mph)	Grade (%)	Stage duration (min)	Total duration (min)
0	Self-paced	0	4	4
1	Self-paced	3	4	8
2	Self-paced	6	4	12
3	Self-paced	9	4	16
4	Self-paced	12	4	20
5	Self-paced	15	4	24
6	Self-paced	18	4	28

Table 5.K.11: McHenry protocol[272]

Stage	Speed (mph)	Grade (%)	Stage duration (min)	Total duration (min)
1	2.0	3	3	3
2	3.3	6	3	6
3	3.3	9	3	9
4	3.3	12	3	12
5	3.3	15	3	15
6	3.3	18	3	18
7	3.3	21	3	21

Table 5.K.12: Stanford protocol[273]

Stage	Speed (mph)	Grade (%)	Stage duration (min)	Total duration (min)
1	3.0	0	2	2
2	3.0	2.5	2	4
3	3.0	5	2	6
4	3.0	7.5	2	8
5	3.0	10	2	10
6	3.0	12.5	2	12
7	3.0	15	2	14
8	3.0	17.5	2	16
9	3.0	20	2	18
10	3.0	22.5	2	20

Table 5.K.13: STEEP protocol[274]

Stage	Speed (mph)	Grade (%)	Stage duration (min)	Total duration (min)
1	1.5	0	1	1
2	2	0	1	2
3	2	1.5	1	3
4	2	3	1	4
5	2.5	3	1	5
6	2.5	5	1	6
7	2.5	7	1	7
8	3	7	1	8
9	3	9	1	9
10	3	11	1	10
11	3.5	11	1	11
12	3.5	13	1	12
13	3.5	16	1	13
14	4.2	16	1	14
15	5	16	1	15

Table 5.K.14**: Taylor protocol**[76]

Stage	Speed (mph)	Grade (%)	Stage duration (min)	Total duration (min)
1	3.5	10.0	3	3
2	7.0	0	3	6
3	7.0	2.5	3	9
4	7.0	5.0	3	12
5	7.0	7.5	3	15

Note: This protocol is used for runners

Appendix L: Magnitudes of increase per stage

Table 5.L.1: Magnitude of increase per stage for the modified Balke protocol

Stage	Stage duration (min)	Speed (mph)	Grade (%)	Workload (mL/kg/min)	METs	% improvement in $\dot{V}O_2$
1	0:00 - 3:59	4	0	24.94	7.13	
2	4:00 - 4:59	4	2	26.87	7.68	7.7
3	5:00 - 5:59	4	4	28.80	8.23	7.2
4	6:00 - 6:59	4	6	30.73	8.78	6.7
5	7:00 - 7:59	4	8	32.66	9.33	6.3
6	8:00 - 8:59	4	10	34.59	9.88	5.9
7	9:00 - 9:59	4	12	36.52	10.43	5.6
8	10:00 - 10:59	4.5	12	40.64	11.61	11.3
9	11:00 - 11:59	5	12	44.77	12.79	10.2
10	12:00 - 12:59	5.5	12	48.90	13.97	9.2

METs, metabolic equivalents; $\dot{V}O_2$, oxygen consumption

Note: Predicted workload was calculated using the ACSM running equation

$$\dot{V}O_2 = (0.2 \times speed \left(\frac{m}{min}\right) + (0.9 \times speed \left(\frac{m}{min}\right) \times \%\, grade + 3.5$$

METs was calculated by dividing workload (mL/kg/min) by 3.5.

% improvement in VO2 per stage was calculated by the percent differences between 2 stages:

$$\frac{Stage\ 2\ workload\ (mL/kg/min) - Stage\ 1\ workload\ (mL/kg/min)}{Stage\ 1\ workload\ (mL/kg/min)} \times 100$$

Table 5.L.2: Magnitude of increase per stage for the modified Bruce protocol

Stage	Stage duration (min)	Speed (mph)	Grade (%)	Workload	METs	% estimated improvement in $\dot{V}O_2$
0	0:00 - 2:59	1.7	0	8.06	2.302	
0.5	3:00 - 5:59	1.7	5	12.16	3.47	50.90
1	6:00 - 8:59	1.7	10	16.26	4.64	33.73
2	9:00 - 11:59	2.5	12	24.67	7.05	51.76
3	12:00 - 14:59	3.4	14	35.57	10.16	44.19
4	15:00 - 17:59	4.2	16	42.22	12.06	18.68

5	18:00 - 20:59	5	18	52.01	14.86	23.18
6	21:00 - 23:59	5.5	20	59.51	17.00	14.43
7	24:00 - 26:59	5.5	22	62.165	17.76	4.46

METs, metabolic equivalents; $\dot{V}O_2$, oxygen consumption

Note: Predicted workload was calculated using the ACSM running equation for stages 0-3

$$\dot{V}O_2 = (0.1 \times speed\left(\frac{m}{min}\right) + (1.8 \times speed\left(\frac{m}{min}\right) \times \%\, grade + 3.5$$

METs was calculated by dividing workload (mL/kg/min) by 3.5.

% improvement in VO2 per stage was calculated by the percent differences between 2 stages:

$$\frac{Stage\ 2\ workload\ (mL/kg/min) - Stage\ 1\ workload\ (mL/kg/min)}{Stage\ 1\ workload\ (mL/kg/min)} \times 100$$

Predicted workload was calculated using the ACSM running equation for stages 4+

$$\dot{V}O_2 = (0.2 \times speed\left(\frac{m}{min}\right) + (0.9 \times speed\left(\frac{m}{min}\right) \times \%\, grade + 3.5$$

METs was calculated by dividing workload (mL/kg/min) by 3.5.

% improvement in VO2 per stage was calculated by the percent differences between 2 stages:

$$\frac{Stage\ 2\ workload\ (mL/kg/min) - Stage\ 1\ workload\ (mL/kg/min)}{Stage\ 1\ workload\ (mL/kg/min)} \times 100$$

Table 5.L.3: Magnitude of increase per stage for the modified Naughton protocol

Stage	Stage duration (min)	Speed (mph)	Grade (%)	Workload	METs	% estimated improvement in $\dot{V}O_2$,
1	0:00 - 1:59	2	0	8.86	2.53	
2	2:00 - 3:59	2	3.5	12.24	3.50	38.11
3	4:00 - 5:59	2	7	15.61	4.46	27.60
4	6:00 - 7:59	2	10.5	18.99	5.43	21.63
5	8:00 - 9:59	2	14	22.37	6.39	17.78
6	10:00 - 11:59	2	17.5	25.74	7.36	15.10
7	12:00 - 13:59	2.6	14	28.03	8.01	8.87
8	14:00 - 15:59	3	14	31.80	9.09	13.46

9	16:00 - 17:59	3.4	14	35.57	10.16	11.87
10	18:00 - 19:59	3.7	14	38.40	10.97	7.96

METs, metabolic equivalents; $\dot{V}O_2$, oxygen consumption

Note: Predicted workload was calculated using the ACSM running equation for stages 0-3

$$\dot{V}O_2 = (0.1 \times speed\left(\frac{m}{min}\right) + (1.8 \times speed\left(\frac{m}{min}\right) \times \%\, grade + 3.5$$

METs was calculated by dividing workload (mL/kg/min) by 3.5.

% improvement in VO2 per stage was calculated by the percent differences between 2 stages:

$$\frac{Stage\ 2\ workload\ (mL/kg/min) - Stage\ 1\ workload\ (mL/kg/min)}{Stage\ 1\ workload\ (mL/kg/min)} \times 100$$

Table 5.L.4: Magnitude of increase per stage for the UOHI Slow Ramp protocol

Stage	Stage duration (min)	Speed (mph)	Grade (%)	Estimated VO2	METs	% estimated improvement in $\dot{V}O_2$,
1	0:00 - 1:59	1.5	0	7.52	2.15	
2	2:00 - 2:59	2	1.7	10.50	3.00	39.63
3	3:00 - 3:59	2	3.4	12.14	3.47	15.62
4	4:00 - 4:59	2	5.1	13.78	3.94	13.51
5	5:00 - 5:59	2	6.8	15.42	4.41	11.90
6	6:00 - 6:59	2	8.5	17.06	4.87	10.64
7	7:00 - 7:59	2	10.2	18.70	5.34	9.61
8	8:00 - 8:59	2	11.9	20.34	5.81	8.77
9	9:00 - 9:59	2	13.6	21.98	6.28	8.06
10	10:00 - 10:59	2	15.3	23.62	6.75	7.46
11	11:00 - 11:59	2	17	25.26	7.22	6.94
12	12:00 - 12:59	2	18.7	26.90	7.69	6.49
13	13:00 - 13:59	2	20.4	28.54	8.15	6.10
14	14:00 - 14:59	2	22.1	30.18	8.62	5.75
15	15:00 - 15:59	2	23.8	31.82	9.09	5.43
16	16:00 - 16:59	2	25	32.98	9.42	3.64

17	17:00 - 17:59	2.5	25	40.35	11.53	22.35
18	18:00 - 18:59	2.5	25	40.35	11.53	0
19	19:00 - 19:59	2.5	25	40.35	11.53	0
20	20:00 - 20:59	2.5	25	40.35	11.53	0
21	21:00 - 21:59	2.5	25	40.35	11.53	0
22	22:00 - 22:59	2.5	25	40.35	11.53	0

METs, metabolic equivalents; $\dot{V}O_2$, oxygen consumption

Note: Predicted workload was calculated using the ACSM running equation for stages 0-3

$$\dot{V}O_2 = (0.1 \times speed\left(\frac{m}{min}\right) + (1.8 \times speed\left(\frac{m}{min}\right) \times \% \, grade + 3.5$$

METs was calculated by dividing workload (mL/kg/min) by 3.5.

% improvement in VO2 per stage was calculated by the percent differences between 2 stages:

$$\frac{Stage\ 2\ workload\ (mL/kg/min) - Stage\ 1\ workload\ (mL/kg/min)}{Stage\ 1\ workload\ (mL/kg/min)} \times 100$$

Appendix M: Ottawa Health Science Network Research Ethics Board (OHSN-REB) Exemption Letter and Approval for TRADE as a Quality Improvement Project

Ottawa Health Science Network Research Ethics Board (OHSN-REB) /
Conseil d'éthique de la recherche du réseau de science de la santé d'Ottawa (CER-RSSO)

May 2, 2023

Jennie Wong
Division of Cardiac Rehabilitation
University of Ottawa Heart Institute
40 Ruskin Street H 2 101A
Ottawa, ON, K1Y 4W7

Re: Cardiopulmonary Exercise Testing Protocol Selection in Cardiovascular Rehabilitation Centres Across Canada

Dear Ms. Wong,

Thank you for your email March 8, 2023 enclosing the above-named project.

Our review of the proposal indicates that your project falls within the context of quality initiative, quality improvement, quality assurance, and/or program evaluation. Consequently, as per the Tri-Council Policy Statement 2, Article 2.5,review by the OHSN-REB is not required.

The UOHI Quality Office will be copied on this letter.

University of Ottawa Heart Institute quality improvement projects must be **registered,** please contact Bonnie Bowes at the UOHI Quality Office at quality@ottawaheart.ca or 613-696-7000 extension 67233.

Please keep this letter for future use. REB review evidence might be requested by journals, should you seek publication at project completion. You could then provide this letter.

The Ottawa Health Science Network Research Ethics Board is constituted in accordance with and operates in compliance with the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans; Health Canada Good Clinical Practice: Consolidated Guideline; Part C Division 5 of the Food and Drug Regulations of Health Canada; and the provisions of the Ontario Health Information Protection Act 2004 and its applicable Regulations.

Yours sincerely,

James Robblee MBA, MD
Vice-Chair
Ottawa Health Science Network Research Ethics Board

cc. UOHI Quality Office

Civic Campus, Box 675, 725 Parkdale Avenue, Ottawa, Ontario, K1Y 4E9
613-798-5555 extension 16719 Fax : 613-761-4311 http://www.ohri.ca/ohsn-reb

Appendix N: TRADE Quality Improvement Registration

June 28, 2023

Jennie Wong, Dr. Jennifer Reed, Matheus Mistura
c/o Jennie Wong

Re: QI 167 Cardiopulmonary Exercise Testing Protocol Selection in Cardiovascular Rehabilitation Centres Across Canada (TRADE)

Dear J. Wong,

Thank you for submitting your Quality Improvement Project and accompanying documents for registration. Your project has been registered with reference no. **QI-167** and end date of **Jun 30, 2024**.

Upon your project's end date, please ensure to report on the results of your project or request an extension by submitting your Summary Results Report to Quality at quality@ottawaheart.ca.

Please file this letter for your reference and reach out with any questions or concerns.

Sincerely,

UOHI Quality Office

613-696-7000 ext. 19305

quality@ottawaheart.ca

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Appendix O: Ottawa Health Science Network Research Ethics Board (OHSN-REB) Approval for PACED

Ottawa Health Science Network Research Ethics Board (OHSN-REB) / Conseil d'éthique de la recherche du réseau de science de la santé d'Ottawa (CÉR-RSSO)

Date:	November 9, 2023
Principal Investigator:	Dr. Jennifer Reed, UOHI/OHIRC
Protocol ID:	20230327-01H
Study Title:	COMPARING V?O2 PEAK VALUES of EXERCISE TESTING PROTOCOLS FOR FEMALES AND MALES WITH CAD
Submission Type:	Initial Application
Review Type:	Full Board
Meeting Date:	June 14, 2023
Date of Approval:	November 6, 2023
Study Approval Expiry Date:	November 6, 2024

Dear Dr. Reed,

An **Institutional approval (OHIRC) letter is required prior to commencing the study** . In order to obtain the institutional approval letter, the ethics, contracts, and departmental notifications tabs of the Clinical Research Registration Form (CRRF) must be approved/marked complete by the reviewing office.

Thank you for submitting the above referenced study. The Ottawa Health Science Network Research Ethics Board (OHSN-REB) has reviewed the application and granted approval for your study. This approval is granted until the expiration date noted above. This research study is to be conducted by the investigator noted above.

The **OHSN-REB ethics approval** for this study is for The University of Ottawa Heart Institute.

Translation of French documentation remains outstanding.

Documents Approved:

Document Name	**Document Version Date**
PACED (#20230327-01H) Protocol, dated October 24, 2023	October 24, 2023
PACED (20230327-01H) English Demographics Questionnaire, dated July 24, 2023	July 24, 2023
PACED (20230327-01H) English Enjoyment Questionnaire, dated July 24, 2023	July 24, 2023
PACED (20230327-01H) English IPAQ Long Form, October 2002	October 1, 2002
PACED (20230327-01H) English Main Informed Consent Form, dated October 24, 2023	October 24, 2023
PACED (20230327-01H) English Participant Exercise Test Feedback Questionnaire, dated July 24, 2023	July 24, 2023
PACED (20230327-01H) English Social Media Post for Recruitment, dated September 15, 2023	September 15, 2023
PACED (20230327-01H) English Tear-Off Flyer for Recruitment, dated September 15, 2023	September 15, 2023
PACED (20230327-01H) English Telephone Recruitment Script - Full version, dated July 24, 2023	July 24, 2023
PACED (20230327-01H) French IPAQ Long Form, July 2023	July 14, 2023

Documents Acknowledged:

Document Name	**Document Version Date**
Summary of Test Results	May 20, 2023

If applicable, the pending translated documents must be uploaded into the "Translated Documents" tab of the Clinical Research Registration Form within 90 days of REB approval.

No deviations from, or changes to, the protocol should be initiated without prior written approval of an appropriate amendment from the OHSN-REB, except when necessary to eliminate immediate hazard(s) to study participants.

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

If the study is to continue beyond the expiry date noted above, a Continuing Review Form must be received by the OHSN-REB on or prior to the full board submission deadline date of the meeting scheduled to occur a minimum of 30 days prior to the study expiry date. If the study has been completed by the expiry noted above, a Study Closure Form must be received by the OHSN-REB.

The OHSN-REB 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); International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2); 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 or with the definition in the Interim Order Respecting Clinical Trials for Medical Devices and Drugs Relating to COVID-19. OHSN-REB is qualified through the CTO REB Qualification Program and is registered with the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protection (OHRP).

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

Sincerely,

Jim Robblee, M.D.
Vice Chairperson
Ottawa Health Science Network Research Ethics Board

/HMc

Appendix P: Institution Approval for PACED

January 23, 2024

Dr. Jennifer Reed

Division of Cardiac Rehabilitation
University of Ottawa Heart Institute
40 Ruskin Street H 2 101A
Ottawa, ON, K1Y 4W7
Canada

Re: UOHI Institutional Approval for Ottawa Health Science Network Research Ethics Board (OHSN-REB) Submission

Local Protocol ID#: 20230327-01H;

COMPARING VO2 PEAK VALUES of EXERCISE TESTING PROTOCOLS FOR FEMALES AND MALES WITH CAD

Dear Dr. Jennifer Reed,

This letter serves as **University of Ottawa Heart Institute (UOHI)** Institutional Approval for the above-referenced study. Please maintain this documentation in your investigator study file.

Based on the information you provided about this study through the Clinical Research Registration Form, you have satisfied the requirements for institutional (UOHI) approval. This includes initial research ethics approval by OHSN-REB, appropriate departmental/service area notifications and execution (fully signed versions) of all agreement(s) required to begin the study locally. Please note there may be additional agreement(s) pending execution that are required to send funds, samples, or data to external sites, but are not required for you to begin your study locally.

Changes and/or additions to your study that may require additional agreement(s) or revisions to existing agreement(s) must be communicated to the UOHI Legal Affairs. This should be undertaken simultaneously with any related OHSN-REB amendment submission.

Changes and/or additions to your study that affect various hospital/institution departments (e.g., pharmacy, Department of Medical Imaging, EORLA, EEG, etc.) must be communicated to the relevant departments.

As mentioned in the 'Response' tab of the Ethics application, you have 3 months from the date of initial OHSN-REB approval to submit French documents including the translation certificate to OHSN-REB through the Translated Documents section of the ethics application (if applicable).

Should you have any questions, please contact REBadministration@ohri.ca

Sent by OHSN-REB Administration on behalf of:

Jennifer Knudson, MSc, CCRP
Manager, Office of Clinical Research and Compliance
University of Ottawa Heart Institute

Civic Campus, Box 675, 725 Parkdale Avenue, Ottawa, Ontario, K1Y 4E9
613-798-5555 extension 16719 Fax : 613-761-4311 http://www.ohri.ca/ohsn-reb

Appendix Q: University of Ottawa Office of Research Ethics and Integrity Letter of administrative approval

18/03/2025

Université d'Ottawa
Bureau d'éthique et d'intégrité de la recherche

University of Ottawa
Office of Research Ethics and Integrity

Lettre d'approbation administrative l Letter of administrative approval

Numéro de dossier / Ethics File Number	H-02-25-11335
Titre du projet / Project Title	COMPARING VO2 PEAK VALUES of EXERCISE TESTING PROTOCOLS FOR FEMALES AND MALES WITH CAD (PACED)
Type de projet / Project Type	Thèse de maîtrise / Master's thesis
CÉR primaire / Primary REB	Réseau de science de la santé d'Ottawa (RSSO) / Ottawa Health Science Network (OHSN)
Statut du projet / Project Status	Approuvé / Approved
Date d'approbation (jj/mm/aaaa) / Approval Date (dd/mm/yyyy)	18/03/2025
Date d'expiration (jj/mm/aaaa) / Expiry Date (dd/mm/yyyy)	19/11/2025

Équipe de recherche / Research Team

Chercheur / Researcher	Affiliation	Role
Jennie WONG	École des sciences de l'activité physique / School of Human Kinetics	Chercheur Principal / Principal Investigator
Jennifer REED	Département d'épidémiologie et santé publique / Department of Epidemiology and Public Health	Superviseur / Supervisor

Conditions spéciales ou commentaires / Special conditions or comments:

OHSN REB Protocol ID: 20230327-01H

550, rue Cumberland, pièce 154
Ottawa (Ontario) K1N 6N5 Canada

550 Cumberland Street, Room 154
Ottawa, Ontario K1N 6N5 Canada

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www.recherche.uottawa.ca/deontologie l www.recherche.uottawa.ca/ethics

18/03/2025

Université d'Ottawa

Bureau d'éthique et d'intégrité de la recherche

University of Ottawa

Office of Research Ethics and Integrity

L'Université d'Ottawa a signé une Entente, conforme aux exigences de la plus récente version de l'EPTC et tout autre règlement ou législation applicable, permettant au CÉR ci-haut nommé d'être désigné comme CÉR primaire pour les projets de recherche où

1) les activités principales de recherche sont menées sous l'autorité ou sous les auspices de l'établissement lié au CÉR primaire et

2) Une partie du projet est également réalisé sous l'autorité ou sous les auspices de l'Université d'Ottawa.

Cette lettre confirme que l'Université d'Ottawa a autorisé que le CÉR primaire soit le CÉR officiel pour l'évaluation et la supervision de ce projet de recherche. Ceci n'est pas une approbation éthique.

Afin de nous aider à garder votre dossier à jour, veuillez soumettre une copie de toutes demandes de modification, renouvellement d'approbation éthique etc. soumis à et approuvé par le CÉR primaire dès qu'elles sont disponibles.

Cette approbation administrative est valide pour la durée indiquée ci-haut et est sujette aux conditions énumérées dans la section intitulée « Conditions spéciales ou commentaires ».

The University of Ottawa has signed an Agreement, compliant with current TCPS guidelines and any other applicable guidelines or legislation regarding multisite review, allowing the REB named above to serve as Board of Record (BoR) for research projects where

1) the main research activities are conducted within the auspices or jurisdiction of the BoR's institution and

2) parts of the project are also conducted under the jurisdiction or auspices of the University of Ottawa.

This letter confirms that the University of Ottawa has authorized the REB named above to serve as Board of Record for the review and oversight of this research project. This is not an REB approval.

In order to help us keep your file up to date, please submit a copy of all amendment requests, project renewals or any other changes submitted to and approved by the BoR, as they become available.

Administrative approval is valid for the period indicated above and is subject to the conditions listed in the section entitled «Special conditions or comments».

Catherine PAQUET
Directeur / Director
Pour/For **Daniel LAGAREC** Président(e) du/ Chair of the **Comité d'éthique de la recherche en sciences de la santé et sciences / Health Sciences and Sciences Research Ethics Board**

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550 Cumberland Street, Room 154
Ottawa, Ontario K1N 6N5 Canada

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Appendix R: MSc Timeline

Table 5. M.1 Detailed timeline for the completion of MSc

Event	Date
Thesis Proposal Defence	April 5th, 2023
Ethics submission to UOHI/ TOH REB	May 20, 2023
Ethics Board Meeting Presentation	June 14, 2023
Review Letter #1 received from the REB	July 10, 2023
Response Letter #1 submitted to REB	July 24, 2023
Review Letter #2 Received from the REB	September 7, 2023
Response Letter #2 submitted to REB	September 20, 2023
Review Letter #3 received from REB	October 18, 2023
Response Letter #3 submitted to REB	October 24, 2023
REB approval attained	November 9, 2023
New Metabolic Cart (Parvo) Training	September 28, 2023 – December 5, 2023
Lactate Device Arrival → many delays to purchase order generation and ability to ship to Canada → additional delays from the purchasing company	April 24, 2024
1st PACED Mock CPET	April 29, 2024
1st PACED Patient Visit	May 16, 2024
2nd PACED Patient Visit	May 20, 2024
20th patient Visit #4 Completed	November 20th, 2024