INTERVAL EXERCISE IN CORONARY ARTERY DISEASE

EFFECTS OF ACUTE AND CHRONIC LOW-VOLUME HIGH-INTENSTITY
INTERVAL EXERCISE ON CARDIOVASCULAR HEALTH IN PATIENTS WITH
CORONARY ARTERY DISEASE

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TITLE: Effects of acute and chronic low-volume high-intensity interval
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Abstract

The merits of low-volume high-intensity interval exercise (HIT) have been established in healthy populations; however, no studies have examined this exercise prescription in patients with coronary artery disease (CAD). The present thesis examined the acute and chronic effects of HIT in patients with CAD.

The first study demonstrated transient improvements in brachial artery endothelial-dependent function, assessed using flow-mediated dilation (FMD), 60-minutes following a single bout of either HIT or moderate-intensity endurance exercise (END) in habitually active patients. The second study demonstrated no effects of training status on the acute endothelial responses to exercise; following 12-weeks of either HIT or END training. However, there was a significant reduction in endothelial-independent function immediately post-exercise, at both pre- and post-training, which requires further examination. The third study demonstrated comparable increases in fitness and resting FMD following 12-weeks of END and HIT, lending support to the notion that favorable adaptations are obtainable with a smaller volume of exercise. Lastly, the fourth study demonstrated no change in heart rate recovery following 12-weeks of END and HIT. However, pre-training heart rate recovery values reported by our sample were in a low risk range, which suggests training induced improvements may only be achievable in populations with attenuated pre-training values.

The results of this thesis provide preliminary evidence supporting the use of HIT in patients with CAD. The findings of favorable transient and chronic improvements following HIT are notable, especially given the HIT protocol involves less time and work

than END, which was modeled after the current exercise prescription in cardiac rehabilitation. Further investigations are necessary, including the assessment of additional physiological indices, the feasibility and adherence to HIT, the inclusion of CAD populations with co-morbidities including heart failure and diabetes, as well as other forms of HIT training including HIT combined with resistance training.

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List of Abbreviations and Symbols

ACE	angiotensin converting enzyme
ACh	acetylcholine
AIT	aerobic interval training
AMS	arterial measurement system
AUC	area under the curve
BF	blood flow
BMI	body mass index
BP	blood pressure
bpm	beats per minute
CABG	coronary artery bypass graft
CAD	coronary artery disease
CVD	cardiovascular disease
DBP	diastolic blood pressure
DICOM	Digital Imaging and Communications in Medicine
dmax	maximum systolic diameter
dmin	minimum diastolic diameter
ECG	electrocardiogram
EDD	end-diastolic diameter
END	moderate-intensity endurance exercise
eNOS	endothelial nitric oxide synthase
FMD	flow-mediated dilation
HIT	high-intensity interval exercise
HR	heart rate
HRR	heart rate recovery
IMT	intima-media thickness
LD	lumen diameter
LDL	low-density lipoprotein
L-NMMA	NG-monomethyl-L-arginine
MAP	mean arterial pressure
MBV	mean blood velocity
MI	myocardial infarction
NO	nitric oxide
NTG	nitroglycerin
PCI	percutaneous coronary intervention
PP	pulse pressure
PPO/PO$_{peak}$	peak power output
RER	respiratory exchange ratio
RH	reactive hyperemia
RPE	rating of perceived exertion
rpm	rotations per minute
SBP	systolic blood pressure

SD	standard deviation
VO_2max	maximal oxygen consumption
VO_2peak	peak oxygen consumption
VSMC	vascular smooth muscle cell

List of Original Manuscripts

This thesis, presented in sandwich format, is based on the following four original manuscripts.

1. Currie, K.D., McKelvie, R.S., MacDonald, M.J. Flow-mediated dilation is acutely improved following high-intensity interval exercise. Medicine & Science in Sports & Exercise. 2012; 44(11): 2057-64.

2. Currie, K.D., McKelvie, R.S., MacDonald, M.J. Brachial artery endothelial responses to acute exercise and chronic training in patients with coronary artery disease. In preparation for submission to the Journal of Applied Physiology (October 2012).

3. Currie, K.D., Dubberley, J.B., McKelvie, R.S, MacDonald, M.J. Low-volume high-intensity interval training in patients with coronary artery disease. In review. Medicine & Science in Sports & Exercise (August 2012).

4. Currie, K.D., Rosen, L.M., McKelvie, R.S., MacDonald, M.J. Heart rate recovery is unchanged in patients with coronary artery disease following 12-weeks of high-intensity interval and moderate-intensity endurance exercise training. Submitted to Applied Physiology, Nutrition, and Metabolism (September 2012).

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1. Currie, K.D., McKelvie, R.S., MacDonald, M.J. Flow-mediated dilation is acutely improved following high-intensity interval exercise. Medicine & Science in Sports & Exercise. 2012; 44(11): 2057-64.

   K.D. Currie's role: study design and coordination; author of ethics application; recruited participants; collected, analyzed, and interpreted all data; primary author of the manuscript

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1.0 INTRODUCTION

Cardiovascular disease (CVD), which encompasses diseases affecting the heart and vasculature, is the leading cause of death worldwide (Mathers et al. 2009). In Canada, CVD is the leading cause of death in women, and second leading cause of death in men (2011), affecting approximately 4.2% of Canadian females and 5.3% of Canadian males over the age of 12 (2009). Coronary artery disease (CAD) is the most common form of CVD, attributing to approximately 54% and 12.2% of CVD deaths in Canada (2011) and worldwide (Mathers et al. 2009), respectively. CVD is the primary cause of hospitalization in Canada (2009), and is estimated to cost the Canadian economy more than $20.9 billion per year in costs associated with mortality, hospitalization, medications, and long-term disability. It is anticipated this number will continue to rise, reaching $28.3 billion by 2020 (Thériault et al. 2010). Consequently, CVD is and will remain, a major burden on Canadian citizens.

Exercise training has been shown to be effective in the primary and secondary prevention of CVD morbidity and mortality (Wannamethee and Shaper 2001). Current cardiac rehabilitation guidelines recommend moderate-intensity endurance exercise (END) (Stone et al. 2009). Despite the effectiveness of this type of exercise training, patient compliance to exercise programs is low, most notably due to a lack of time (Barbour and Miller 2008). Interval exercise training has gained considerable attention as an alternative form of exercise training for patients with CAD (Cornish et al. 2011); however, the interval exercise programs examined to date have employed isocaloric or isovolumetric protocols, where the duration of the interval protocol is comparable to the

END protocol. Time-efficient, low-volume high-intensity interval exercise (HIT) has been shown to elicit comparable physiological adaptations to END in healthy populations (Hood et al. 2011; Little et al. 2010); however, this type of training has yet to be examined in populations with CAD.

The overall purpose of this review of literature will be to discuss the role of exercise interventions in the treatment of CAD. A brief background on CAD will be provided including a discussion of coronary artery anatomy, the pathophysiology of CAD, and an overview of traditional CAD risk factors. Details will be provided on emerging non-traditional risk factors. The primary focus of this section will be endothelial function. Indices of cardiorespiratory fitness, carotid artery indices, and heart rate indices will then be reviewed. The remainder of the literature review will discuss the role of exercise interventions in the treatment of CAD, and their impact on traditional and non-traditional risk factors. The currently accepted exercise prescription in cardiac rehabilitation will be outlined and, interval exercise training will be discussed as a potential novel treatment strategy for patients with CAD.

2.0 REVIEW OF LITERATURE

2.1 Coronary Artery Disease (CAD)

As the name implies, CAD is a disease of the coronary arteries, which are responsible for supplying oxygenated blood to the cardiac muscle of the heart. CAD is defined as the presence of atherosclerotic plaques within the coronary arteries either resulting in the narrowing (stenosis) or occlusion of the artery. Coronary blood flow is divided between the right and left coronary arteries, which provide blood to their respective sides of the heart. Each artery branches into additional arteries, which are responsible for supplying oxygenated blood to a specific section of the heart. Therefore, reduced or occluded blood flow through any of these arterial segments could have deleterious effects on the cardiac muscle, and cardiac function.

2.1.1 Coronary Artery Anatomy

Coronary arteries are composed of 3 layers: the tunica intima, tunica media, and tunica adventitia. The tunica adventitia is the outmost layer, which is primarily composed of collagen fibers, interlaced with bands of elastic fibers. The collagen fibers help to create a rigid sheath around the artery, which functions to anchor the vessel as well as prevent it from over distending. The middle layer is referred to as the tunica media. It contains concentrically arranged layers of vascular smooth muscle cells (VSMCs) embedded in a network of connective tissue. The primary role of the tunica media is to elicit vasoconstriction or vasodilation of the artery via the contraction or relaxation of the VSMCs. The external and internal elastic membrane describe the thin layer of elastic fibers which line the border between the media and adventitia, and media and tunica

intima, respectively. The media is also connected to these layers by collagen fibers. The

tunica intima is the innermost layer of the artery. It is composed of the endothelium, a

thin layer of endothelial cells that act as the interface between the artery and the blood,

and a sub-endothelial layer of connective tissue (Humphrey and McCulloch 2003).

2.1.2 The Pathophysiology of CAD

The "response-to-injury" hypothesis describes the initiation of the atherosclerotic

cascade (Ross et al. 1977). Briefly, injury to the endothelium, via chemical or mechanical

factors, increases the susceptibility of the arterial wall to infiltration by low-density

lipoproteins (LDL). LDL infiltration, as well as the initial endothelial injury, triggers an

inflammatory response leading to leukocyte infiltration, and the transformation of

monocytes to macrophages. Foam cells are formed when highly oxidized LDL are

engulfed by sub-endothelial macrophages. Vascular smooth muscle migration from the

media to intima layer advances the atherosclerotic cascade to the formation of fatty

streaks. Lastly, fibrous plaques are formed by the accumulation of extracellular lipid (via

oxidized LDL) and vascular smooth muscle content, as well as the degradation of the

extracellular matrix (Ross et al. 1977).

2.1.3 Traditional Risk Factors for CAD

The incidence of CVD is associated with risk factors, a term coined by Dr. Thomas

Dawber during his work with the Framingham Heart Study (Levy 1981). The study

followed over 5000 men and women free from CVD for 24 years to determine the

relationship between indices, termed risk factors, and the development of CVD. Since

then, risk factors have been divided into non-modifiable and modifiable categories. Non-

modifiable risk factors cannot be influenced by medical or lifestyle interventions, and can

include age, male sex, and family history. Conversely, modifiable risk can be altered by

medical and lifestyle interventions. The American Heart Association has identified 6

modifiable risk factors for CAD including hypertension, hypercholesterolemia, physical

inactivity, diabetes, overweight and obesity, and tobacco smoking (Lloyd-Jones et al.

2009).

Evidence suggests changes in traditional risk factors only account for

approximately 60% of the risk reduction observed with physical activity or exercise

(Mora et al. 2007), leaving the remaining 40% unaccounted for. Therefore, it is not

surprising that a series of non-traditional risk factors for CAD have emerged. Indices of

endothelial function, cardiorespiratory fitness, carotid artery indices, and heart rate

indices will be discussed in more detail as possible non-traditional risk factors for CAD.

The primary focus will be endothelial function.

2.2 Endothelial Function

Green at al. (2008) suggested the remaining 40% of risk reduction observed with

exercise might be attributed to vascular adaptations. In particular, exercise causes

repeated increases in shear stress on the endothelium in the arterial tree, which may elicit

favorable adaptations. As described above, the endothelium is a thin layer of cells lining

the inside of the artery at the lumen interface. The role of the endothelium in vasodilation

was first documented in 1980. In their highly publicized study, Furchgott and Zawadzki demonstrated acetylcholine (ACh) mediated relaxation of prepared rabbit thoracic aorta rings was abolished when the endothelial layer was denuded (Furchgott and Zawadzki 1980). Their work revealed the presence of an endothelial-derived substance, released in response to ACh activation of the muscarinic receptors, which caused relaxation of the VSMCs. This factor was later identified by Ignarro et al. (1987) as the potent vasodilator, nitric oxide (NO). NO is formed in endothelial cells from the conversion of the amino acid, L-arginine, to an oxidized nitrogen atom (NO), and L-citrulline. The NO pathway is displayed in Figure 1. The reaction is catalyzed by the enzyme endothelial nitric oxide synthase (eNOS), which can be activated by shear stress, via membrane bound mechanoreceptors (Corson et al. 1996), or by receptor activation by ACh or bradykinin (Moncada and Higgs 1993). Once generated, NO is capable of diffusing to the vascular smooth muscle cells, where it induces smooth muscle relaxation.

Endothelial function can be assessed by measuring the change in arterial diameter in response to hormonal and physical influences. Assessments can be made invasively using intravascular ultrasound, or non-invasively using conventional ultrasound. Endothelial-dependent dilation describes vasodilation dependent on the formation of endothelial-derived substances, such as NO. Endothelial-independent dilation describes vasodilation not dependent on the endothelium, and is assessed using an exogenous vasodilator, such as nitroglycerin (NTG), which bypasses the endothelial layer and acts directly on the vascular smooth muscle layer. Employing a combination of endothelial-

dependent and –independent assessments in research investigations is pivotal to

providing a comprehensive understanding of the regulation of endothelial function.
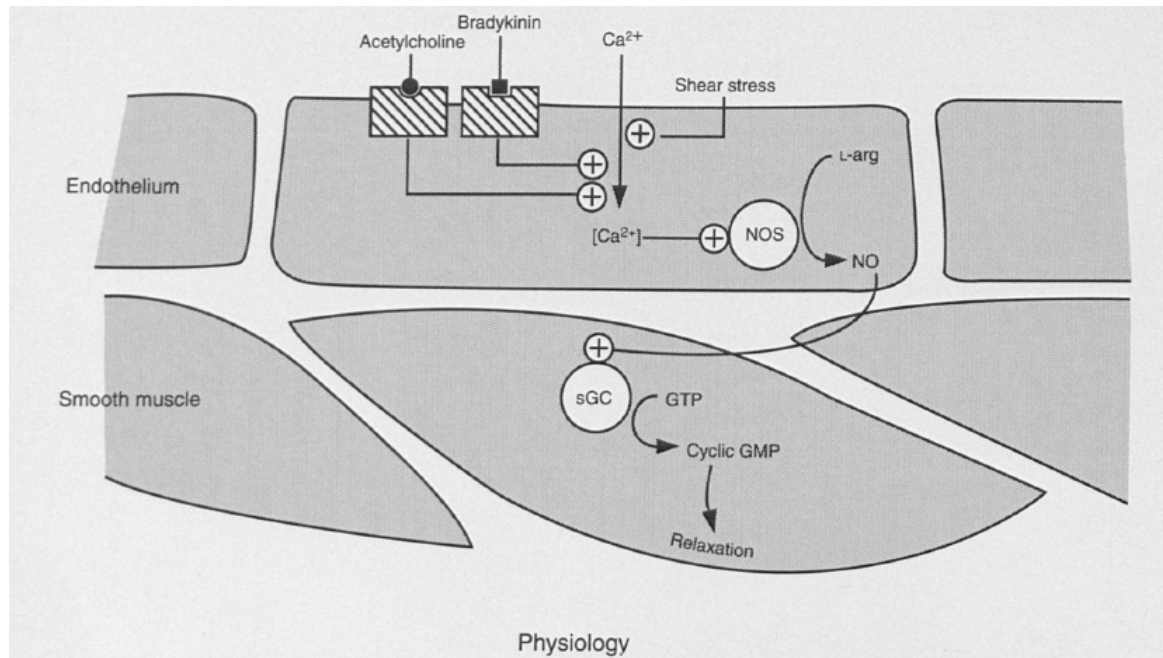
Figure 1. Shear stress or receptor activation of vascular endothelium by bradykinin or acetylcholine results in an influx of calcium. Reproduced with permission from (Moncada and Higgs 1993), Copyright Massachusetts Medical Society.

2.2.1 Endothelial-Dependent Assessments: Flow-Mediated Dilation (FMD)

Intravascular ultrasound assessments are useful because they provide access to

arteries inaccessible by conventional ultrasound. Given the invasive nature of the

intravascular ultrasound, the technique has limited use in non-clinical research

environments. Consequently, non-invasive assessments using conventional ultrasound

have been established. Flow-mediated dilation (FMD) is the most widely used technique

for the non-invasive assessment of endothelial-dependent function.

The FMD technique is based on the principle that an increase in blood flow through an artery increases the shear stress forces exerted on the endothelium, which in turn activates the mechanoreceptors and elicits the production of NO and subsequent dilation of the artery. First described by Celermajer and colleagues in 1992, the FMD technique involved inflation of a pneumatic tourniquet on the thigh above systolic blood pressure for a period of 4-5 minutes (Celermajer et al. 1992). Reactive hyperemia describes the increase in blood flow and shear stress in the artery upon cuff release. Celermajer et al. used longitudinal ultrasound images of the femoral artery collected at baseline and following cuff deflation to determine the change in diameter in response to the reactive hyperemic stimulus. At the time, it was assumed the FMD technique was assessing endothelial-dependent, NO-mediated vasodilation. This was later confirmed by Joannides et al. (1995) who demonstrated the abolishment of flow-dependent dilation, or FMD, in the presence of the NO synthase inhibitor NG-monomethyl-L-arginine (L-NMMA). While this study examined the radial artery, the same responses have been demonstrated in the brachial (Lieberman et al. 1996) and femoral (Kooijman et al. 2008) arteries. However, there is evidence to suggest FMD may not solely be attributed to NO pathways (Tschakovsky and Pyke 2005); therefore, results should be interpreted with caution.

2.2.1.1 Technical Aspects of the FMD Technique

Since its inception, countless efforts have been made to standardize the FMD technique (Corretti et al. 2002; Harris et al. 2010; Pyke and Tschakovsky 2005; Thijssen et al. 2011). The most recent guidelines were published in 2011, and highlight the

historical progression of the FMD technique to its current application. Issues requiring

consolidation included the placement of the occlusion cuff, the duration of the ischemic

period, the duration of post-occlusion measurements, and data analysis (Thijssen et al.

2011). The current recommendations for NO-mediated endothelial-dependent

assessments recommend distal cuff placement (Doshi et al. 2001) above systolic blood

pressure for a period of 5-minutes (Mullen et al. 2001). Historically, post-occlusion

measurements were collected for 60 seconds following cuff release (Celermajer et al.

1992); however, time to peak dilation can vary depending on the sample population.

Therefore, current guidelines recommend post-occlusion measurements for a minimum of

3 minutes (Black et al. 2008; Thijssen et al. 2011).

     FMD can be assessed in any conduit or resistance artery; however, the brachial

artery has been shown to be an accepted surrogate for the coronary arteries, which is

relevant for populations with CAD. Relationships between coronary and brachial artery

endothelial function have been demonstrated using ACh and FMD techniques,

respectively in individuals with (Anderson et al. 1995) and without CAD (Teragawa et al.

2005). While there is merit in demonstrating the magnitude of endothelial responses is

comparable between arteries, ACh and flow-mediated stimuli activate the endothelium

via differing mechanisms. A more practical study was conducted by Takase et al. (1998)

in a patient population with suspected CAD. In their study, adenosine triphosphate was

infused in the proximal portion of the coronary arteries to elicit increased downstream

blood flow. They demonstrated a strong correlation between flow-mediated increases in

coronary artery diameter and FMD of the brachial artery, which provides support for the

use of brachial artery FMD as a surrogate measure of coronary artery endothelial function.

2.2.1.2 FMD Analysis

Arterial diameter dimensions for the FMD technique can be obtained using B-mode ultrasound or duplex ultrasound when permitted. Duplex ultrasound enables the simultaneous collection of arterial diameters using B-mode ultrasound, and blood velocity measurements using pulsed-wave Doppler ultrasound. The relevance of blood velocity measurements is described later. Arterial diameters can be analyzed at end-diastole, or throughout the entire cardiac cycle (Kizhakekuttu et al. 2010) to determine the pre-occlusion, and peak post-occlusion diameters using ultrasonic calipers or edge-tracking software when applicable. The FMD response should be reported in absolute and relative terms (Corretti et al. 2002), described in equations (1) and (2) respectively.

(1) $\text{Absolute FMD (mm)} = (\text{Peak Post - Occlusion Diameter}) - (\text{Pre - Occlusion Diameter})$

(2) $\text{Relative FMD (\%)} = \left(\dfrac{\text{Absolute FMD}}{\text{Pre - Occlusion Diameter}} \right) \times 100$

Blood velocity measurements are an important element of the FMD response, as they can be used to quantify the shear stress stimulus obtained from the application and subsequent release of the occlusion cuff. Mean blood velocity (MBV) can be used to calculate blood flow and shear rate, described in equations (3) and (4) respectively.

(3) Blood Flow $(ml \cdot min^{-1}) = \Pi r^2 \times MBV$

(4) Shear Rate $= \left(\dfrac{8 \text{ x MBV}}{\text{Lumen Diameter}} \right)$

Pyke and Tschakovsky (2005) made an interesting observation that despite the name *flow*-mediated dilation, the increased shear stress on the endothelium, rather than increased flow, is the stimulus for vasodilation. Shear rate is considered an adequate surrogate for shear stress, and should be included in FMD assessments. Pyke et al. (2004) previously reported that a smaller arterial diameter experiences a larger shear stress stimulus, and therefore a greater FMD response compared to an artery with a larger baseline lumen diameter. However, when shear rate was controlled to create a uniform stimulus between different sized arteries, the FMD response was no longer related to baseline diameter. Thus, it was concluded that FMD should be normalized to the shear rate to account for the magnitude of stimulus received by distinct vessels (Pyke and Tschakovsky 2005). The shear rate should be calculated as the shear rate area under the curve (AUC) until the peak post-occlusion diameter (Black et al. 2008). Normalized FMD is calculated as the ratio of the relative FMD to the AUC. Recent evidence, however, suggests the process of normalization violates established statistical assumptions for normalization, and therefore may not be an appropriate calculation (Atkinson et al. 2009). There is no consensus on the use of normalized FMD, therefore caution should be used when calculating and interpreting normalized FMD values, particularly for arteries of different caliber. Normalization may be suitable for within-subject comparisons that demonstrate strong relationships between FMD and shear rate (Thijssen et al. 2011).

Regardless, shear rate AUC should be presented as a separate value as an index of the

FMD stimulus.

2.2.2   Endothelial-Independent Assessments

Following its production, NO diffuses to the VSMCs where it elicits vasodilation.

Consequently, the VSMCs play a crucial role in endothelial-dependent dilation.

Endothelial-independent assessments are important because they assess the functioning of

VSMCs using an exogenous NO donor, such as NTG or sodium nitroprusside.

Assessments are typically performed after the FMD test, at least 10-minutes following

cuff release to allow the artery to return to baseline diameter (Corretti et al. 2002). A 0.4

mg dose of an exogenous donor (NTG) is used to elicit the maximal obtainable

vasodilation. Previous guidelines recommended ultrasound assessments for 3-4 minutes

following administration (Corretti et al. 2002). However, recent evidence demonstrates

peak diameter can occur past that time point (Thelen et al. 2008); therefore measurements

should be collected for 10 minutes following administration. Endothelial-independent

responses can be presented in absolute and relative terms, as described above.

2.2.3   Endothelial Dysfunction

Endothelial dysfunction is the term used to describe an impaired capacity of the

endothelium to elicit vasodilation in response to physical and hormonal influences. The

dysfunction is primarily attributed to impairments in the NO-pathway, given its role in

endothelial-dependent dilation. However, the site of dysfunction could be the VSMCs

(Adams et al. 1998), which highlights the importance of performing endothelial-independent assessments in combination with FMD assessments. As previously described, the "response-to-injury" is the most commonly accepted theory describing the initiation of the atherosclerotic cascade. Endothelial dysfunction increases the susceptibility of the endothelium to injury. Therefore, it is not surprising that atherosclerosis and endothelial dysfunction are often found to coexist. Compared to individuals with smooth coronary arteries, individuals with evidence of coronary atherosclerosis demonstrated impaired flow-mediated responses in the coronary (Cox et al. 1989) and brachial (Kaku et al. 1998; Lieberman et al. 1996) arteries. Additionally, there is evidence of impaired NO production and decreased eNOS protein expression in atherosclerotic human arteries (Oemar et al. 1998). The evidence of a relationship between impaired endothelial-independent function and the presence of atherosclerosis is less definitive, and suggests patients with CAD have either maintained (Lieberman et al. 1996; Takase et al. 2008) or impaired (Neunteufla et al. 1997; Zhang et al. 2000) endothelial-independent responses.

Several studies have demonstrated an increased risk of cardiovascular morbidity and mortality in concert with attenuated FMD values (Thijssen et al. 2011). In healthy populations, increased risk of cardiovascular events is associated with a relative FMD value $\leq 2.4\%$ for men, and $\leq 3.0\%$ for women (Yeboah et al. 2007). Patients with CAD are at an increased risk of future cardiovascular events and death with a FMD $\leq 1.9\%$ (Karatzis et al. 2006), and as high as $< 7.5\%$ (Akcakoyun et al. 2008). Additionally, Kitta et al. (2009) demonstrated that CAD patients with persistently impaired FMD values ($\leq$

5.5%) after 6-months of optimized anti-atherosclerotic therapy had an increased risk of cardiovascular events and mortality compared to patients who improved their FMD. In conclusion, the evidence suggests endothelial function may serve as a clinically relevant index, and therapeutic target, in the treatment of CAD.

2.3 Cardiorespiratory Fitness

Cardiorespiratory fitness, otherwise referred to a physical fitness or exercise capacity, is a measure of how well your body can transport oxygen to working muscles during an exercise bout, and can be assessed using sub-maximal or maximal exercise tests. Sub-maximal exercise tests can be used to predict maximal capacity; therefore while they may not represent a true measure of an individual's maximum, they are useful in populations where maximal exercise is contraindicated (Noonan and Dean 2000). Maximal tests involving the measurement of oxygen consumption, referred to as a VO_2max, are considered the gold standard for cardiorespiratory fitness assessments. Historically, the criteria for VO_2max has included: (1) a plateau in oxygen consumption despite further increase in workload, (2) heart rate within 10-15 bpm of their age predicted maximum heart rate calculated using the equation 220-age, and (3) a respiratory exchange ratio ≥ 1.10 (Howley et al. 1995). These criteria are usually not satisfied, especially in untrained or clinical populations. Therefore peak oxygen consumption (VO_2peak) is commonly reported in lieu of VO_2max. VO_2peak can be presented relative to body mass ($ml \cdot kg^{-1} \cdot min^{-1}$) to allow the comparison of fitness levels between individuals of different sizes.

Fitness decreases with age (Franklin et al. 2000); however, physical activity can help to ameliorate the decline. Tanaka et al. (2000) performed a cross-sectional comparison of cardiorespiratory fitness levels across age cohorts and physical activity groups. In the middle-aged cohort, recreationally active and exercise trained men reported higher fitness levels than sedentary age-matched males. In elderly males, only endurance trained individuals reported significantly higher fitness levels than recreationally active and sedentary males, which suggests an increased volume of exercise is necessary in old age to infer the benefits of improved fitness. Interestingly, the fitness levels reported in the middle-aged and elderly cohorts were lower than the young cohort, regardless of physical activity level. Therefore, it appears physical activity is only capable of attenuating the age-associated reduction in fitness. This is further supported by Kasch et al. (1995) who reported a 5% per decade decline in fitness in physically active men over a 28-year period, compared to detrained men who experienced a 19% per decade decline in fitness.

A meta-analysis of population-based studies revealed physical activity and fitness levels have different risk reductions (Williams 2001), which suggests fitness should be considered as a CVD risk factor distinct from the traditional risk factor of physical activity. Traditional CVD risk factors are associated with low fitness levels in adolescent and adults (Carnethon et al. 2005). Additionally, several studies have demonstrated increased risk of cardiovascular events (Laukkanen et al. 2004; Talbot et al. 2002) and cardiovascular mortality (Blair et al. 1996; Laukkanen et al. 2004) in populations with lower fitness levels, even when controlling for traditional risk factors. Finally, Kavanagh

et al. (2002) demonstrated VO$_2$peak is the single best predictor of death in cardiac

patients. Therefore, cardiovascular fitness should be considered as a relevant risk factor

for CVD morbidity and mortality.

2.4 Carotid Artery Indices

2.4.1 Arterial Stiffness

The carotid arteries share the same anatomical layers as the coronary arteries

described above. Arterial stiffness describes a decreased capacity of a vessel to distend in

responses to increases in pressure or volume. It occurs naturally with age (Tanaka et al.

2000; Vaitkevicius et al. 1993), most commonly in large elastic arteries including the

aorta and carotid arteries, and has been attributed to modifications in the structural

composition of the artery. Fragmented elastin fibers and the accumulation of collagen in

the medial and adventitial layers make the vessel more rigid and less likely to distend.

These modifications can be caused by a myriad of factors including increased luminal

pressure, inflammation, and advance glycation end products (Zieman et al. 2005).

Associations between collagen synthesis and degradation and arterial stiffness have been

demonstrated in normotensive and hypertensive individuals (McNulty et al. 2006) , and

patients with dilated cardiomyopathy (Bonapace et al. 2006). However, this is a relatively

new area of research, and further work is needed to delineate the relationship between

collagen turnover and arterial stiffness.

Arterial stiffness can be assessed invasively using intravascular ultrasound and

pressure sensors, and non-invasively using conventional ultrasound, applanation

tonometry, photoplethysmographic sensors, or magnetic resonance imaging. Arterial

stiffness measurements can also be made regionally or locally. Aortic pulse wave velocity

is a regional index of arterial stiffness, and is currently considered the gold standard

technique for non-invasive assessments of arterial stiffness. It is a measure of the speed of

the arterial pulse wave between the carotid and femoral arterial sites (O'Rourke et al.

2002), which is commonly assessed using applanation tonometry. In theory, the faster the

pulse wave velocity, the stiffer the arterial segment. In apparently healthy men and

women, an aortic pulse wave velocity ≥ 11.8 m·s^{-1} is associated with a 48% increased risk

of first major CVD event (Mitchell et al. 2010). Additional evidence suggests an increase

of 1 m·s^{-1} corresponds to a 15% increased risk of cardiovascular mortality (Vlachopoulos

et al. 2010). While there is obvious merit in the assessment of pulse wave velocity in at-

risk populations, unpublished observations from our laboratory suggests poor day-to-day

reliability of pulse wave velocity assessments in elderly individuals with and without

CAD (Souza-Barros et al. 2011). Therefore, future research needs to establish the

reliability of these assessments in clinically relevant at-risk populations.

Local arterial stiffness measurements are commonly assessed using a combination

of B-mode ultrasound for the collection of arterial diameters, and applanation tonometry

for the simultaneous assessment of local arterial pressures. There are a number of indices

of local arterial stiffness including, but not limited to distensibility, compliance, and

stiffness index (O'Rourke et al. 2002). Distensibility takes into consideration the initial

dimensions of the artery, and is a measure of the relative change in volume for a given

pressure. It is described in equation (5):

$$(5) \ \text{Distensibility} \ = \ \frac{\Pi\left(\dfrac{\text{dmax}}{2}\right)^2 - \Pi\left(\dfrac{\text{d min}}{2}\right)^2}{\Pi\left(\dfrac{\text{d min}}{2}\right)^2 \times PP}$$

where dmax is the maximal systolic diameter, dmin in the minimum diastolic diameter, and PP is the carotid pulse pressure. A comparison of regional and local arterial stiffness measurements demonstrate a strong correlation between aortic pulse wave velocity and carotid artery distensibility in healthy individuals (Paini et al. 2006). The strength of the correlation is weakened with an increasing number of co-morbidities, suggesting aortic and carotid stiffness does not occur proportionally in diseased states. Taken together, the evidence suggests that indices of arterial stiffness should be interpreted with caution, and that local and regional arterial stiffness measurements should be not be used synonymously in clinical populations. However, local arterial stiffness measurements, specifically at the carotid artery, are still relevant in clinical populations. Decreased carotid artery distensibility is associated with the presence of atherosclerotic plaques in the aorta and carotid arteries (van Popele et al. 2001). Additionally, coronary artery distensibility is impaired in coronary artery sites with occult atherosclerosis (Nakatani et al. 1995), which suggests an association between local artery stiffness and atherosclerosis.

Compared to regional arterial stiffness, the literature on the relationship between indices of local arterial stiffness and cardiovascular risk are not as well defined. In patients with manifest arterial disease, carotid artery stiffness was not associated with an increased risk of future cardiovascular events or death (Dijk et al. 2005). Additionally, asymptomatic individuals demonstrated no relationship between indices of carotid artery

stiffness and mortality (which was primarily attributed to CAD) (Stork et al. 2004). Conversely, several studies demonstrate associations between decreased carotid artery distensibility and increased risk of cardiovascular events (Barenbrock et al. 2002; Tsivgoulis et al. 2006). Thus, future research is warranted on the association between local arterial stiffness and CVD risk.

2.4.2 Intima-Media Thickness (IMT)

Carotid artery intima-media thickness (IMT) describes the thickness of the arterial wall from the lumen-intima interface to the media-adventitial interface, and can be measured using B-mode ultrasound. IMT increases with age (Juonala et al. 2008), and is elevated in asymptomatic individuals who present with traditional risk factors for CVD (Urbina et al. 2002). The research on the relationship between IMT and cardiovascular risk is plentiful, with several systematic review articles highlighting their main findings. In sum, an increase in IMT of 0.1 mm has been shown to increases one's risk of myocardial infarction (MI) and stroke by 10-15% and 13-18% respectively (Lorenz et al. 2007). Additionally, increased cardiovascular risk has also been described for IMT > 0.75 mm (Aminbakhsh and Mancini 1999) and > 1 mm (Bots et al. 2002). The main limitation in this area of literature is the measurement technique, as different laboratories assess carotid IMT using different standards (Kanters et al. 1997). Therefore, caution should be exercised when interpreting IMT results. Regardless, there is clear evidence linking increased IMT and future risk for cardiovascular morbidity and mortality; therefore, the examination of this index in response to therapeutic strategies is warranted.

2.5 Heart Rate Indices

2.5.1 Resting Heart Rate

Resting heart rate is considered an independent cardiovascular risk factor. In healthy individuals, increased resting heart rate was associated with cardiovascular and coronary death (Kannel et al. 1987). This relationship is further confirmed when controlling for confounding cardiovascular risk factors (Kristal-Boneh et al. 2000). Additionally, resting heart rate is associated with increased risk of cardiovascular death in patients with CAD (Diaz et al. 2005). Recent evidence suggests for each increment in resting heart rate of 10 bpm, there is approximately an 18% and 10% increased risk of death due to CAD for women and men, respectively (Nauman et al. 2010).

2.5.2 Heart Rate Recovery

Heart rate recovery is defined as the immediate decline in heart rate following an exercise bout. It provides an index of sympathetic withdrawal and parasympathetic reactivation following exercise (Lahiri et al. 2008). While it is not considered a cardiovascular risk factor, an attenuated heart rate recovery is predictive of mortality in populations with CAD (Vivekananthan et al. 2003). Previous literature supports the use of maximal (Cole et al. 1999) or sub-maximal exercise bouts (Cole et al. 2000), with measurements occurring at 1 and 2-minutes post-exercise, although 2-minute measurements have been shown to have the strongest association with mortality risk (Shetler et al. 2001). Currently, there is no consensus on the clinical cut off value. The most commonly reported heart rate recovery value is < 12 bpm at 1-minute post-exercise

(Cole et al. 1999). However, other studies have demonstrated increased mortality risk with heart rate recovery values of < 25 bpm after 1-minute (Jouven et al. 2005), and < 22 bpm (Lahiri et al. 2008) and ≤ 42 bpm (Cole et al. 2000) after 2-minutes post-exercise.

2.6 Exercise Training in CAD

Earlier forms of cardiac rehabilitation believed individuals who had suffered a recent cardiac event should be confined to bed rest, since the stress imposed on the heart by activities of daily living was likely to cause further harm or even death. Despite evidence of the beneficial effects of physical activity following a MI throughout the 1930-1950s, exercise-based cardiac rehabilitation programs were not formally adopted until the 1960s (1993). Since the 1960s, there has been an extensive growth in the number of studies examining the acute and chronic effects of exercise on patients with CAD in an attempt to determine the optimal cardiac rehabilitation exercise prescription.

2.6.1 Chronic Effects of Exercise: Current Cardiac Rehabilitation Exercise Guidelines

First conceptualized by Hellerstein and colleagues in the 1950s, the original exercise-based cardiac rehabilitation involved 3 stages: inpatient, immediate outpatient, and recovery and return to work (1993). Current cardiac rehabilitation guidelines refer to these stages as phase I, phase II, and phase III (ACSM 1991). Additionally, the initial exercise prescription, which involved moderate-intensity endurance exercise (END), is similar to what is currently prescribed by cardiac rehabilitation programs (ACSM 1991;

Stone et al. 2009). There have been modifications to the exercise prescription since its

inception in the 1960s, specifically, the addition of resistance exercises (McCartney and

McKelvie 1996; Stone et al. 2009). The remainder of this discussion will focus on the

END prescription of phase II cardiac rehabilitation programs.

2.6.1.1 FITT Prescription

Cardiac rehabilitation exercise prescription is commonly structured using the FITT

formula: frequency, intensity, time (or duration), and type (ACSM 1991; Stone et al.

2009). Frequency refers to how often a patient exercises. Similar to public heath

guidelines, cardiac rehabilitation programs advocate for exercise participation to occur on

most days of the week (ACSM 1991; Stone et al. 2009). During phase II of cardiac

rehabilitation, patients will typically have access to weekly-supervised exercise sessions

for a specified period of time (3-6 months) before assuming full responsibility of their

exercise participation. While exercise on most days of the week should elicit the greatest

adaptations, it is common for cardiac rehabilitation programs, and exercise-training

studies, to employ 2-3 supervised exercise sessions per week. This is supported by an 18-

year follow-up of 3500 men and women with CAD, which demonstrated a minimum of 1

exercise session per week was associated with lower all-cause mortality compared to no

weekly activity (Moholdt et al. 2008).

Intensity describes how hard the exercise is, and can be prescribed in absolute or

relative terms; however it is more frequently expressed in relative terms as a percentage

of the individual's maximal capacity. Intensity can be based on maximum heart rate and

VO$_2$peak, heart rate/VO$_2$peak reserve, or ratings of perceived exertion (RPE) (ACSM 1991; Warburton et al. 2006). Cardiac patients are recommended to work between 40-80% of their heart rate or VO$_2$peak reserve (Stone et al. 2009; Warburton et al. 2006), which is described as "somewhat hard to hard" on the Borg RPE scale (Borg 1998). Moderate-to-high intensity exercise is associated with a lower mortality risk than lower-intensity exercise in patients with CAD (Moholdt et al. 2008). Additionally, Schnohr et al. (2012) recently demonstrated that exercise intensity, rather than duration, was more important in determining all-cause and CAD mortality in approximately 5000 men and women during a 18-year follow-up. Thus, when applicable, cardiac rehabilitation programs should aim to incorporate higher-intensity exercise.

It is recommended that exercise duration lasts between 20-60 minutes (Warburton et al. 2006), with additional time for warm-up and cool-down exercises. Duration is closely linked to intensity; therefore, higher-intensity exercise can involve shorter exercise durations than low and moderate-intensity exercise sessions. Exercise progression can include either an increase in the exercise intensity or duration, with the timing of the progression dependent on the patient's progress. Lastly, the type of exercise performed can include a variety of activities, which focus on incorporating large muscle masses, including but not limited to walking, arm and leg ergometry, and machine-based stair climbing (Warburton et al. 2006). Equipment availability, and the functional capacity of the patient will dictate which activities are included in the exercise prescription.

2.6.1.2 Supporting Evidence for END

One of the most highly publicized studies supporting the use of exercise training in the treatment of CAD was performed by Hambrecht et al. (2004). In their study, 100 patients were randomized to 12-months of exercise training, or a percutaneous coronary intervention (PCI), for treatment of their CAD. At a 1-year follow-up following both interventions, the exercise-training group reported higher event-free survival rates, and greater improvements in fitness compared to the PCI group. Additionally, the exercise intervention was more cost-effective, costing approximately half of what the PCI intervention cost.

The evidence supporting END in the treatment of patients with CAD is definitive. A systematic review and meta-analysis of 48 randomized controlled trials demonstrates exercise training reduces all-cause and cardiovascular mortality, as well as modifying traditional CVD risk factors including decreasing systolic blood pressure, and cholesterol and triglyceride levels compared to the current standard of care (no exercise intervention) (Taylor et al. 2004). As previously described, modifications in traditional risk factors with exercise training do not fully account for the resulting risk reduction (Mora et al. 2007). Thus it is not surprising that evidence of modifications in non-traditional risk factors have also been observed following END training interventions.

There is convincing evidence that END training improves cardiorespiratory fitness (Giallauria et al. 2006b; Hambrecht et al. 2004; Hao et al. 2002; Luk et al. 2012; Rognmo et al. 2004; Wisloff et al. 2007) in patients with CAD. END training in CAD has also been shown to improve coronary artery endothelial-dependent function (Hambrecht et al.

2003), brachial artery FMD (Luk et al. 2012; Walsh et al. 2003), and heart rate recovery (Giallauria et al. 2006a; Giallauria et al. 2006b; Hai et al. 2010; Hao et al. 2002; Tsai et al. 2005; Wu et al. 2006). The evidence on carotid artery indices is less definitive. Two studies suggest arterial stiffness decreases with END training in patients with CAD (Edwards et al. 2004; Laskey et al. 2012); however, neither of these studies examined indices of local carotid artery stiffness. While there is evidence that individuals with cardiovascular risk factors including obesity, diabetes, hypertension, and hypercholesterolemia may experience reductions in carotid IMT with exercise training (Thijssen et al. 2012), there are no studies which have examined IMT changes with END training in patients with CAD.

2.6.1.3 Main Limitations

Despite the evidence demonstrating improved survival rates and modifications to traditional and non-traditional CVD risk factors with endurance exercise training, cardiac rehabilitation participation rates are low. In Canada and the United States, it is estimated that approximately 30% of patients with CVD are referred and enrolled in cardiac rehabilitation programs (Grace et al. 2011; Suaya et al. 2007). Additionally, for patients enrolled in cardiac rehabilitation programs, attendance declines as the duration of the program continues, reaching approximately 50% by 1-year (Barbour and Miller 2008). Taken together, the evidence suggests that 1-year following a cardiac event, only 15% of the population is actively participating in exercise-based programs for the secondary prevention of future cardiovascular events and mortality. A "lack of time" is one of the

most commonly cited barriers for low exercise participation (Barbour and Miller 2008; Evenson and Fleury 2000; Stutts 2002), while other reasons include a "lack of motivation", financial reasons, and personal or professional conflicts (Barbour and Miller 2008; Evenson and Fleury 2000). Regardless of the reason, there is a need for the development of strategies for increasing exercise program compliance in cardiac rehabilitation exercise programs.

2.6.2 Acute Effects of Exercise

The acute physiological responses to an exercise bout are commonly examined to determine the magnitude of the exercise stimulus, as well as the feasibility of the exercise prescription. Several studies have examined the acute cardiovascular responses to a single bout of exercise in healthy populations, including indices of arterial stiffness (Heffernan et al. 2007; Kingwell et al. 1997) and FMD (Harris et al. 2008; Llewellyn et al. 2012); however, there is limited evidence on the acute cardiovascular responses to exercise in patients with CAD. A few studies have compared the acute responses of steady state (endurance) and interval exercise in CVD populations, which will be in the subsequent section. The lack of acute exercise investigations in patients with CAD highlights a gap in the literature. Clinical populations are likely to respond differently to an exercise bout compared to healthy populations; therefore, further examinations on this topic are warranted.

2.6.3 Interval Exercise

Interval exercise is described as alternating bouts of higher-intensity exercise with periods of rest or lower-intensity exercise. This type of exercise has been examined extensively in healthy populations; however, there has been a recent increase in the number of studies examining the effectiveness of interval exercise training in populations with CVD.

2.6.3.1 Acute Responses to Interval Exercise

To date, there are no investigations that have examined the acute cardiovascular responses in patients with CAD during the recovery period following a single interval exercise bout. However, the acute cardiovascular responses during interval exercise have been examined in populations with CVD. Meyer et al. (1996) observed acceptable increases in indices of cardiac stress, metabolic stress, catecholamines and leg fatigue in patients with CAD and congestive heart failure during 3 different interval bouts. This was followed up by a study that demonstrated comparable increases in heart rate, systolic blood pressure, cardiac output and leg fatigue during steady-state and interval exercise in CVD patients (Meyer et al. 1998). Lastly, in an examination of interval exercise there were no post-exercise elevations in troponin T, indicating the high-intensity exercise did not elicit myocardial injury (Guiraud et al. 2011). In sum, these studies demonstrate that interval exercise does not elicit detrimental changes in cardiovascular functioning, and therefore should be considered safe for patients with CAD.

2.6.3.2 Chronic Effects of Interval Exercise

The effects of interval exercise training in patient populations with CAD have been recently reviewed (Cornish et al. 2011; Guiraud et al. 2012). The articles highlight improvements in numerous physiological indices with interval exercise training; however, this discussion will only focus on the investigations that examined the indices discussed in this literature review. These recent reviews also highlight that there are a variety of interval exercise protocols currently being employed in populations with CAD, each demonstrating favorable improvements. While there is currently no consensus on the optimal interval protocol, recent work from Guiraud et al. (2011) has suggested shorter work periods interspersed with short passive recovery periods is optimal compared to longer work periods and active recovery. The chronic effects of this interval protocol, however, have yet to be established.

Aerobic interval training (AIT) is a highly publicized investigated interval protocol that involves 4, 4-minute intervals at 80-90% of VO_2peak (85-95% of peak heart rate) separated by 3-minute recovery periods at 50-60% of VO_2peak (60-70% of peak heart rate). AIT has been shown to increase VO_2peak in patients with CAD (Munk et al. 2009) after 6-months of training. Additionally, when compared to the current exercise prescription in cardiac rehabilitation, END, AIT has been shown to elicit superior improvements in VO_2peak following 10 (Rognmo et al. 2004) and 12-weeks of training (Moholdt et al. 2012; Wisloff et al. 2007) in patients with CAD. AIT has also been shown to improve brachial artery FMD (Moholdt et al. 2012; Munk et al. 2009; Wisloff et al. 2007), decrease resting heart rate (Moholdt et al. 2012; Munk et al. 2009), improve

quality of life (Moholdt et al. 2012; Wisloff et al. 2007), and reduce PCI restenosis (Munk et al. 2009). However, there is limited evidence of modifications to traditional CVD risk factors, as AIT was unable to improve body mass index (BMI), blood pressure, and cholesterol levels (Munk et al. 2009; Rognmo et al. 2004; Wisloff et al. 2007)

Warburton et al. (2005) compared the effectiveness of combined interval and resistance exercise training to combined endurance and resistance exercise training. Both groups trained 2 days per week for 16-weeks. The interval prescription involved 30-minutes of alternating 2-minute intervals at 90% of heart rate/VO_2peak reserve separated by 2-minute recovery periods at 40%, while the endurance protocol involved 30-minutes of continuous exercise at 65% of heart rate/VO_2peak reserve. They observed comparable increases in VO_2peak; however, resting heart rate and blood pressure were unchanged. This study demonstrated the effectiveness of a different interval exercise protocol in patients with CAD.

No studies have examined the effect of interval exercise training on indices of arterial stiffness or carotid artery IMT in patients with CAD. Additionally, only one study has examined heart rate recovery in response to interval training, and reported no change in this index following 12-weeks of AIT (Moholdt et al. 2012). Regardless, it is apparent the literature on the effects of interval exercise training in populations with CAD is still developing, and that further research is necessary to examine all of the possible outcomes, as well as determine regulatory pathways. No studies to date have reported adverse events during interval training in individuals with CAD, which supports the acute exercise findings by Meyer et al. (1998; 1996). Additionally, no studies reported poor compliance

to the interval programs, which is supported by Bartlett et al. (2011) who demonstrated interval exercise was perceived to be more enjoyable than endurance exercise.

One of the major limitations of the interval exercise examinations to date is that many interval programs are designed to be isocaloric or isovolumetric when compared to traditional END programs (Rognmo et al. 2004; Warburton et al. 2005; Wisloff et al. 2007). In particular, the interval exercise prescription is either matched to an END prescription for energy expenditure or total training volume, typically resulting in a more physically demanding or longer duration interval prescription. While there is merit in this particular type of study design, increasing the duration or the difficulty of an interval exercise prescription does not appear to be advantageous given that a lack of time and motivation are common barriers to exercise compliance in cardiac rehabilitation. A shorter duration program, commonly referred to as low-volume, interval exercise prescription would be beneficial if it was capable of eliciting comparable cardiovascular adaptations as the current exercise prescription of END.

Meyer et al. (1990) demonstrated superior reductions in resting heart rate, systolic blood pressure, and rate-pressure product following 3.5 weeks of low-volume interval exercise training in patients with CAD, compared to an END training program matched for duration. Total work was higher in the END group, which suggests the interval stimulus was capable of eliciting favorable improvements in cardiovascular function despite involving less work. This early study lends support to the continued investigation of low-volume interval exercise prescriptions in patients with CAD; however, no further research has been conducted in this specific area since this investigation. Low-volume

interval exercise training has been used extensively in practical and research settings in healthy populations. Wingate protocols, which involve repeated 30-second all-out efforts, have been shown to improve VO$_2$peak (Astorino et al. 2012; Rakobowchuk et al. 2008), as well as decrease peripheral arterial stiffness and increase lower limb FMD (Rakobowchuk et al. 2008) in young healthy individuals. This particular type of training is very time efficient. When compared to traditional endurance exercise training which consisted of 4.5 hours of exercise per week, the Wingate protocol consisted of 1.5 hours per week, only 10-minutes of which was the high-intensity exercise (Rakobowchuk et al. 2008). These studies did not, however include observations of favorable changes in resting blood pressure or body composition. Additionally, the feasibility of Wingate training has been questioned. Headaches and nausea have been reported as common acute side effects. As well, the "all-out" nature of the protocol would prohibit its use in clinical populations, unless training sessions were medically supervised. Therefore, more practical low-volume interval exercise protocols are being developed and tested. Specifically, a 20-minute high-intensity interval exercise (HIT) protocol involving 10, 1-minute intervals at near maximal intensities separated by 1-minute active recovery periods has demonstrated physiological adaptations in healthy young (Little et al. 2010) and older (Hood et al. 2011) participants, as well as individuals with type 2 diabetes (Little et al. 2011), in as little as 6 exercise sessions. This type of practical, low-volume HIT training has yet to be examined in a clinical population with CAD.

In conclusion, the research on cardiovascular effects of exercise training in CAD is continuing to evolve. Recent research highlights the importance of examining the

relationship between CAD and non-traditional risk factors including brachial artery FMD, cardiorespiratory fitness, carotid artery indices, and resting heart rate and heart rate recovery. Additionally, there is growing evidence to support the continued investigation of interval exercise training in populations with CAD. While the interval training studies to date have demonstrated favorable improvements in traditional and non-traditional risk factors, most have involved higher-volume interval prescriptions. Time efficient low-volume HIT training is effective in healthy populations, but has yet to be thoroughly examined in a patient population with CAD. Future research should investigate this exercise-training model as a possible exercise prescription for cardiac rehabilitation programs.

3.0 CHAPTER 3: PURPOSE

The primary aim of the present thesis was to compare the acute and chronic effects of low-volume, high-intensity interval exercise (HIT) and the current exercise prescription in cardiac rehabilitation, higher-volume moderate-intensity endurance exercise (END), on indices of cardiovascular health in patients with CAD.

The specific aims of individual studies were:

1. To examine the effects of a single bout of HIT and END on brachial artery endothelial function in habitually active patients with CAD.

2. To examine the effects of a single bout of sub-maximal dynamic exercise on brachial artery endothelial function before, and following 12-weeks of HIT and END training in patients with CAD.

3. To compare the effects of 12-weeks of HIT and END training on cardiorespiratory fitness and resting measures of cardiovascular health in patients with CAD.

4. To compare the effects of 12-weeks of HIT and END training on heart rate recovery and acute exercise responses in patients with CAD.

4.0 CHAPTER 4: FLOW-MEDIATED DILATION IS ACUTELY IMPROVED FOLLOWING HIGH-INTENSITY INTERVAL EXERCISE

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Flow-Mediated Dilation Is Acutely Improved after High-Intensity Interval Exercise

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ABSTRACT

CURRIE, K. D., R. S. MCKELVIE, and M. J. MACDONALD. Flow-Mediated Dilation Is Acutely Improved after High-Intensity Interval Exercise. Med. Sci. Sports Exerc., Vol. 44, No. 11, pp. 2057–2064, 2012. **Purpose**: Cardiovascular disease is characterized by decreased endothelial function. Chronic exercise training improves endothelial function in individuals with cardiovascular diseases; however, the acute endothelial responses to a single bout of exercise are not consistent in the literature. This study investigated whether a single bout of moderate-intensity endurance exercise (END) and low-volume high-intensity interval exercise (HIT) on a cycle ergometer resulted in similar acute changes in endothelial function. **Methods**: Ten individuals (66 ± 11 yr) with coronary artery disease (CAD) participated in two exercise sessions (END and HIT). Endothelial-dependent function was assessed using brachial artery flow-mediated dilation (FMD) preexercise and 60 min postexercise. Brachial artery diameters and velocities were determined using Doppler ultrasound before and after a 5 min ischemic period at all time points. Endothelial-independent function was assessed using a 0.4-mg sublingual dose of nitroglycerin. **Results**: The total work performed was higher in END (166 ± 52 kJ) compared with HIT (93 ± 28 kJ) exercise ($P < 0.001$). Endothelial-dependent function improved ($P = 0.01$) after END (absolute FMD preexercise, 0.24 ± 0.18 mm; postexercise, 0.31 ± 0.24 mm) and HIT (absolute FMD preexercise, 0.25 ± 0.13 mm; postexercise, 0.29 ± 0.13 mm), with no differences between exercise conditions. A time effect for FMD normalized to the shear rate area under the curve was also observed ($P = 0.02$) after END (preexercise, 0.005 ± 0.004; postexercise, 0.010 ± 0.011) and HIT (preexercise, 0.005 ± 0.004; postexercise, 0.009 ± 0.011). Endothelial-independent function responses were unchanged after END and HIT ($P > 0.05$). **Conclusions**: HIT and END resulted in similar acute increases in brachial artery endothelial-dependent function in a population with dysfunction at rest, despite the difference in exercise intensities. **Key Words**: ENDOTHELIUM, CORONARY ARTERY DIEASE, BRACHIAL ARTERY, HEMODYNAMICS

The presence (42) and severity (10) of coronary artery disease (CAD) is associated with endothelial dysfunction, which is defined as a decreased ability of the endothelium to induce vasodilation in response to specific stimuli, and is associated with an imbalance between vasoconstrictors and vasodilators (9). Endothelial dysfunction is linked to classic risk factors for CAD including hypercholesterolemia (12), hypertension (19), inactivity (11), and obesity (3). Evidence also suggests endothelial dysfunction is a precursor to the atherosclerotic cascade (34). Endothelial function, therefore, is an important therapeutic target and risk assessment marker for individuals with CAD. Brachial artery endothelial function is an accepted noninvasive surrogate for coronary artery endothelial function

(35) and can be assessed using the well-established technique called flow-mediated dilation (FMD) (9,37).

Traditional endurance exercise training improves endothelial function in individuals with CAD (14), and improvements in endothelial function with exercise training are suggested to account for up to 40% of the associated risk reduction (13). Although endurance training has been demonstrated to be effective for patients with CAD, it is time consuming, and compliance is relatively low (1). Interval exercise training has gained considerable attention as an innovative treatment strategy for individuals with decreased aerobic functional capacity (39). A recent review of interval exercise training studies in patients with CAD highlights greater improvements in many physiological indices, including brachial artery endothelial function, in comparison with moderate-intensity endurance exercise (END) training (8). However, the major limitation in all of these previous investigations is that the interval exercise training bouts used for comparison were matched in terms of energy expenditure to the endurance exercise protocol. There are no studies that have compared relatively time efficient, low-volume interval exercise training to endurance exercise protocols in patients with CAD. Given that a lack of time is a commonly cited barrier to cardiac rehabilitation exercise adherence (1), low-volume interval exercise training would be

an advantageous treatment approach if it elicits similar physiological benefits.

FMD responses have emerged as valuable indicators of vascular function, both after chronic exercise training and after acute bouts of exercise. Investigations of the acute response to single bouts of exercise of different modes can provide comparative information about the magnitude of the cardiovascular stimulus and mechanisms of chronic adaptations with training. Stimulus response exercise studies form the basis of the design of evidence-based exercise training interventions. The acute effect of a single bout of exercise on endothelial function in patients with CAD is unknown. In addition, there is no consensus on the acute endothelial response to exercise in different populations. Previous investigations have demonstrated reductions (21,30,31), improvements (15,16,38), and no change (15,16,30,31) in endothelial-dependent function after different modes, intensities, and durations of acute exercise. The purpose of this study was therefore to examine the acute effects of both a single bout of low-volume high-intensity interval exercise (HIT) and END on endothelial function in individuals with CAD who would typically qualify for a community-based cardiac rehabilitation program. Previous acute exercise investigations have used endurance exercise (15,16,31,38) and isocaloric interval exercise (30,38); however, no studies have examined low-volume HIT. Brachial artery endothelial function was selected as the primary outcome given its association with disease severity and future risk (40). Previous investigations have demonstrated postexercise increases in FMD approximately 1 h after the cessation of exercise (15,16); therefore, we hypothesized that FMD would be acutely increased in patients with CAD after both exercise bouts.

METHODS

Participants

Nine males and one female with documented CAD were recruited from the Centre for Health Promotion and Rehabilitation, Department of Kinesiology, McMaster University (Hamilton, Ontario, Canada). CAD was defined as encompassing at least one of the following criteria: angiographically documented stenosis ≥50% in at least one major coronary artery; prior history of myocardial infarction (MI), percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG) surgery; positive exercise stress test determined by positive nuclear scan, or symptoms of chest discomfort accompanied by ECG changes. Exclusion criteria included smoking within 3 months, noncardiac surgical procedure within 2 months, MI or CABG within 2 months, PCI within 1 month, New York Heart Association class II–IV symptoms of heart failure, documented valve stenosis, documented severe chronic obstructive pulmonary disease, symptomatic peripheral arterial disease, unstable angina, uncontrolled hypertension, uncontrolled ventricular dysrhythmia, premenopausal women, pregnancy, and any musculoskeletal abnormality that would limit exercise participation. Participants with diabetes mellitus were included if they were non–insulin dependent and had stable blood glucose levels determined from daily monitoring. All participants were recreationally active (two or more exercise sessions per week) and underwent recent exercise stress tests (within 4 ± 2 months); therefore, exercise intensities were determined from the raw data of their recent test. All protocols were reviewed and approved by the Hamilton Health Sciences/Faculty of Health Sciences Research Ethics Board, conforming to the Helsinki Declaration on the use of human subjects, and written informed consent was obtained from participants before participation. Participant characteristics, medical history, and medications are described in Table 1.

Study Protocol

This study used a within-subject, repeated-measure design. Participants attended two testing sessions separated by an average of 11 d (range, 2–35 d). Timing of sessions differed between participants, but within-subject sessions were scheduled at the same time of day. Measures of brachial artery endothelium-dependent and endothelium-independent function were collected after 30 min of supine rest (preexercise) and 60 min after the exercise bout (postexercise). Participants were instructed to abstain from exercise for 24 h and caffeine and alcohol consumption for 12 h before each session. Testing took place 4 h postprandial after the consumption of a standardized meal replacement drink (235 mL of Ensure; Abbott Nutrition, Saint-Laurent, QC, Canada). Medications were kept constant throughout the study, except for vasoactive medications, which were withheld on testing days. All testing was performed in a temperature-controlled room (23°C ± 1°C).

TABLE 1. Participant characteristics (n = 10, 1 female).

Variable	
Age (yr)	66 ± 11
Height (m)	1.73 ± 0.07
Weight (kg)	80.0 ± 8.3
BMI (kg·m^{-2})	26.8 ± 3.1
$\dot{V}O_{2peak}$ (mL·kg^{-1}·min^{-1})	28.6 ± 5.6
CAD criteria, number	
MI	4
PCI	6
CABG	4
Medication classification, number	
ACE inhibitors	5
Angiotensin II inhibitors	1
Antiplatelets	9
β-blockers	5
Calcium channel blockers	5
Diuretics	2
Nitrates	1
Statins	10
Non–insulin-dependent diabetics, number	3
Time since primary event (yr)	8.5 ± 6.8

Data are expressed as mean ± SD unless indicated otherwise.
ACE, angiotensin-converting enzyme; BMI, body mass index; $\dot{V}O_{2peak}$, peak oxygen consumption.

Exercise Protocols

Each exercise bout was performed on an electrically braked cycle ergometer (Excalibur Sport V2.0; Lode BV, Groningen, The Netherlands) and involved a 5 min warm-up at 10% of peak power output (PO_{peak}). The END protocol was based on the Canadian Association of Cardiac Rehabilitation exercise guidelines (33) and involved 30 min of continuous exercise at 55% PO_{peak}. The HIT protocol was modeled after a previously used protocol in young males (17) and involved ten 1-min bouts at 80% PO_{peak} separated by 1-min bouts at 10% PO_{peak}. The order of END and HIT was randomized between participants. Heart rate was measured continuously during exercise using a single-lead (CC5) ECG (model ML 123; ADInstruments, Colorado Springs, CO). Exercise heart rates were averaged into 5-s bins. Mean exercise heart rate is the average of all 5-s bins, whereas peak heart rate is reported as the highest 5-s bin. Total work (kJ) performed during each exercise bout was calculated by multiplying the power output (W) by the duration of the exercise bout.

Assessment of Endothelium-Dependent and Endothelium-Independent Function

All endothelial function measurements were conducted in the supine position. Heart rate and brachial blood pressure were assessed using a single-lead ECG and an automated blood pressure measurement system (model CBM-700; Omron Colin Medical Corporation, San Antonio, TX). FMD was used to assess brachial artery endothelium-dependent function on the basis of previously established guidelines (9,37).

Longitudinal B-mode images of the right brachial artery were collected for five cardiac cycles using a 10-MHz linear array probe (System FiVe; GE Medical Systems, Horton, Norway) positioned 3–5 cm proximal to the antecubital fossa at a frame rate of 11 frames per second, followed by 30 s of blood velocity measurements acquired in pulsed-wave mode (4 MHz). Blood velocity raw audio signals were continuously analyzed by an external spectral analysis system (model Neurovision 500 M TCD; Multigon Industries, Yonkers, NY). The system applies a fast Fourier transformation to the raw audio signals to determine continuous intensity weighted mean blood velocity (MBV). The MBV was sampled at 200 Hz during the FMD tests using commercially available hardware (Powerlab model ML 795, ADInstruments). Upon completion of preocclusion measurements, a pneumatic cuff positioned on the forearm distal to the antecubital fossa was inflated using a rapid cuff inflator (model E20 and AG101; Hokanson, Bellevue, WA) to an occlusion pressure of 200 mm Hg. After 5 min of occlusion, the cuff was released and MBV signals were acquired for 90 s, followed by a B-mode image of the right brachial artery for 12 cardiac cycles at a frame rate of 11 frames per second.

Endothelium-independent function was assessed 10 min postcuff release using a 0.4-mg sublingual spray of nitro-glycerin (NTG) (9,37). Longitudinal B-mode images of the right brachial artery were collected pre-NTG (five cardiac cycles) and at 3 and 4 min post-NTG (12 cardiac cycles).

Data Analysis

Brachial artery blood velocity. Preocclusion and postocclusion MBV were analyzed offline using LabChart 7 Pro for Windows (Powerlab ML 795, ADInstruments) in 3-s average time bins after correcting for angle of insonation (all ≤68°). Mean blood flow (preocclusion) was determined by multiplying brachial artery cross-sectional area by MBV. Preocclusion brachial artery resistance was calculated as mean brachial arterial pressure divided by mean blood flow. Recently published FMD guidelines advocate for the normalization of FMD responses to the entire reactive hyperemic stimulus rather than normalizing to the peak stimulus (37). Shear rates for each 3-s MBV bin during the 90-s postocclusion period were calculated using the following equation: shear rate = 8MBV/preocclusion end-diastolic diameter. The entire reactive hyperemic stimulus was quantified as the shear rate area under the curve (AUC).

Brachial artery diameter. B-mode images were stored in Digital Imaging and Communications in Medicine (DICOM) format for later offline editing and analysis. Using commercially available software (Sante DICOM Editor, Version 3.0.12; Santesoft, Athens, Greece), the end-diastolic frames, determined by the R-spike of the ECG trace, were extracted and stacked in a new DICOM file for determination of brachial artery diameters. Diameters at end-diastole were determined using semiautomated edge detection software program (Artery Measurement System (AMS) Image and Data Analysis, Gothenburg, Sweden). The program identifies the borders of the arterial wall within a selected region of interest on the basis of the contrasting intensity of brightness between the arterial wall and lumen, and it determines the diameter from approximately 100 points of measurement within the region of interest. Preocclusion and pre-NTG diameters were determined from the average of the five end-diastolic frames. Peak postocclusion FMD diameter was determined from the 12 end-diastolic frames. Peak post-NTG diameter was determined as the maximum diameter from the 12 end-diastolic frames collected at 3 and 4 min. FMD is expressed in the following formats, where ED stands for end-diastolic:

$$\text{absolute FMD} = \text{postocclusion}_{\text{ED diameter}} - \text{preocclusion}_{\text{ED diameter}}$$

$$\text{relative FMD} = 100\left(\frac{\text{absolute FMD}}{\text{preocclusion}_{\text{ED diameter}}}\right)$$

$$\text{normalized FMD} = \frac{\text{relative FMD}}{\text{AUC}}$$

Endothelium-independent dilation is expressed in absolute and relative units. Intraclass correlation coefficients for pre-exercise FMD values were as follows: absolute FMD (0.89), relative FMD (0.89), and normalized FMD (0.85).
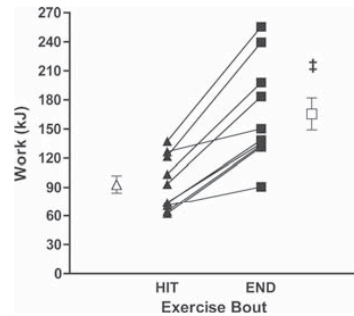
FIGURE 1—Total work performed (kJ) during HIT and END bouts. Individual (*closed*) and mean (*open*) values for HIT (*triangle*) and END (*square*) are presented. ‡ $P < 0.001$ for HIT versus END.

Statistical Analysis

Statistical analyses were performed using Statistical Package for Social Science software, version 11.5 (SPSS, Chicago, IL). Exercise heart rates were compared using a paired t-test. Pre- and postexercise measures for END and HIT were compared using 2-way repeated-measures analyses of variance. Data are presented as mean ± SD, unless otherwise noted, with $P < 0.05$ considered statistically significant.

RESULTS

All participants completed the HIT protocol; however, only 8 of 10 participants could complete the END protocol because two participants stopped because of volitional fatigue. Mean exercise heart rate was significantly higher during END (END, 117 ± 22 bpm; HIT, 110 ± 20 bpm; $P < 0.05$); however, there was no significant difference in peak exercise heart rates between exercise conditions (END, 130 ± 26 bpm; HIT, 126 ± 26 bpm; $P = 0.28$). Total work performed was higher during the END protocol (Fig. 1, $P < 0.001$).

FMD results are presented in Figure 2. Absolute and normalized FMD were significantly increased postexercise ($P < 0.05$), with no significant differences between exercise conditions. Relative FMD was unchanged. Brachial artery diameters, AUC, and endothelial-independent responses are presented in Table 2. There was no difference in preexercise AUC, a measure of the shear stress stimulus, between visits. AUC decreased postexercise ($P < 0.01$), with no differences between HIT and END. There were no differences in preexercise diameters between visits. Pre- and postocclusion brachial artery diameters were increased 60 min postexercise compared with preexercise, with no significant differences between exercise conditions. In addition, pre- and postexercise pre-NTG diameters were not significantly different from the pre- and postexercise preocclusion FMD
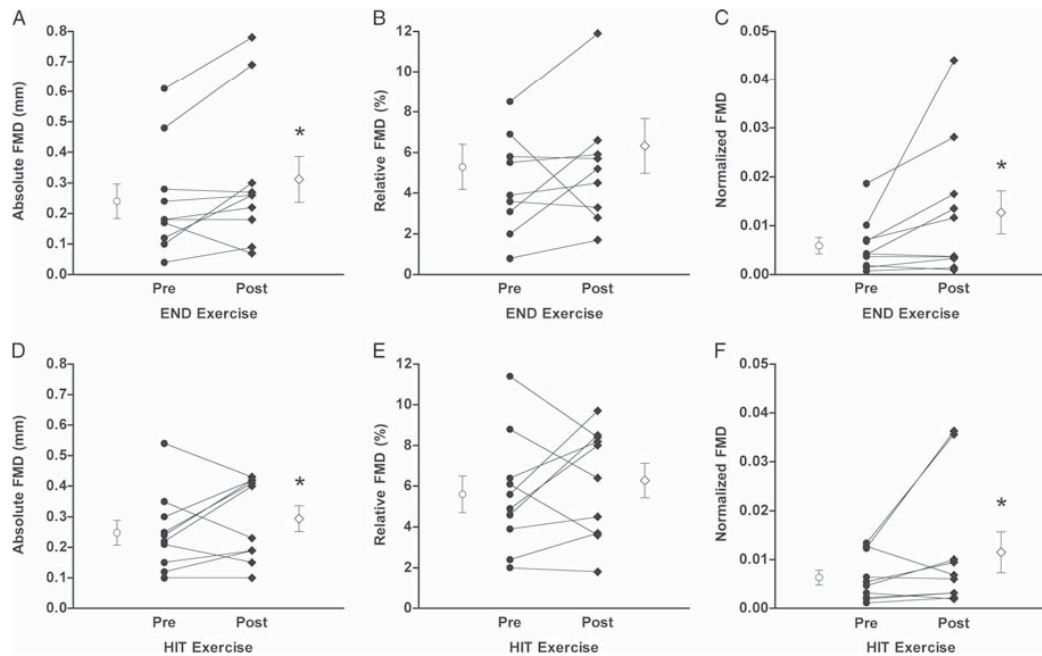
FIGURE 2—Absolute (A, D), relative (B, E), and normalized (C, F) brachial artery FMD responses before and 60 min after END and HIT, respectively. Individual (*closed*) and mean (*open*) values for pre- (*circle*) and postexercise (*diamond*) are presented. *$P \leq 0.05$ for pre- versus postexercise.

TABLE 2. Brachial artery diameters, shear rate AUC, and NTG responses pre- and 60 min post-END and HIT exercises.

Variable	END		HIT	
	Preexercise	Postexercise	Preexercise	Postexercise
Preocclusion diameter (mm)	4.56 ± 0.88	4.78 ± 1.01*	4.57 ± 0.90	4.81 ± 1.05*
Peak postocclusion diameter (mm)	4.80 ± 0.95	5.09 ± 1.13*	4.82 ± 0.93	5.10 ± 1.07*
Pre-NTG diameter (mm)†	4.54 ± 0.95	4.84 ± 1.14*	4.58 ± 1.00	4.77 ± 1.08*
Peak post-NTG diameter (mm)†	5.07 ± 1.02	5.39 ± 1.19*	5.14 ± 1.09	5.33 ± 1.17*
Shear rate AUC	1350 ± 1015	1126 ± 897*	1270 ± 737	1091 ± 879*
Absolute NTG (mm)	0.53 ± 0.12	0.55 ± 0.15	0.56 ± 0.17	0.56 ± 0.16
Relative NTG (%)	12.1 ± 2.7	11.8 ± 3.4	12.4 ± 3.2	12.0 ± 3.1

Data are expressed as mean ± SD.
* $P < 0.01$ versus preexercise.
† $n = 9$.

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diameters, confirming the artery had returned to preocclusion conditions before initiating the endothelial-independent dilation test. Absolute and relative NTG responses were unchanged with exercise, with no differences between exercise conditions.

Hemodynamic variables are reported in Table 3. There were no differences in preexercise heart rate, brachial artery blood pressure, mean brachial artery blood flow, and brachial artery vascular resistance between visits, and these variables were unchanged 60 min postexercise with no significant difference between exercise conditions ($P \geq 0.05$).

DISCUSSION

The major novel finding from the present work is similar acute increases in brachial artery FMD 60 min after a single bout of END and HIT exercises, despite the difference in exercise intensities and durations. This is the first study to examine the acute effects of HIT and END on brachial artery endothelial-dependent and endothelial-independent function in individuals with CAD.

Relative FMD values from our sample are comparable with relative FMD values reported by other investigations in populations with CAD and, on average, are smaller than relative FMD values reported in healthy populations (4,27). Absolute FMD values are comparable with values reported in healthy middle-age and elderly men and women (27). Our results demonstrate comparable acute improvements in brachial artery endothelial-dependent dilation after both END and HIT in the face of unchanged endothelial-independent dilation. These findings are consistent with observations of acute improvements in FMD approximately 60 min after a single bout of endurance exercise in middle-age men and women (15,16). Improvements in brachial artery FMD

have also been reported 16–18 h after a single bout of exercise in middle-age men, with HIT eliciting greater improvements than END (38). The FMD test is based on the principle that increased blood flow through an artery in response to a period of occlusion increases the shear stress on the endothelium. The elevated shear stress activates potassium channels, which causes an influx of calcium into the endothelial cells (7,25). Intracellular calcium activates the endothelial nitric oxide synthase (eNOS) enzyme, leading to the formation of the potent vasodilator, nitric oxide (NO) (5,22). Flow-mediated increases in arterial diameter, therefore, are largely NO dependent (20). Leg cycling exercise increases blood flow and shear stress to the nonexercised limbs (36). Not surprisingly, several studies have demonstrated elevations in NO formation after an acute exercise bout (18,30). Resting levels of both eNOS protein expression and NO production are impaired in individuals with atherosclerosis (24,41). Therefore, an increased capacity to produce NO postexercise could explain our observation of improved postexercise NO-dependent brachial artery FMD. Preocclusion FMD arterial diameters were increased postexercise, which has been previously demonstrated in acute exercise studies and could be attributed to decrease sympathetic activation and increased circulating vasodilators (15). In the current study, the postexercise reactive hyperemic stimulus, determined by the AUC, decreased. The magnitude of the shear stress stimulus is inversely proportional to arterial diameter (28); therefore, the postexercise reduction in AUC was expected given the increase in preocclusion arterial diameter. Despite this reduction in the postexercise hyperemic stimulus, the dilation normalized to AUC was significantly larger after both END and HIT. The absence of a change in endothelial-independent induced dilation after HIT and END is in support of previous acute exercise

TABLE 3. Hemodynamic variables pre- and 60 min post-END and HIT exercises.

Variable	END		HIT	
	Preexercise	Postexercise	Preexercise	Postexercise
Heart rate (bpm)	57 ± 8	63 ± 11	58 ± 6	62 ± 9
Systolic blood pressure (mm Hg)	121 ± 16	119 ± 11	120 ± 13	123 ± 13
Diastolic blood pressure (mm Hg)	70 ± 10	68 ± 7	69 ± 7	70 ± 6
Mean arterial pressure (mm Hg)	87 ± 11	85 ± 8	86 ± 8	87 ± 8
Mean blood flow (mL·min⁻¹)	32 ± 13	39 ± 19	33 ± 16	43 ± 24
Resistance (mm Hg·mL⁻¹·min)	3.2 ± 1.7	2.9 ± 1.7	3.2 ± 1.5	2.9 ± 2.1

Data are expressed as mean ± SD.

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investigations (16,21,30,31,38) and lends further support to the ability of exercise to selectively stimulate endothelial-dependent pathways acutely after exercise.

In contrast to our observations, several studies have demonstrated acute postexercise reductions in endothelial function after exercise. The discrepancy between these studies and our findings could be attributed to differences in study design and population. McGowan et al. (21) demonstrated acute impairments in brachial artery FMD immediately after isometric handgrip exercise in persons medicated for hypertension. Unlike our study design, endothelial function was assessed in the exercised limb. The observed postexercise reduction in FMD could therefore be attributed to the localized depletion of eNOS in the exercising muscle vascular beds. Increased oxidative stress, including the production of superoxide, has been reported after acute exercise (23). Superoxide anions are capable of reacting with NO to form peroxynitrate (2), thereby depleting available NO stores. Silvestro et al. (31) demonstrated elevated reactive oxygen species and decreased brachial artery FMD immediately after maximal leg exercise in individuals with peripheral arterial disease. Interestingly, the administration of vitamin C abolished any reductions in FMD, suggesting the antioxidant effects of vitamin C counteracted the endothelial impairment produced with exercise. Conversely, several studies demonstrated increased antioxidant capacity after acute exercise (30,38). We did not examine antioxidant capacity; however, it remains possible that postexercise increases in FMD could be attributed to acute increases in NO because of the protective effects of enhanced antioxidant capacity rather than increased NO production. Despite a significant increase in absolute FMD after both END and HIT, relative FMD values were not statistically different. Relative FMD expresses the absolute change in diameter relative to the preocclusion diameter. Because preocclusion diameters were significantly larger after both exercise bouts, the increase may have negated the increased absolute change. Likewise, the lack of significance could be attributed to our sample size. Absolute and normalized FMD results demonstrate sufficient power (absolute >70%, normalized >95%), whereas the relative FMD results were underpowered (<60%).

Systolic, diastolic, and mean brachial arterial pressures were unchanged 60 min after both END and HIT. The absence of postexercise reductions in blood pressure could be attributed to the baseline blood pressure values of our sample. Previous investigations in normotensive and hypertensive groups revealed greater postexercise reductions in blood pressure in individuals with hypertension (6,26). All participants in the current study were medically treated for blood pressure; consequently, the average preexercise blood pressure values fall within the normotensive range. Vascular resistance, which is affected by sympathetic tone (32), was unchanged after both END and HIT, thereby providing further support for a NO-mediated improvement in endothelial function with exercise, rather than improved vascular tone due to sympathetic modifications.

Several exercise-training studies in healthy populations have demonstrated the physiological and performance merits of time-efficient, low-volume interval exercise (17,29). Six weeks of sprint interval exercise training produced similar improvements in peripheral endothelial-dependent function as traditional endurance exercise in healthy young males (29). The average exercise duration per week was 1.5 h for sprint interval (only 10 min of which was high-intensity exercise) and 4.5 h for traditional endurance exercise. Our findings extend the literature on low-volume HIT to a clinical population with endothelial dysfunction. Although there was only a 10-min difference in exercise durations between the HIT and END protocols, total work performed was significantly lower during HIT, equating to approximately 60% of the work performed during END. The findings from this study warrant the examination of low-volume HIT in a cardiac rehabilitation exercise-training program.

Limitations. This study included a small sample size and an uneven distribution of men and woman. Although the crossover study design does strengthen the power of the study, a larger sample would be valuable. The exercise program from which we recruited our participants had low female membership; therefore, we were only able to recruit one female. Exercise intensities were determined from the participants' most recent exercise stress test, which occurred approximately 4 months before their participation in the study. Although the assessment of maximal exercise capacity at the beginning of the study may have provided more accurate exercise intensities, all participants were habitually active; therefore, it is unlikely that the new tests would have yielded greatly different results. Participants were taking some medications known to influence endothelial function; however, all medications were monitored throughout the study and kept constant between testing days. Our ultrasound did not permit us to capture both diameters and blood velocity data simultaneously. For this reason, shear rate was calculated using the baseline brachial artery diameter. Despite the limitation of our equipment, our findings remained significant after normalizing to shear rate AUC. Lastly, the collection of exercise blood pressure values would have provided more information about the different exercise stimuli; however, we were unable to measure blood pressure during the exercise bouts.

CONCLUSIONS

Endothelial function has gained considerable attention within the past few decades as a relevant clinical marker of primary and secondary risk of cardiovascular disease and a valuable research tool for examining regulation of vascular function. This study demonstrated improved acute endothelial-dependent dilation 60 min after both END and HIT exercises protocols in patients with CAD with impaired endothelial function. These acute improvements support further investigations comparing chronic training with both

END and HIT exercises as a therapeutic strategy for individuals with cardiovascular diseases.

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5.0 CHAPTER 5: BRACHIAL ARTERY ENDOTHELIAL RESPONSES TO ACUTE EXERCISE AND CHRONIC TRAINING IN PATIENTS WITH CORONARY ARTERY DISEASE

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Abstract

Coronary artery disease (CAD) is characterized by endothelial dysfunction. In habitually active patients with CAD, we previously demonstrated a single bout of exercise increased brachial artery endothelial-dependent function (assessed using flow-mediated dilation, FMD) 60-minutes post-exercise, in the face of unchanged endothelial-independent function (assessed using nitroglycerin administration, NTG). The current study examined the effects of 12-weeks of exercise training on the acute brachial artery endothelial responses to a single bout of exercise in patients with CAD. Assessments were performed on 19 patients with CAD (63 ± 8 yrs) at rest and 20-minutes post-exercise (recovery), at pre- and post-training time points. For FMD, brachial artery diameters and velocities were measured using Duplex ultrasound at baseline, and for 3-minutes following a 5-minute ischemic period. Endothelial-independent function was assessed for 10-minutes following a 0.4 mg dose of NTG. Training improved FMD (4.6 ± 2.4 % vs. 5.8 ± 2.3 %, $p \leq 0.001$ for pre- vs. post-training), but there was no interaction or effect of acute exercise. There was no training effect for NTG; however, NTG was acutely decreased in recovery at both pre- and post-training time points (pre-training: 22.0 ± 5.6 % vs. 14.4 ± 5.7 %; post-training: 22.6 ± 6.0 % vs. 12.6 ± 5.6 %, $p \leq 0.001$ for rest vs. recovery). Brachial artery diameters were larger during recovery compared to rest ($p \leq 0.05$), which may explain the attenuated NTG responses. Regardless of the mechanisms, post-exercise reductions in NTG dilation have not been previously reported, and highlight the necessity to perform both endothelial-dependent and –independent assessments.

Introduction

Coronary artery disease (CAD) is characterized by endothelial dysfunction, which is defined as a decreased capacity of the endothelium to elicit vasodilation (1). Brachial artery endothelial-dependent function, an accepted non-invasive surrogate for coronary artery function (25), can be assessed using the technique flow-mediated dilation (FMD) (1, 26), which has been shown to be largely mediated by NO (13). CAD severity prior to revascularization is negatively associated with FMD (12, 19), and patients with CAD demonstrate attenuated FMD values compared to healthy individuals (13, 19, 24, 31). Endothelial-independent function, which can be measured using nitroglycerin (NTG), is commonly assessed in combination with FMD to confirm whether impairments in vasodilation are attributed to the endothelial or vascular smooth muscle layers (1). Previous evidence suggests patients with CAD demonstrate either maintained (13, 24) or impaired (19, 31) NTG responses compared to healthy individuals.

Increased resting FMD has been reported following 12-weeks of exercise training in patients with CAD, while NTG-mediated dilation was unchanged (5, 30). We previously demonstrated a single bout of exercise was capable of acutely increasing FMD 60-minutes post-exercise in habitually active patients with CAD in the face of unchanged NTG responses (2). Our previous findings suggest acute exercise transiently increased endothelial-dependent function in a population characterized with endothelial dysfunction. While these observations may be clinically relevant, our patients were habitually active and therefore we could not ascertain whether the observations were attributed to their training status. Cross-sectional investigations of the relationship

between training status and endothelial responses have observed post-exercise

impairments in FMD in untrained individuals, while fit individuals experience increased

or unchanged post-exercise FMD responses (7, 20). No cross-sectional studies have

examined this relationship in patients with CAD, nor have any studies examined the

effect of an exercise training intervention on the acute endothelial responses to a single

bout of exercise in patients with CAD. Therefore, the purpose of this study was to

examine the effect of 12-weeks of exercise training on the acute brachial artery

endothelial-dependent and –independent responses immediately following a single bout

of sub-maximal exercise in patients with CAD. We hypothesized FMD would be

transiently impaired 20-minutes following an acute bout of exercise prior to 12 weeks of

training, but this impairment would be abolished or reversed with training. NTG

responses were not expected to change following acute exercise, or with exercise training.

Materials and Methods

Participants

Patients with documented CAD were recruited from the Cardiac Health and

Rehabilitation Centre at the Hamilton Health Sciences General Site (Ontario, Canada).

Inclusion criteria included the presence of CAD, which was defined as the patient having

at least one of the following: angiographically documented stenosis ≥50% in at least one

major coronary artery; prior history of myocardial infarction (MI), percutaneous coronary

intervention (PCI), or coronary artery bypass graft (CAGB) surgery; positive exercise

stress test determined by a positive nuclear scan, or symptoms of chest discomfort

accompanied by electrocardiographic (ECG) changes of > 1mm horizontal or down sloping ST segment depression. Exclusion criteria included smoking within three months, non-cardiac surgical procedure within two months, MI or CABG within two months, PCI within one month, NYHA class II-IV symptoms of heart failure, documented valve stenosis, documented severe chronic obstructive pulmonary disease, symptomatic peripheral arterial disease, unstable angina, uncontrolled hypertension, uncontrolled atrial arrhythmia or ventricular dysrhythmia, insulin requiring diabetes mellitus, and any musculoskeletal abnormality that would limit exercise participation. Twenty-four patients were recruited; however, one patient was excluded due to high resting diastolic blood pressure (>100 mm Hg). Therefore, 23 patients were included in the study. Four patients dropped out of the study due to reasons unrelated to the exercise interventions. Therefore, 19 patients were included in the final analysis for the study. The study protocol was reviewed and approved by the Hamilton Health Sciences/Faculty of Health Sciences Research Ethics Board, conforming to the Helsinki Declaration on the use of human subjects, and written informed consent was obtained from patients prior to participation.

Study Design

Testing took place at baseline (pre-training) and following the completion of 12-weeks of exercise training (post-training). Within each visit, assessments of brachial artery-dependent and -independent function were performed before and after a sub-maximal exercise bout (rest/recovery). The timing of sessions differed between participants, but within-subject sessions were scheduled at the same time of day. Prior to

testing sessions, participants were instructed to fast for at least 8 hours, and to abstain

from exercise for 24 hours, and caffeine and alcohol consumption for 12 hours.

Medications and vitamins were kept constant throughout the study, except for

nitroglycerin, which was withheld on testing days. Height (cm) and weight (kg) were

measured, and body mass index (BMI) was calculated. All testing was performed in a

temperature-controlled room ($23.1 \pm 1.2°$ C).

Exercise Training Protocols

Patients were stratified to 1 of 2 exercise training programs based on their resting

pre-training relative FMD. The 2 exercise training programs included: moderate-intensity

endurance exercise (END) or high-intensity interval exercise (HIT) training. Exercise

intensities for each protocol were based on the peak power output (PPO) achieved during

a medically supervised pre-training peak exercise test on a cycle ergometer (data not

presented). Patients attended two supervised exercise sessions per week at the Cardiac

Health and Rehabilitation Centre, which included a 10-15 minute standardized warm-up

and cool-down involving light aerobic exercise and upper and lower body stretching.

END began with continuous cycling for 30-minutes at 58% PPO (range 51-65%) (23),

then progressed to 40-minutes for weeks 5-8, and 50-minutes for weeks 9-12. HIT

involved 10, 1-minute intervals at 89% PPO (range 80-104%) separated by 1-minute

intervals at 10% PPO (11). The progression involved increasing intensity every month to

elicit the same pre-training absolute workloads.

Acute Sub-maximal Exercise Bout

Patients performed the same absolute sub-maximal exercise bout pre- and post-training. The exercise bout began with a 3-minute unloaded warm-up on a cycle ergometer (Excalibur Sport V2.0, Lode BV, Groningen, The Netherlands), followed by 4, 3-minute stages at increasing intensities of 20%, 40%, 60% and 80% of pre-training PPO. The exercise bout was designed to elicit a sub-maximal exercise response, but was different from the END and HIT protocols.

Brachial Artery Assessments

All brachial artery endothelial function measurements were collected in the supine position. Resting measurements were performed following 30-minutes of quiet rest, while recovery measurements were performed approximately 20-30 minutes following the cessation of exercise. Heart rate and brachial artery blood pressure were measured throughout testing using a single-lead (CC_5) ECG (model ML 123, ADInstruments Inc., Colorado Springs, CO, USA) and non-invasive hemodynamic monitor (Nexfin, BMEYE, Amsterdam, The Netherlands).

Brachial artery endothelial-dependent function was assessed using the FMD test, based on previously established guidelines (1, 26). Duplex ultrasound (Vivid Q, GE Medical Systems, Horten, Norway) was used to capture simultaneous images of the right brachial artery (13 MHz) and blood velocity measurements (4 MHz) throughout the FMD protocols. Pre-occlusion images of the right brachial artery were collected 3-5 cm proximal to the antecubial fossa for 30-seconds at a frame rate of 7.7 frames·s^{-1}. A 5-

minute period of ischemia was initiated by inflating a pneumatic cuff positioned on the

forearm distal to the antecubial fossa to an occlusion pressure of 200 mm Hg using a

rapid cuff inflator (model E20 and AG101, Hokanson, Bellevue, WA, USA). Upon cuff

release, duplex post-occlusion images and blood velocity measurements were collected

continuously for 3-minutes. Duplex images were stored in Digital Imaging and

Communications in Medicine (DICOM) format for offline analysis. End-diastolic frames,

determined by the R-spike of the ECG trace, were extracted and stacked in a new DICOM

file using commercially available software (Sante DICOM Editor, Version 3.0.12;

Santesoft, Athens, Greece), and analyzed using semi-automated edge-tracking software

[AMS (Artery Measurement System) Image and Data Analysis; Gothenburg, Sweden] as

previously described (2). Pre-occlusion diameters were determined from the 30-second

average. Post-occlusion diameters were averaged in rolling 5-cycle bins (6), and peak

post-occlusion diameter was defined as the maximum 5-cycle average. Absolute and

relative FMD were calculated as previously described (2). We previously reported day-to-

day intraclass correlations coefficients of 0.89, and coefficients of variation of 21% for

both absolute and relative FMD in a patient population with CAD (2).

Continuous intensity weighted mean blood velocity (MBV) signals were obtained

using an external spectral analysis system (model Neurovision 500M TCD, Multigon

Industries, Yonkers, NY, USA), and sampled at 200 Hz using commercially available

hardware (Powerlab model ML795, ADInstruments, Colorado Springs, CO, USA). MBV

was analyzed offline using LabChart 7 Pro for Windows (Powerlab ML 795,

ADInstruments, Colorado Springs, CO, USA) by correcting the angle of insonation (all

≤70˚). Mean blood flow was calculated by multiplying brachial artery cross-sectional area by MBV. Post-occlusion reactive hyperemic blood flows and MBV were averaged into 5-cycle bins to align with the 5-cycle diameter bins. Peak reactive hyperemic blood flow is reported as the maximum value during the 3-minute post-occlusion period. Shear rate for each bin was calculated by multiplying the MBV bin by 8, and dividing it by the corresponding reactive hyperemic 5-cycle bin. The reactive hyperemic stimulus until peak dilation was quantified as shear rate area under the curve (AUC).

Endothelial-independent function was assessed through administration of 0.4 mg sublingual spray of NTG applied 10-minutes after cuff release (1). Longitudinal B-mode images (8 MHz) of the right brachial artery were collected at a frame rate of 22.9 frames·s^{-1} prior to administration of NTG (pre-NTG; 10 cardiac cycles), and for 10 cardiac cycles every minute post-NTG up to 10-minutes. End-diastolic frames were extracted and stacked, and peak-NTG diameters were determined from the average of 10 cardiac cycles at each minute. NTG results are expressed in absolute and relative units. In patients with CAD, we previously reported intraclass correlations of 0.90, and coefficients of variation of 4% for both absolute and relative NTG-mediated dilation (2).

Statistical Analysis

Statistical analyses were performed using SigmaStat, version 3.1 (Systat Software Inc., San Jose, CA, USA). Data were first analyzed using factorial (Group: END versus HIT) repeated measures analyses of variance; however, no group effects were observed. Therefore, groups were pooled and data were analyzed using two-way repeated measure

(training: pre, post; acute: rest, recover) analyses of variance, with Tukey's multiple comparison post hoc procedures performed on significant interactions. Data are presented as mean ± SD, with p≤0.05 considered statistically significant.

Results

Participant characteristics, medical history, and medications are presented in Table 1.

Table 1. *Participant characteristics*

Variable	
Age, yr	63 ± 8
Height, m	1.75 ± 0.07
Weight, kg	87.9 ± 17.0
BMI, kg·m^{-2}	28.6 ± 4.4
Time since CAD event, mo	5 ± 2
CAD criteria, number	13
MI	13
PCI	5
CABG	
Medication classification, number	
ACE inhibitors	13
Anti-Platelets	19
β-Blockers	15
Calcium channel blockers	2
Diuretics	3
Statins	18

Data expressed as mean ± SD. ACE, angiotensin-converting enzyme. BMI, body mass index. CABG, coronary artery bypass graft. CAD, coronary artery disease. MI, myocardial infarction. PCI, percutaneous coronary intervention.

Brachial Artery Responses

Brachial artery diameters are presented in Table 2. All brachial artery diameters were increased during recovery compared to rest at both pre- and post-training time

points. There were significant interactions for FMD diameters ($p \leq 0.05$). Pre-occlusion and peak reactive hyperemic diameters were larger during recovery ($p \leq 0.001$) compared to rest. Post-training recovery pre-occlusion and peak reactive hyperemia diameters were also larger than pre-training recovery values ($p \leq 0.01$). For NTG-mediated dilation, there was a significant interaction for pre-NTG diameters ($p = 0.015$). Recovery pre-NTG diameters were larger than resting pre-NTG diameters at both pre- and post-training ($p \leq 0.001$), with post-training recovery diameters larger than pre-training recovery values ($p \leq 0.01$). For peak-NTG diameters, there was a significant acute effect (recovery > rest, $p \leq 0.05$) and training effect (post-training > pre-training, $p \leq 0.05$), but no interaction.

Absolute and relative FMD responses are presented in Figure 1. There was a main effect for training for FMD. Absolute and relative FMD were increased at post-training compared to pre-training ($p \leq 0.001$). There was no effect of acute exercise for FMD. NTG results are presented in Figure 2. There was a significant interaction for absolute ($p = 0.05$) and relative ($p = 0.04$) NTG responses. Post-hoc analyses revealed absolute and relative NTG were decreased in recovery compared to rest at both pre- and post-training; however, there was no difference in the magnitude of reduction as a result of the training state.

FMD hemodynamic indices, and times to peak dilation are presented in Table 2. There was no significant effect of acute exercise or training on peak reactive hyperemic blood flow, shear rate AUC, and time to peak dilation during the FMD and NTG assessments.

Hemodynamic Responses

Heart rate and blood pressure indices are also presented in Table 2. Two patients had changes to their beta-blocker medication, and one patient was put on a calcium channel blocker during the study period; therefore they were excluded from the hemodynamic analyses. There were main effects of training and acute exercise for heart rate. Recovery heart rates were higher than rest values ($p \leq 0.001$), while heart rate was lower at post-training compared to pre-training ($p = 0.04$). Systolic blood pressure was decreased in recovery ($p = 0.02$), but was unchanged following training. Diastolic blood pressure was unaffected by training and acute exercise.

Table 2. *FMD, NTG, and hemodynamic indices at rest and recovery, at pre- and post-training*

Variable	Pre-Training		Post-Training	
	Rest	Recovery	Rest	Recovery
FMD Indices				
Pre-occlusion diameter, mm	4.52 ± 0.76	4.83 ± 0.83*	4.51 ± 0.74	5.03 ± 0.86*†
Peak RH diameter, mm	4.72 ± 0.75	5.06 ± 0.85*	4.77 ± 0.76	5.31 ± 0.88*†
Time to peak RH diameter, s	62 ± 29	64 ± 33	61 ± 27	85 ± 33
Peak RH blood flow, ml·min^{-1}	351 ± 177	309 ± 139	321 ± 148	342 ± 168
AUC	16586 ± 13081	13855 ± 13861	13456 ± 11699	16071 ± 10155
NTG Indices				
Pre-NTG diameter, mm	4.54 ± 0.63	4.93 ± 0.71*	4.59 ± 0.61	5.17 ± 0.78*†
Peak-NTG diameter, mm	5.52 ± 0.69	5.63 ± 0.72§	5.61 ± 0.65‡	5.79 ± 0.72§‡
Time to peak NTG diameter, min	7 ± 2	8 ± 2	8 ± 2	8 ± 2
Hemodynamic Indices				
Heart rate, bpm				
Systolic BP, mm Hg	56 ± 7	64 ± 9*	53 ± 4‡	60 ± 5*‡
Diastolic BP, mm Hg	126 ± 14	118 ± 12§	124 ± 12	120 ± 12§
	63 ± 6	62 ± 6	63 ± 8	64 ± 8

Data expressed as mean ± SD. AUC, area under the curve. BP, blood pressure. FMD, flow-mediated dilation. NTG, nitroglycerin. RH, reactive hyperemia. *$p \leq 0.001$, rest vs. recovery within the same time point. †$p < 0.01$ vs. pre-training recovery. ‡$p < 0.05$, pre-training vs. post-training. §$p < 0.05$, rest vs. recovery.
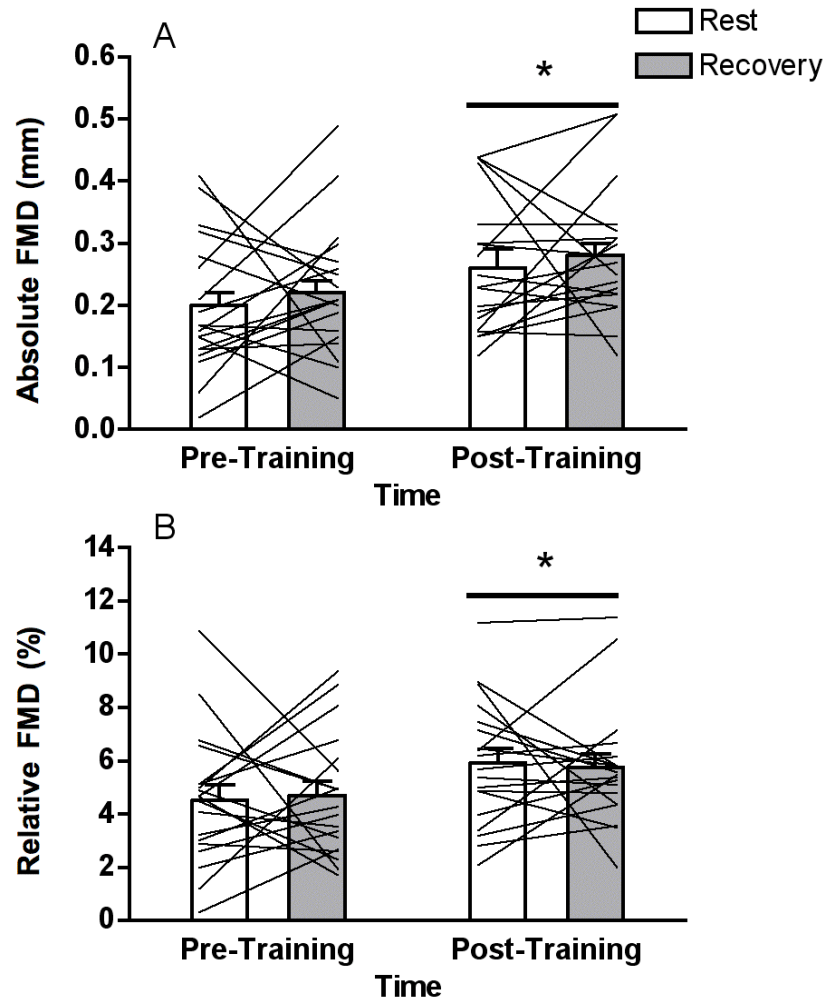
Fig 1. Absolute (A) and relative (B) brachial artery flow-mediated dilation (FMD) responses at rest (white) and 20-minutes into exercise recovery (grey) at pre- and post-training time points. Lines represent individual patient responses. *p≤0.001, pre-training vs. post-training.
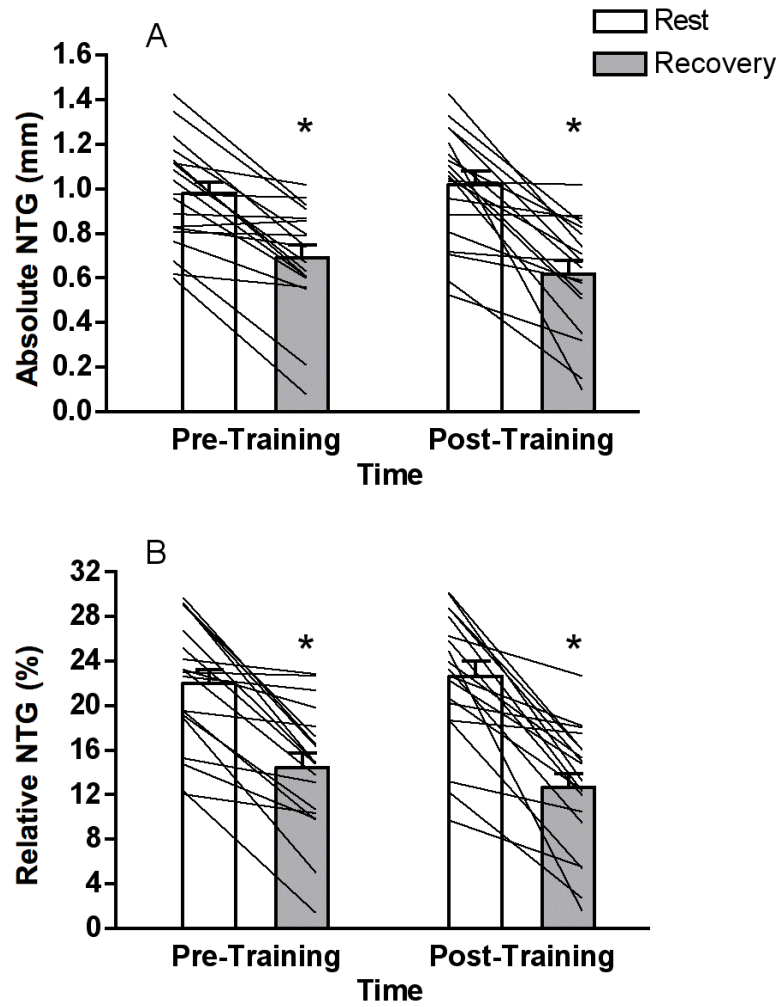
Fig 2. Absolute (A) and relative (B) changes in brachial artery nitroglycerin-mediated dilation (NTG) at rest (white) and 20-minutes into exercise recovery (grey) at pre- and post-training time points. Lines represent individual patient responses. *p≤0.001, rest vs. recovery.

Discussion

This study demonstrated that 12-weeks of exercise training did not change the acute brachial artery endothelial responses to a single bout of sub-maximal exercise. This finding is supported by McGowan et al. (15) who observed no change in the brachial artery endothelial responses to a bout of isometric handgrip exercise following 8-weeks of training in hypertensive patients on medication. While the acute FMD responses were unchanged following exercise, we did report a reduction in NTG-mediated dilation during recovery at both pre- and post-training time points. This observation was unexpected, and has not been previously reported.

As previously described, it is well established that patients with CAD demonstrate impaired endothelial-dependent function (13, 19, 25, 31); whereas the evidence on endothelial-independent function is not as definitive, and suggests endothelial-independent responses in patients with CAD are either impaired (19, 31) or maintained (13, 24) compared to healthy controls. Our resting NTG responses of 20-22% are comparable to values reported in healthy populations (14, 19), which suggests our sample had normal NTG responses during baseline conditions. However, recovery values of 12-14% are comparable to values reported in CAD patients who have "impaired" endothelial-independent function (19). While it may appear that both absolute and relative NTG-mediated dilation were "impaired" in recovery, post-exercise vasodilation may explain the observations.

The combination of endothelial-dependent and –independent assessments is important because they provide a comprehensive look at the mechanisms involved in

vasodilation. NTG assessments are used as a control to ensure vascular smooth muscle function is normal. As a result, FMD results should be interpreted in the context of NTG results. Few previous acute exercise studies have assessed both FMD and NTG responses, which in light of our current findings might limit the ability to assemble an accurate understanding of vascular regulation from previous findings. More importantly, even fewer investigations report measurements of NTG diameters (2, 9). We observed a reduction in absolute and relative NTG-mediated dilation during recovery, which is in contrast to previous studies that demonstrate no change after exercise (2, 9, 21, 22, 28). Our observations may be explained by post-exercise vasodilation. Pre-NTG diameters were significantly larger during recovery compared to rest. There is evidence to suggest a larger arterial diameter has a reduced dilatory capacity compared to a smaller arterial diameter (27). As a result, increased diameters during recovery would have a smaller dilatory range, therefore resulting in an attenuated NTG response.

A 0.4 mg dose of NTG is believed to elicit the maximum obtainable diameter (1). However, our data suggests that a maximum obtainable diameter may not have been reached. Peak-NTG diameters reached during recovery were significantly larger compared to rest at both pre- and post-training time points. If there is an upper limit for vasodilation, it was likely reached during the recovery conditions. Nevertheless, this observation suggests that there may be additional factors influencing NTG-mediated vasodilation. As a result, the concept of decreased vascular smooth muscle function during recovery cannot be rule out. Future examinations will need to decipher the true

mechanism to explain our observation of a post-exercise reduction in NTG-mediated dilation.

We observed no change in FMD following sub-maximal exercise at both pre- and post-training time points, which in contrast to our previous finding of increased FMD 60-minutes following a single-bout of both END and HIT exercise (2). The evidence on FMD responses following acute exercise is less than definitive. Previous investigations have demonstrated increases (7, 9, 28, 29), decreases (7, 14, 15, 21, 22), and no change (3, 9, 21, 22) in FMD following exercise. Taken together, the literature to date suggests the acute FMD responses to exercise are variable, which is further supported by the large variability in our patient responses (Figure 1). The most likely explanation for the discrepancies between studies is the differences in acute exercise intervention, study populations, and timing of measurements. Specifically, acute exercise bouts have included isometric handgrip exercise (15, 28), and high-intensity (2, 21) and maximal exercise (22), while assessments were made immediately (15, 22, 28) and 60-minutes post-exercise (2, 9, 21). Populations examined have included patients with intermittent claudication (22), hypertension (15), post-menopausal women (9), and healthy men and women (9, 21, 22, 28).

It is unlikely the absence of a change in FMD during recovery is attributed to the change in brachial artery diameter. In our previous investigation, pre-occlusion brachial artery diameters were significantly larger following the acute exercise bouts, and significant improvements in FMD were still observed (2). In the present study, both pre-occlusion and peak reactive hyperemia diameters were elevated in recovery compared to

rest. Thus, despite starting from a larger baseline arterial diameter, the vessel was capable of dilating to the same absolute and relative capacity. The inability to elicit further dilation in recovery, resulting in improved FMD responses may therefore be attributed to post-exercise increases in oxidative stress. Superoxide anions produced during exercise (16, 29) are capable of scavenging available NO, thereby decreasing its bioavailability. There is also evidence that the FMD test may not be fully mediated by NO; therefore additional factors should be considered. Blunted FMD responses have been observed with increased sympathetic stimulation (10). While it unlikely sympathetic activity influenced our results, due to increased brachial artery diameters in recovery, it highlights the fact that alternative factors should be considered in the FMD response.

The purpose of the study was to examine the effect of "training status" on the acute brachial artery endothelial responses to exercise; however, we did not observe a change in the acute responses following 12-weeks of exercise training. Previous cross-sectional investigations, which have demonstrated differences between inactive and active populations, used habitually active individuals (7, 20). Our previous study used patients who were habitually active for more than 8 years since their primary CAD event (2). In the present study, we recruited patients 5 months after their primary CAD event. Therefore, it remains possible that a longer training period may have elicited different acute brachial artery endothelial responses following exercise.

Time to peak dilation during the FMD and NTG assessments were unaffected by acute exercise and exercise training, suggesting the time course of brachial artery responses remained consistent throughout the study. Peak reactive hyperemic blood flow,

and shear rate AUC were also unchanged following acute exercise and 12-weeks of training. Blood flow is regulated by downstream resistance vessels; therefore, our findings suggest downstream vascular resistance was unaffected during the study. As shear rate AUC is used to quantify the reactive hyperemic stimulus, the absence of a change in AUC suggests a similar hyperemic stimulus across the FMD tests, which would support the observation of unchanged FMD following acute exercise. However, we did observe larger FMD values post-training, which suggest the artery was more responsive to the hyperemic stimulus post-training. Increased brachial artery FMD responses have been observed following 12-weeks of endurance (5, 30) and interval (17, 18, 30) exercise training in patients with CAD. These observations are primarily attributed to increased antioxidant capacity, and/or increased NO bioavailability (4, 30). NTG-mediated dilation at rest was unchanged with training, which has been reported by other training studies (18, 30).

Limitations

Our findings did not support our hypothesis, as we did not observe an effect of training on the acute brachial artery endothelial responses to a single bout of exercise. First, the absence of a change in FMD responses following exercise at either pre- and post-training time points may be attributed to the sub-maximal exercise bout. While we attempted to create an exercise stimulus that was distinct from the 2 exercise training modalities, the exercise stimulus may not have been large enough to elicit endothelial changes. The exercise protocols employed by our previous study elicited peak heart rates

equal to 83% of the age-predicted heart rate maximum (2), while in the current study

patients reached 76% of their age-predicted heart rate maximum. Second, we performed

measurements 20-30 minutes post-exercise; however, only one other study used this time

point. While the assessment of endothelial function 60-minutes post-exercise would

enable a more direct comparison to our previous findings, time constraints did not permit

us to assess this time point. Third, we had 4 patients drop out of the study, and had to

exclude a small number of patients from specific analyses due to medication changes.

While our sample size was large enough to demonstrate statistical significance, a larger

sample would have been desired. We also pooled the 2 exercise training conditions into 1

group for analysis. While our preliminary statistical analyses support this decision, a large

sample size would also have the ability to detect group differences. Finally, recovery

measurements were performed approximately 45-60 minutes following the first dose of

NTG. While there is evidence to demonstrate repeated FMD tests have no effect on the

subsequent test (8), no studies have determined the effect of repeated NTG doses.

Therefore, it remains possible the first dose given during resting conditions may have

influenced our recovery measurements.

Conclusions

NTG-mediated dilation is clinically relevant for patients with CAD, since NTG is

commonly prescribed to patients to alleviate symptoms of angina. Our findings of

attenuated NTG responses 30-minutes following exercise are in contrast to previous

reports of unchanged FMD responses, and suggest transient "impairments" in endothelial-

independent dilation, which are not corrected following exercise training. The most likely reason for these observations is an increase in arterial diameters during the recovery period, resulting in a reduced dilatory capacity. However, given that this is the first study to report post-exercise reductions in NTG-mediated dilation, further research is required to delineate the mechanisms. Endothelial-dependent dilation, on the other hand, was unaffected by acute exercise, but showed significant improvements following exercise training. Overall, this study identifies a major limitation of previous acute exercise interventions, and highlights the necessity to perform both endothelial-dependent and – independent assessments for a more global understanding of endothelial function.

Acknowledgement

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6.0 CHAPTER 6: LOW-VOLUME HIGH-INTENSITY INTERVAL TRAINING IN PATIENTS WITH CORONARY ARTERY DISEASE

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Abstract

Purpose: Isocaloric interval exercise training programs have been shown to elicit improvements in numerous physiological indices in patients with coronary artery disease (CAD). Low-volume high-intensity interval exercise training (HIT) is effective in healthy populations; however its effectiveness in cardiac rehabilitation has not been established. This study compared the effects of 12-weeks of HIT, and higher-volume moderate-intensity endurance exercise (END), on brachial artery flow-mediated dilation (FMD), cardiorespiratory fitness (VO_{2peak}), and carotid artery health in patients with CAD. **Methods:** Twenty-two patients with documented CAD were stratified into HIT (n=11) or END (n=11) based on pre-training FMD. Both groups attended 2 supervised sessions per week for 12-weeks. END performed 30-50 minutes of continuous cycling at 58% peak power output (PPO), while HIT performed 10, 1-minute intervals at 89% PPO separated by 1-minute intervals at 10% PPO per session. **Results:** Relative FMD was increased post-training (END: $4.4 \pm 2.6\%$ vs. $5.9 \pm 3.6\%$; HIT: $4.6 \pm 3.6\%$ vs. $6.1 \pm 3.4\%$, $p \leq 0.001$ pre- vs. post-training) with no differences between groups. A training effect was also observed for relative VO_{2peak} (END: 18.7 ± 5.7 ml·kg^{-1}·min^{-1} vs. 22.3 ± 6.1 ml·kg^{-1}·min^{-1}; HIT: 19.8 ± 3.7 ml·kg^{-1}·min^{-1} vs. 24.5 ± 4.5 ml·kg^{-1}·min^{-1}, $p < 0.001$ for pre- vs. post-training), with no group differences. Indices of carotid artery stiffness were unchanged with training. **Conclusions:** Low-volume interval exercise training provides an alternative to the current, more time intensive prescription for cardiac rehabilitation. HIT elicited similar improvements in fitness and FMD as END, despite differences in exercise duration and intensity.

Introduction

Paragraph Number 1 Interval training has gained considerable attention as a suitable exercise program for patients with coronary artery disease (CAD). Investigations employing various types of interval protocols in CAD patients demonstrate training-induced improvements in numerous physiological indices (18-20, 30, 38, 39). Additionally, when compared to the current exercise program used in cardiac rehabilitation of high-volume moderate-intensity endurance exercise (END), interval exercise has been shown to elicit superior improvements in indices of cardiorespiratory fitness (30, 38, 39) and endothelial function (39). These prior investigations, however, employed isocaloric protocols, where the energy expenditure of the interval bout was matched to that of the END bout. No studies have examined the effectiveness of an interval protocol not matched to END for energy expenditure in patients with CAD.

Paragraph Number 2 Low-volume interval protocols, which are not matched for energy expenditure, are time-efficient strategies that have been shown to be effective in healthy populations (11, 29). Given that "lack of time" is the most commonly cited barrier to exercise adherence in cardiac rehabilitation (3), a low-volume, high-intensity interval protocol may be a superior treatment strategy in terms of adherence if the resultant physiological benefits are comparable. The purpose of this study was to compare the effects of 12-weeks of END and low-volume high-intensity interval exercise training (HIT) on endothelial function, cardiorespiratory fitness, and carotid artery structure and function in patients with CAD. These indices were chosen for examination because they are related to future risk of mortality (15, 21, 26). Based on evidence from investigations

in healthy populations, it was hypothesized that the effects of HIT would be comparable to those found with END for the indices examined.

Methods

Patients

Paragraph Number 3 Twenty-seven males and three females with documented CAD were recruited from the Cardiac Health and Rehabilitation Centre at the Hamilton Health Sciences General Site (Ontario, Canada). Three males and 1 female dropped out due to reasons unrelated to the exercise interventions. Three patients had changes to their beta-blockers, while 1 patient was put on a calcium channel blocker during the study period. Therefore, 22 patients were included in the study. Inclusion criteria included the presence of CAD, which was defined as the patient having at least one of the following: angiographically documented stenosis ≥50% in at least one major coronary artery; prior history of myocardial infarction (MI), percutaneous coronary intervention (PCI), or coronary artery bypass graft (CAGB) surgery; positive exercise stress test determined by a positive nuclear scan, or symptoms of chest discomfort accompanied by electrocardiographic (ECG) changes of >1 mm horizontal or down sloping ST-segment depression. Exclusion criteria included smoking within three months, non-cardiac surgical procedure within two months, MI or CABG within two months, PCI within one month, NYHA class II-IV symptoms of heart failure, documented valve stenosis, documented severe chronic obstructive pulmonary disease, symptomatic peripheral arterial disease, unstable angina, uncontrolled hypertension, uncontrolled atrial

arrhythmia or ventricular dysrhythmia, and any musculoskeletal abnormality that would

limit exercise participation. The study protocol was reviewed and approved by the

Hamilton Health Sciences/Faculty of Health Sciences Research Ethics Board, conforming

to the Helsinki Declaration on the use of human subjects, and written informed consent

was obtain from patients prior to participation. Participant characteristics, medical history

and medications are presented in Table 1.

TABLE 1. Participant characteristics and exercise training data

Variable	END n=11	HIT n=11
Age, yr	68 ± 8	62 ± 11
Height, m	1.70 ± 0.08	1.75 ± 0.09
Weight, kg	79.3 ± 15.9	86 .0 ± 19.0
BMI, kg·m^{-2}	27.3 ± 4.2	27.9 ± 4.9
CAD criteria, number		
MI	6	7
PCI	8	6
CABG	3	4
Medication classification, number		
ACE inhibitors	5	8
Anti-Platelets	11	10
β-Blockers	7	10
Calcium channel blockers	2	0
Diuretics	2	2
Statins	10	10
Exercise Training Data		
Total work, kJ	3918 ± 1048	1736 ± 792*
Mean work/session, kJ	172 ± 56	88 ± 348†
Mean heart rate, bpm	100± 9	116 ± 12*
Attendance, /24 sessions	22 ± 3	19 ± 4

Data expressed as mean ± SD. ACE, angiotensin-converting enzyme; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention. *$p \leq 0.001$ vs. END; †$p \leq 0.01$ vs. END.

Study Protocol

Paragraph Number 4 This study employed a between subject, repeated measure

design. Brachial artery endothelial-dependent function, which was assessed using flow-

mediated dilation (FMD), was the primary outcome. Therefore, in order to ensure

equivalent FMD values between exercise groups, patients were stratified based on their

pre-training relative brachial artery FMD into END or HIT. Assessments were performed

at baseline (pre-training), and following 12-weeks of exercise training (post-training).

Timing of sessions was different between participants, but within-subject sessions were

scheduled at the same time of day. Prior to testing sessions, participants were instructed to

fast for at least 8 hours, to abstain from exercise for 24 hours, caffeine and alcohol

consumption for 12 hours, and to take all medications and vitamins as usual, except for

nitroglycerin (NTG) which was withheld on testing days. All testing was performed in a

temperature-controlled room ($23.1 \pm 1.2°$ C).

Paragraph Number 5 Height (cm) and weight (kg) were measured, and body mass

index (BMI) was calculated. Seated blood pressure was measured in triplicate using an

automated oscillometric device (Dinamap Pro 100, Critikon LCC, Tampa, FL, USA)

following 10-minutes of quiet rest. The first was considered a calibration measure; so

brachial blood pressure was determined from the average of the second and third

measures (27).

Cardiorespiratory Fitness Assessment

Paragraph Number 6 Fitness was assessed using a medically supervised graded

exercise test to exhaustion on a cycle ergometer (Ergoline, Bitz, Germany). Heart rate

was monitored throughout the test using a 12-lead ECG (MAC 5500, General Electric,

Freiburg, Germany). Following a brief warm up, participants cycled at approximately 70

rpm for 1-minute at a workload of 100 KPM. After the first minute the workload was increased 100 KPM every minute until exhaustion. Expired gas was analyzed using a semi-automated metabolic cart (Vmax 229, SensorMedics Corporation,Yorba Linda, CA, USA), and oxygen consumption was determined at peak (VO_{2peak}) and anaerobic threshold (respiratory quotient = 1.0) from breath-by-breath samples averaged over 20-seconds. One participant did not complete the post-training test due to a musculoskeletal injury (unrelated to the exercise training); therefore analysis was performed on 21 patients (END=10; HIT=11).

Carotid Artery Assessments

Paragraph Number 7 All measurements were performed in the supine position following 10-minutes of quiet rest. Heart rate and beat-to-beat brachial artery blood pressures were measured throughout the testing session using a single-lead (CC5) ECG (model ML 123, ADInstruments Inc., Colorado Springs, CO, USA) and hemodynamic monitor (Nexfin, BMEYE, Amsterdam, The Netherlands). Resting heart rate is reported as the average value from a 5-minute sample collected after the rest period.

Paragraph Number 8 Images of the right common carotid artery were collected at a frame rate of 22.9 frames·s^{-1} using B-mode ultrasound (8 MHz) (Vivid Q, GE Medical Systems, Horten, Norway). Simultaneous carotid artery pressure waveforms were collected from the left common carotid artery using applanation tonometry (model SPT-301, Millar Instruments Inc., Houston, TX, USA). Since pressures collected with this technique are sensitive to hold-down pressure, absolute carotid artery blood pressures

were determined from the calibration of the waveforms to the simultaneous brachial

artery blood pressures. Diastolic and mean arterial pressures are similar in conduit arteries

when an individual is in the supine position; therefore carotid minimum and mean

pressures were equated to the brachial diastolic and mean arterial blood pressures (23).

Systolic blood pressure, on the other hand, is amplified throughout the arterial tree;

therefore carotid artery systolic blood pressure was determined from the extrapolation of

the maximum and calibrated pressures (13).

   Paragraph Number 9 Ultrasound images were stored in Digital Imaging and

Communications in Medicine (DICOM) format for offline analysis using a semi-

automated edge-tracking system [AMS (Artery Measurement System) Image and Data

Analysis, Gothenburg, Sweden] as previously described (6). Measurements of minimal,

mean, and maximal carotid artery diameters were determined from 10 heart cycles.

Intima-media thickness (IMT) at end-diastole of the far wall was determined from the

average of 10 heart cycles. The ratio of wall thickness to lumen diameter (wall/lumen

ratio) was calculated by dividing the IMT by the mean carotid artery lumen diameter.

Carotid artery distensibility was determined using the equation:

$$\text{Distensibility} = \frac{\Pi\left(\frac{d\,max}{2}\right)^2 - \Pi\left(\frac{d\,min}{2}\right)^2}{\Pi\left(\frac{d\,min}{2}\right)^2 \times PP}$$

where dmax is the maximal diameter, dmin is the minimal diameter, and PP is the carotid

pulse pressure (24). High quality carotid waveforms could not be collected in 2

individuals; therefore, brachial blood pressures were used to calculate distensibility in those instances.

Brachial Artery Assessments

Paragraph Number 10 All brachial artery endothelial function assessments were conducted in the supine position following the carotid assessments. Brachial artery endothelial-dependent function was assessed using the FMD test, based on previously established guidelines (5, 35). Duplex ultrasound (Vivid Q) was used to capture simultaneous images of the right brachial artery (13 MHz) at a frame rate of 7.7 frames·s⁻¹, and blood velocity measurements (4 MHz) throughout the FMD protocol. Baseline pre-occlusion images and velocities were collected 3-5 cm proximal to the antecubial fossa for 30-seconds. A pneumatic cuff positioned on the forearm distal to the antecubial fossa was inflated using a rapid cuff inflator (model E20 and AG101, Hokanson, Bellevue, WA, USA) to an occlusion pressure of 200 mm Hg. Following 5-minutes of occlusion, the cuff was released and duplex post-occlusion images and velocities were collected for 3-minutes. Duplex images were stored in DICOM format for offline analysis. End-diastolic frames, determined by the R-spike of the ECG trace, were extracted and stacked in a new DICOM file using commercially available software (Sante DICOM Editor, Version 3.0.12, Santesoft, Athens, Greece). Brachial artery diameters were determined using edge-detection software (AMS). Pre-occlusion diameters were determined from the average of the 30-second sample. Post-occlusion diameters were averaged in rolling 5-cycle bins (35). Peak post-occlusion diameter was defined as the maximum 5-cycle

average. Absolute FMD was calculated as the difference between the peak post-occlusion diameter and pre-occlusion diameter. Relative FMD is the ratio of the absolute FMD to the pre-occlusion diameter. We previously reported day-to-day intraclass correlations coefficients in a similar population of 0.89 for absolute and relative FMD (6).

Paragraph Number 11 Blood velocity raw audio signals were continuously analyzed by an external spectral analysis system (model Neurovision 500M TCD, Multigon Industries, Yonkers, NY, USA). The system applies a Fast Fourier transformation to the raw audio signals to determine continuous intensity weighted mean blood velocity (MBV). The MBV was sampled at 200 Hz during the FMD tests using commercially available hardware (Powerlab model ML795, ADInstruments, Colorado Springs, CO, USA), and analyzed offline using LabChart 7 Pro for Windows (Powerlab ML 795, ADInstruments, Colorado Springs, CO, USA). MBV signals were corrected for the angle of insonation (all ≤70°). Blood flow was calculated by multiplying brachial artery cross-sectional area by MBV. Post-occlusion reactive hyperemic blood flows and MBV were averaged into 5-cycle bins to align with the 5-cycle diameter bins. Peak reactive hyperemic blood flow is reported as the maximum value during the 3-minute post-occlusion period. Shear rate for each bin was calculated by multiplying the MBV bin by 8, and dividing it by the corresponding reactive hyperemic 5-cycle bin. The reactive hyperemic stimulus until peak dilation was quantified as shear rate area under the curve (AUC).

Paragraph Number 12 Endothelial-independent function was assessed 10-minutes following cuff release using a 0.4 mg sublingual spray of NTG (5). Longitudinal B-mode images (8 MHz) of the right brachial artery were collected prior to administration of NTG (pre-NTG; 10 cardiac cycles), and for 10 cardiac cycles every minute post-NTG up to 10-minutes at a frame rate of 22.9 frames·s^{-1}. End-diastolic frames were extracted and stacked, and peak-NTG diameter was determined from the average of 10 cardiac cycles at each minute. NTG results are expressed in absolute and relative units. One participant declined the NTG assessment due a history of severe headaches; therefore NTG results are reported for 21 patients.

Exercise Training Protocols

Paragraph Number 13 Participants attended 2 supervised sessions per week for 12-weeks at the Cardiac Health and Rehabilitation Centre at the Hamilton Health Sciences General Site (Hamilton, Ontario). Each session involved a 10-15 minute standardized warm-up and cool-down involving light aerobic exercise, and dynamic stretching. Exercise intensities for each protocol were based on the peak power output (PPO) achieved during the pre-training exercise stress test. The prescription for END was based on the Canadian Association of Cardiac Rehabilitation exercise guidelines (33), and involved continuous cycling at 58% of PPO (range 51-65%). Participants progressed from 30 minutes (weeks 1-4) of cycling, to 40 minutes (weeks 5-8), to 50 minutes (weeks 9-12). The protocol for HIT was based on previous research in healthy middle-aged adults (11), and involved 10, 1-minute cycling intervals at 89% PPO (range 80-104%) separated

by 1-minute intervals at 10% PPO. Rather than increasing duration, workload was increased every 4 weeks to elicit the heart rate responses achieved during 80% pre-training PPO. Consequently, patients were training at 102% pre-training PPO during weeks 5-8, and 110% pre-training PPO for weeks 9-12. In addition to the supervised training sessions, patients were instructed to exercise at least one additional day per week, using similar exercise durations and intensities as their exercise protocol. Unsupervised sessions were tracked using Polar heart rate monitors (RS300X, Polar Electro Inc., Lake Success, NY, USA).

Statistical Analysis

    Paragraph Number 14 Statistical analyses were performed using Statistical Package for Social Science software, version 11.5 (SPSS, Chicago, IL, USA). Factorial (Group: END versus HIT) repeated-measures (pre- versus post-training) analyses of variance were used to compare indices of cardiorespiratory fitness, brachial artery endothelial function, carotid artery structure and function, and resting hemodynamics. Group differences in pre-training characteristics and exercise training data were compared using independent t-tests. Data are presented as mean ± SD, with p≤0.05 considered statistically significant.

Results

    Paragraph Number 15 There were no differences in pre-training age, height, weight or BMI between HIT and END (p≥0.05). Post-training weight decreased (END: -

1.2 ± 1.8 kg; HIT: -0.6 ± 2.2 kg, $p \leq 0.05$). Exercise training data is reported in Table 1.

The END group performed twice as much total work and average work per supervised

exercise session compared to the HIT group ($p \leq 0.05$). The HIT group had higher mean

heart rates during the supervised sessions than the END group. HIT trained at $73 \pm 10\%$

of their age predicted maximal heart rate, while END trained at $65 \pm 4\%$. There was no

difference in exercise attendance between exercise groups. There were also no group

differences in the frequency or duration of unsupervised exercise sessions ($p \geq 0.05$).

During the 12-week training period, END performed 14 ± 14 unsupervised exercise

sessions for 45 ± 3 minutes per session, while HIT performed 11 ± 10 unsupervised

sessions for 40 ± 17 minutes per session. HIT trained at 68 ± 5 % of their age-predicted

heart rate maximum during the unsupervised sessions, which was higher than the END

group, which trained at $60 \pm 7\%$ ($p < 0.05$).

Paragraph Number 16 Cardiorespiratory fitness indices and exercise-training data

are presented in Table 2. After 12-weeks of training, fitness increased 19% and 24% in

the END and HIT groups, respectively. Relative VO_{2peak}, relative VO_2 at anaerobic

threshold, and peak power output were significantly larger post-training, with no

differences between exercise groups. There was no change in heart rate at peak or

anaerobic threshold following training or between exercise groups.

Paragraph Number 17 Brachial artery FMD results are reported in Figure 1.

Absolute and relative FMD were increased post-training, with no differences between

exercise groups. NTG results are reported in Figure 2. Absolute and relative NTG

responses were unchanged with training, with no differences between groups. Baseline

brachial artery diameters for the FMD and NTG tests, time to peak dilation, and FMD

peak reactive hyperemic blood flows and AUC are reported in Table 3. There was no

difference in pre-occlusion FMD diameters and pre-NTG diameters between exercise

groups, and diameters were unchanged post-training. Pre-occlusion FMD diameters were

also not significantly different from the pre-NTG diameters at pre- and post-training,

suggesting the artery had returned to a baseline state prior to administration of NTG.

Time to peak dilation during the FMD and NTG assessments were unchanged with

training, with no differences between exercise groups. Peak dilation during the FMD test

occurred around 1-minute post-cuff release, whereas maximal NTG-mediated diameters

were observed between 7 and 8 minutes after administration. Peak reactive hyperemic

blood flows and shear rate AUC were unchanged with training, with no differences

between groups.

TABLE 2. Cardiorespiratory fitness data pre- and post-training

Variable	END		HIT	
	Pre-	Post	Pre-	Post-
Peak Exercise Capacity				
Relative VO$_2$ peak, ml·kg^{-1}·min^{-1}	18.7 ± 5.7	22.3 ± 6.1*	19.8 ± 3.7	24.5 ± 4.5*
Peak HR, bpm	120 ± 24	123 ± 16	133 ± 16	139 ± 15
RER	1.21 ± 0.06	1.25 ± 0.08	1.25 ± 0.12	1.23 ± 0.09
Peak power output, W	108 ± 30	133 ± 42*	133 ± 51	159 ± 52*
Anaerobic Threshold				
Relative VO$_2$, ml·kg^{-1}·min^{-1}	13.2 ± 2.2	15.3 ± 3.3*	14.4 ± 2.0	17.7 ± 3.0*
HR, bpm	96 ± 12	99 ± 10	103 ± 13	110 ± 18

Data are mean ± SD. HR, heart rate; RER, respiratory exchange ratio; VO$_2$, oxygen
consumption. Anaerobic data and RER data n=18 (END=9; HIT=9). Peak HR n=20
(END=10; HIT=10). *p≤0.001 vs. pre-training.
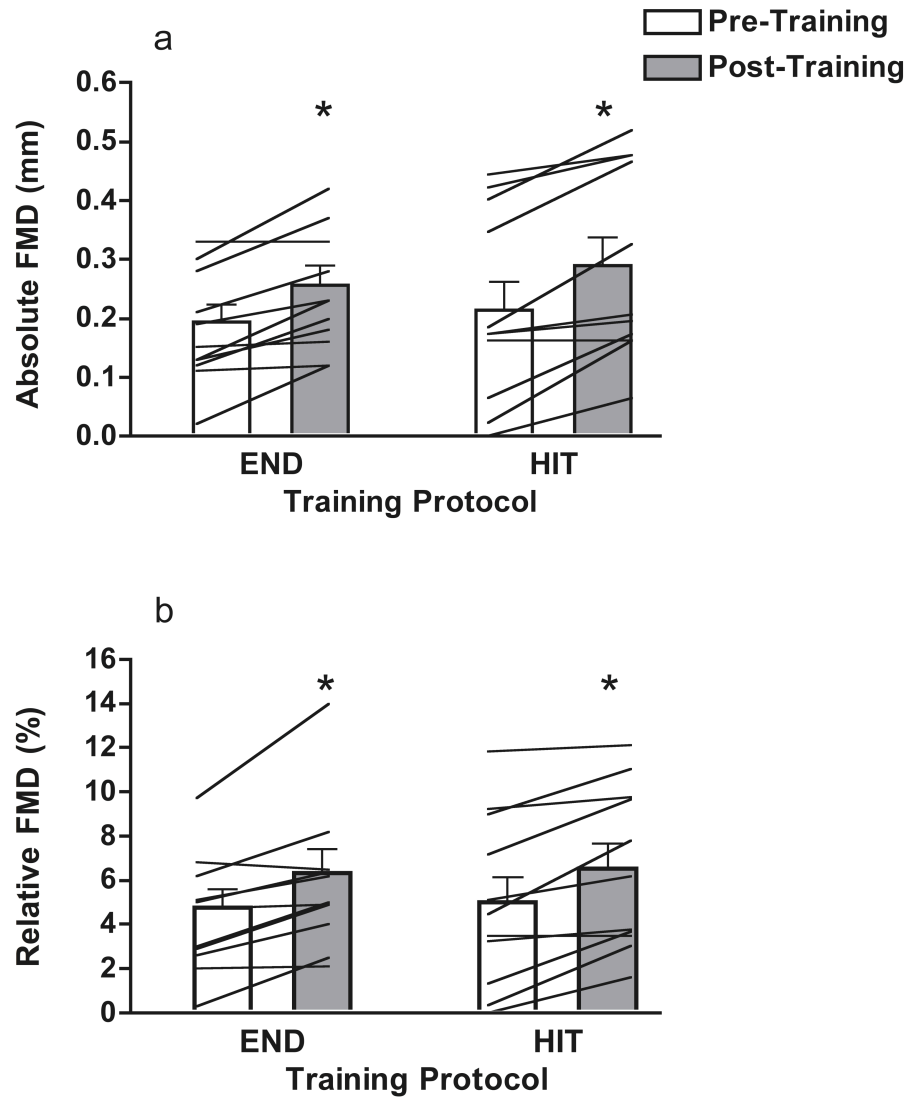
Figure 1. Absolute (a) and relative (b) brachial artery flow-mediated dilation (FMD) responses pre- (white) and post-training (grey) for END (moderate-intensity endurance exercise) and HIT (low-volume high-intensity interval exercise) groups. *p≤0.001 vs. pre-training.
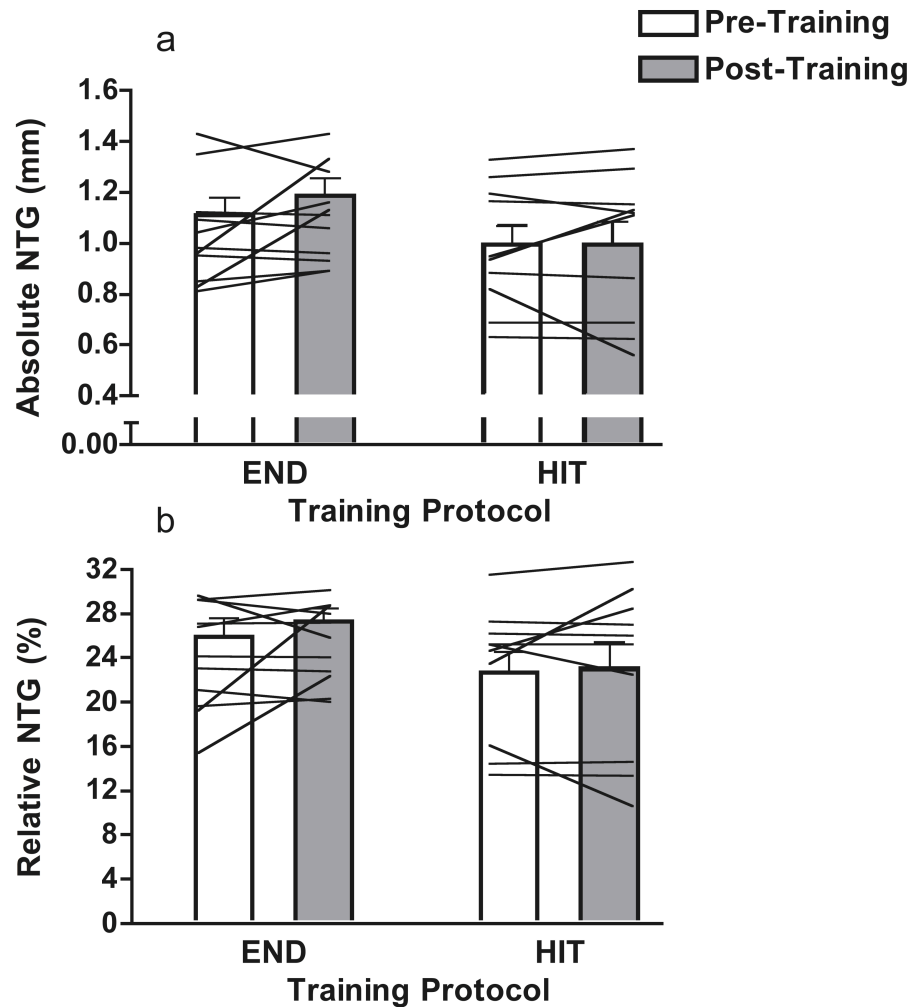
Figure 2. Absolute (a) and relative (b) brachial artery nitroglycerin (NTG) mediated dilation responses pre- (white) and post-training (grey) for END (moderate-intensity endurance exercise) and HIT (low-volume high-intensity interval exercise) groups.

Paragraph Number 18 Resting hemodynamics and indices of carotid artery function and structure are presented in Table 4. There were no differences between exercise groups for any of the indices. Seated brachial diastolic blood pressure, and

resting heart rate decreased post-training. Seated brachial systolic blood pressure, and

carotid artery distensibility and pulse pressure were unchanged post-training; however

carotid artery IMT and wall/lumen ratio were decreased following 12-weeks of END and

HIT.

TABLE 3. FMD and NTG indices pre- and post-training

| Variable	END		HIT	
	Pre-	Post	Pre-	Post-
Pre-occlusion EDD, mm	4.30 ± 0.75	4.32 ± 0.75	4.52 ± 0.70	4.52 ± 0.60
Peak RH BF, ml·min^{-1}	295 ± 189	247 ± 115	322 ± 129	346 ± 133
AUC	16077 ± 12639	14021 ± 9559	13356 ± 13197	18720 ± 17988
Time to Peak RH, s	62 ± 28	68 ± 25	59 ± 32	66 ± 34
Pre-NTG EDD, mm	4.38 ± 0.63	4.39 ± 0.51	4.48 ± 0.54	4.50 ± 0.65
Time to Peak NTG, min	7 ± 2	8 ± 2	7 ± 1	8 ± 2

Data are mean ± SD. EDD, end-diastolic diameter; BF, blood flow; NTG, nitroglycerin; RH, reactive hyperemia. NTG measurements n=21 (END=10; HIT=11).

TABLE 4. Indices of resting hemodynamics and carotid artery function and structure pre- and post-training.

Variable	END		HIT	
	Pre-	Post	Pre-	Post-
Seated SBP, mm Hg	124 ± 17	118 ± 19	124 ± 16	121 ± 9
Seated DBP, mm Hg	75 ± 10	68 ± 10*	81 ± 11	79 ± 10*
Heart Rate, bpm	55 ± 10	52 ± 8*	60 ± 7	57 ± 6*
Carotid PP, mm Hg	50 ± 11	50 ± 10	57 ± 14	53 ± 10
Distensibility, mm Hg^{-1}	0.0031 ± 0.0019	0.0030 ± 0.0011	0.0025 ± 0.0006	0.0028 ± 0.0005
IMT, mm	0.78 ± 0.21	0.77 ± 0.19†	0.74 ± 0.13	0.73 ± 0.13†
Mean LD, mm	7.24 ± 0.61	7.17 ± 0.64	6.71 ± 0.83	6.81 ± 0.91
Wall/Lumen Ratio, %	12.7 ± 3.1	12.2 ± 2.9†	13.1 ± 3.6	12.7 ± 3.8†

Data are mean ± SD. DBP, diastolic blood pressure; IMT, intima-media thickness; LD, lumen diameter; PP, pulse pressure; SBP, systolic blood pressure. Carotid PP n=20 (END=10; HIT=10). IMT and wall/lumen ratio n=21 (END=10; HIT=11). *p<0.01 vs. pre-training; †p<0.05 vs. pre-training.

Discussion

     Paragraph Number 19 This is the first study to examine the effectiveness of low-volume HIT in patients with CAD. We demonstrated comparable increases in brachial artery FMD and cardiorespiratory fitness, and reductions in resting hemodynamics and carotid artery IMT in both END and HIT training programs, despite the fact that the END group performed approximately twice as much total work as the HIT group. Schnohr and colleagues (32) recently demonstrated that cycling intensity, rather than duration, is more closely associated with determining the risk of all-cause and cardiovascular mortality in men and women. Our findings lend further support to the notion that exercise intensity may be more important than exercise duration in terms of cardiovascular health. In summary, low-volume HIT provides the same benefit as END, and therefore may be suitable exercise prescription for patients with CAD.

Cardiorespiratory Fitness

     Paragraph Number 20 Previous investigations in patients with CAD demonstrate comparable (38) and superior improvements in cardiorespiratory fitness with interval exercise training (30, 39) when compared to traditional endurance exercise. While we did not observe a difference in the magnitude of change in fitness between END and HIT, the 24% increase in relative VO_{2peak} observed following HIT is larger than the changes observed in these previous interval exercise investigations (18, 20, 30, 38). Low-volume HIT also increased relative VO_{2peak} at anaerobic threshold, similar to the findings reported by Warburton and colleagues (38). Collectively these findings demonstrate improved

cardiorespiratory fitness in patients with CAD following 12-weeks of low-volume HIT,

which is relevant to increasing patient survival rates (21).

Brachial Artery Endothelial Function

Paragraph Number 21 Impairments in endothelial function, termed endothelial

dysfunction, are associated with the presence of CAD (16). Brachial artery endothelial

function is an accepted non-invasive surrogate for coronary artery endothelial function

(34). Our study demonstrates comparable increases in absolute and relative FMD values

following 12-weeks of END and HIT. The lack of change in pre-occlusion diameters, and

peak reactive hyperemic blood flow and shear rate AUC between pre- and post-training

assessments suggests a comparable FMD stimulus. Shear rate AUC provides an estimate

of the shear stress on the endothelium, which is inversely proportional to arterial

diameter. The lack of change in shear stress stimulus, therefore, could be attributed to

similar pre- and post-training pre-occlusion brachial artery diameters. Blood flow is

regulated by downstream resistance vessels. We did not observe any changes in peak

reactive hyperemic blood flow with training; therefore it appears exercise training did not

affect resistance vessel function. The findings of a comparable FMD stimulus pre- and

post-training lend support to an increased capacity of the endothelium to respond to a

given stimulus following 12-weeks of exercise training.

Paragraph Number 22 Training induced improvements in FMD have been reported

by other studies employing lower-limb interval (18, 20, 39) and endurance (9, 39)

exercise in CAD patients. It has previously been established that flow-mediated increases

in brachial artery diameter are largely mediated by the vasodilator, nitric oxide (NO) (8).

CAD is associated with impairments in NO production, and decreased protein expression

of eNOS, the enzyme required for NO production (25). Training induced improvements

in FMD, therefore, may be attributed to increased NO bioavailability. Four weeks of

cycling exercise training in humans increased basal release of NO in the forearm (14),

and coronary eNOS protein expression (10). Comparable increases in NO production

were also observed following 3 weeks of interval exercise training in individuals with left

ventricular dysfunction (7). An alternative explanation may be a reduction in basal

oxidative stress. Reactive oxygen species, specially superoxide anions, are capable of

quenching available NO stores (4), decreasing NO bioavailability. Four weeks of exercise

training in patients with CAD increased endothelial function, and decreased NAD(P)H

oxidase (1), the precursor to superoxide. Increased antioxidant status was also

demonstrated in heart failure and CAD patients following interval exercise training (39).

Therefore, our training induced improvements in FMD may be attributed to increased

antioxidant capacity.

Paragraph Number 23 Currently, there is no consensus regarding a clinical cut off

value for brachial artery FMD (35). Increased cardiovascular morbidity and mortality has

been shown to be associated with a persistently impaired relative FMD value < 5.5%

following optimized anti-atherosclerotic therapy in patients with existing CAD (15). The

pre-training FMD averages for both END and HIT were below 5.5%, suggesting our sample was at an increased risk of future cardiovascular events. We observed a 34% and 33% increase in endothelial-dependent function in the END and HIT groups, respectively, resulting in post-training group averages above 5.5%. Our findings suggest 3-months of both END and HIT were capable of improving patient survival rates by decreasing their future risk of cardiovascular events and mortality. It is also worth noting that these adaptations occurred with only 12-weeks of exercise training, and that a longer exercise-training program may translate into further increases in FMD.

Paragraph Number 24 We observed no change in NTG-mediated vasodilation following both training programs, which is consistent with other training studies (14, 20, 39). The absence of endothelial-independent improvements with exercise training lends further support to the ability of both HIT and END to selectively improve endothelial-dependent pathways.

Hemodynamic and Carotid Artery Indices

Paragraph Number 25 Resting heart rate and diastolic blood pressure were decreased following training in both END and HIT. Resting heart rate reductions have been reported by other interval exercise training studies (18, 20), and are likely attributed to modifications in the autonomic control of the heart (19). An elevated resting heart rate is associated with increased risk of mortality from CAD (22). For each increment of 10 bpm, there is approximately an 18% and 10% increased risk of death for women and men, respectively. The average reduction in heart rate observed in both END and HIT was <10

bpm, therefore not clinically significant. However, reductions were observed with only 12-weeks of training, and in a population receiving beta-blockade therapy.

Paragraph Number 26 A reduction in diastolic blood pressure following interval exercise training has been previously reported (20). END resulted in a 10% reduction in diastolic blood pressure compared to a 3% with HIT; however, the reductions observed with HIT are comparable to reductions reported by a meta-analysis of exercise training studies (12). Systolic blood pressure was not significantly lower following training, which contradicts the findings of the meta-analysis. However, previous interval exercise studies in CAD reported no training induced reductions in systolic blood pressure (20, 30, 38, 39). While we expected to observe a reduction in systolic blood pressure with exercise training, the absence of a change could be attributed to the normotensive pre-training state of our patients (due to anti-hypertensive medications), or the sample size.

Paragraph Number 27 No interval exercise training studies in patients with CAD have examined changes in indices of carotid artery function or structure. Increased carotid artery IMT and decreased aortic distensibility are present in patients with CAD (2). Additionally, increased carotid artery IMT is related to risk of adverse events in patients with CAD (26), while reduced carotid distensibility is related to increased risk of ischemic stroke (37). Our assessments of carotid artery function are comparable to values reported in middle-aged and hypertensive populations (24). We observed no change in carotid artery distensibility following 12-weeks of END or HIT, which is consistent with low-volume interval exercise in healthy populations (29). The absence of a change in distensibility is not surprising since brachial blood pressures during the carotid

assessments (not reported), carotid pulse pressure, and carotid lumen diameter were unchanged with training. A longer training period may be required to observe training induced adaptations in these indices.

Paragraph Number 28 Carotid artery IMT and wall/lumen were decreased following both END and HIT. A review of exercise training studies and arterial wall thickness reveals reductions or no change in carotid IMT with exercise training (36). Increased risk of cardiovascular events have been demonstrated in populations with an IMT >1 mm (28). Additionally, increasing IMT by >0.1 mm is associated with a 10-18% increased risk of cardiovascular events (17). While the magnitude of reductions in IMT following END and HIT were <0.1 mm, the average IMT reported by both exercise groups were below the clinical cut off value of 1 mm, suggesting our participants are at a decreased risk for future cardiovascular events. Wall/lumen ratio is considered an index of arterial structure. Hypertensive adults demonstrate increased wall/lumen ratios and decreased arterial distensibility, suggesting the mechanical environment of increased pressures leads to structural alterations in wall thickness (31). The observed reduction in wall/lumen ratio following END and HIT is likely attributed to the reduction in IMT in the face of unchanged lumen diameter.

Limitations

Paragraph Number 29 We aimed to recruit an equal number of both men and women; however, we had limited access to female patients with CAD. Therefore, only 2 women were included in the study. While they were distributed between the 2 exercise

groups, a larger female sample would be more representative of the cardiac rehabilitation population. The study did not include a control group with no exercise intervention. Rather, we used the current standard of care (END) as the control group. Previous interval training studies employing a non-exercise control group found no change in physiological indices (20, 39). Participants attended 2 supervised training sessions per week, and exercised 1 additional day per week. While our prescription satisfies the cardiac rehabilitation guidelines, public health agencies advocate for individuals to participant in activity during most days of the week. We observed significant training adaptations with only 3 days of exercise per week; however, larger adaptations may have been observed by increasing training frequency.

Paragraph Number 30 There is recent evidence to suggest carotid plaque rather than IMT is a stronger indicator of mortality risk in patients with CAD (26). While we observed significant reductions in IMT post-training, the assessment of carotid plaque in this population may be more sensitive, and therefore should be included in future studies. Lastly, there are a variety of interval exercise training protocols currently being used. We chose the ratio of 1:1 for the high and lower intensity exercise intervals based on its success in middle-aged populations (11). However, alternative time-efficient interval protocols should be tested. What is important is that our protocol was time-efficient, and involved approximately half of the work involved in a traditional endurance exercise session. We believe these features may be appealing to populations who are not motivated, or do not have the time to exercise.

Conclusions

Paragraph Number 31 Given that "lack of time" is the most commonly cited barrier to exercise adherence in cardiac rehabilitation, time-efficient exercise programs pose an advantageous treatment strategy for patients with cardiovascular diseases. This study demonstrated training induced improvements in fitness and other physiological indices following 12-weeks of END and time-efficient low-volume HIT, with no difference in the magnitude of response between exercise programs. While it is difficult to draw conclusions regarding the clinical impact of the adaptations observed, the ability to elicit improvements towards a reduced future risk of mortality is noteworthy, especially given the HIT group performed approximately half the amount of work than the END group. This study also demonstrated the feasibility of low-volume HIT in cardiac rehabilitation. We reported no adverse events, and no difference in exercise program adherence, despite differences in exercise intensities. In conclusion, the findings from this study support the continued investigation of alternative exercise prescriptions for individuals with CAD, including low-volume HIT protocols.

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7.0 CHAPTER 7: HEART RATE RECOVERY IS UNCHANGED IN PATIENTS WITH CORONARY ARTERY DISEASE FOLLOWING 12-WEEKS OF HIGH-INTENSITY INTERVAL AND MODERATE-INTENSITY ENDURANCE EXERCISE TRAINING

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Abstract

Attenuated heart rate recovery responses following acute exercise are associated with increased risk of mortality. Moderate-intensity endurance exercise training (END) increases heart rate recovery in patients with coronary artery disease (CAD). The effect of low-volume high-intensity interval exercise training (HIT) on heart rate recovery in this population is unknown. The purpose of this study was to compare the effects of 12-weeks of END and HIT on heart rate recovery in patients with CAD. Fourteen males with documented CAD participated in 12-weeks of END (n=7) or HIT (n=7) exercise training. END consisted of 30-50 minutes of continuous cycling at 58% peak power output (PPO). HIT involved 10, 1-minute intervals at 89% PPO separated by 1-minute intervals at 10% PPO. Heart rate recovery at 1 and 2-minutes was measured pre- and post-training using a sub-maximal exercise bout. Following 12-weeks of END and HIT, there was no change in heart rate recovery values reported at 1-minute (END: 40 ± 12 vs. 37 ± 19; HIT: 31 ± 8 vs. 35 ± 8, $p \geq 0.05$ for pre- vs. post-training) or at 2-minutes (END: 44 ± 18 vs. 43 ± 19; HIT: 42 ± 10 vs. 50 ± 6, $p \geq 0.05$ for pre- vs. post-training). In conclusion, neither END nor HIT exercise programs elicited training-induced improvements in heart rate recovery in patients with CAD. The absence of improvements with training may be attributed to the low risk, pre-training heart rate recovery values of our sample.

Introduction

Patients with coronary artery disease (CAD) have a reduced life expectancy compared to individuals free from disease (Roger et al. 2012). The treatment of CAD involves a myriad of interventions aimed at secondary disease prevention and improving survival rates (Smith et al. 2006). Heart rate recovery, defined as the fall in heart rate immediately post-exercise, is an indicator of autonomic function and demonstrates a strong correlation with mortality risk in healthy (Cole et al. 1999; Cole et al. 2000) and CAD (Vivekananthan et al. 2003) populations. Cardiac rehabilitation exercise training interventions, which typically employ moderate-intensity endurance exercise (END), have been shown to increase heart rate recovery after 8 (Hai et al. 2010) and 12-weeks of training (Giallauria et al. 2006a; Giallauria et al. 2006b; Hao et al. 2002; Tsai et al. 2005; Wu et al. 2006). Isocaloric interval exercise protocols, which are matched to END for energy expenditure, have gained considerable attention as a suitable exercise prescription for individuals with CAD. Previous investigations examining the effects of isocaloric interval exercise training in cardiac rehabilitation settings demonstrate improvements in indices of resting hemodynamics, cardiorespiratory fitness, endothelial function, and left ventricular morphology and function (Moholdt et al. 2012; Munk et al. 2010; Munk et al. 2009b; Rognmo et al. 2004; Warburton et al. 2005; Wisloff et al. 2007). Low-volume high-intensity interval exercise (HIT), which involves less time and less work than END, has been shown to be effective in healthy populations (Hood et al. 2011; Little et al. 2010); however, no studies have examined the effect of HIT training in populations with CAD. Therefore, the purpose of this study was to compare the effects of 12-weeks of

END and HIT on heart rate recovery in patients with CAD. It was hypothesized both training programs would increase heart rate recovery in patients with CAD.

Materials and Methods

Participants

Patients with documented CAD were recruited from the Cardiac Health and Rehabilitation Centre at the Hamilton Health Sciences General Site (Ontario, Canada). Inclusion criteria included the presence of CAD, which was defined as the patient having at least one of the following: angiographically documented stenosis ≥50% in at least one major coronary artery; prior history of myocardial infarction (MI), percutaneous coronary intervention (PCI), or coronary artery bypass graft (CAGB) surgery; positive exercise stress test determined by a positive nuclear scan, or symptoms of chest discomfort accompanied by electrocardiographic (ECG) changes of > 1mm horizontal or down sloping ST segment depression. Exclusion criteria included smoking within three months, non-cardiac surgical procedure within two months, MI or CABG within two months, PCI within one month, NYHA class II-IV symptoms of heart failure, documented valve stenosis, documented severe chronic obstructive pulmonary disease, symptomatic peripheral arterial disease, unstable angina, uncontrolled hypertension, uncontrolled atrial arrhythmia or ventricular dysrhythmia, insulin requiring diabetes mellitus, and any musculoskeletal abnormality that would limit exercise participation. Twenty-four males were recruited; however, 1 patient was excluded due to high resting blood pressure (diastolic >100 mm Hg). Therefore, 23 patients were enrolled in the study. Four patients

dropped out due to medical reasons unrelated to the exercise training, 3 patients had medication changes during the study, and 2 patients had unusable exercise data. Therefore, a total of 14 patients were included in the final analysis. All protocols were reviewed and approved by the Hamilton Health Sciences/Faculty of Health Sciences Research Ethics Board, conforming to the Helsinki Declaration on the use of human subjects, and written informed consent was obtain from patients prior to participation.

Study Design

Heart rate recovery was assessed using a sub-maximal exercise bout, which was performed before the initiation of the exercise training programs (pre-training), and following 12-weeks of exercise training (post-training). Within-subject sessions were scheduled at the same time of day to minimize the effects of circadian rhythms (Niemela et al. 1994). Prior to pre-and post-training testing, participants were instructed to fast for at least 8 hours, and to abstain from exercise for 24 hours, and caffeine and alcohol consumption for 12 hours. Medications and vitamins were kept constant throughout the study, except for nitroglycerin, which was withheld on testing days. All testing was performed in a temperature-controlled room (23.0 ± 1.2 ˚C). Height and weight were measured with shoes removed, and body mass index (BMI) was calculated.

Heart Rate Recovery Assessments

Resting measures of heart rate and beat-to-beat brachial artery blood pressures were assessed in the supine position following a 10-minute rest period using a single-lead

(CC5) ECG (model ML 123; ADInstruments Inc., Colorado Springs, CO, USA) and a non-invasive hemodynamic monitor (Nexfin; BMEYE, Amsterdam, The Netherlands). Resting heart rate and blood pressure measures are reported as the average value from a 5-minute sample collected after the rest period.

The exercise intensities for the sub-maximal exercise bout were based on the peak power output (PPO) achieved during the pre-training peak exercise test (data not reported). Following a 3-minute unloaded warm-up on a cycle ergometer (Excalibur Sport V2.0; Lode BV, Groningen, The Netherlands), participants completed 4, 3-minute stages at increasing intensities of 20%, 40%, 60% and 80% of pre-training PPO. The same absolute intensities were used for the post-training sub-maximal exercise bout. Heart rate and blood pressure were monitored throughout the sub-maximal bout, and ratings of perceived exertion (RPE) using the Borg 6-20 RPE Scale (Borg 1998) were recorded at the end of each exercise stage.

Immediately upon exercise cessation, heart rate was recorded continuously for 5-minutes in the supine position. Exercise heart rates were averaged in 5-second bins. Mean heart rate was calculated as the average heart rate during the entire exercise bout. Peak heart rate was determined as the peak of the 5-second bins. Heart rate recoveries at 1-minute and 2-minutes post-exercise were determined by subtracting heart rate at each time point (10-second average) from the peak 5-second exercise heart rate.

Exercise Training

Patients were stratified into END (n=7) or HIT (n=7) based on pre-training brachial artery endothelial function (data not reported). Patients attended 2 supervised exercise sessions per week for 12-weeks. Briefly, END began with 30-minutes of continuous cycling at 58% PPO, based on the Canadian Association of Cardiac Rehabilitation exercise guidelines (Stone et al. 2009), then progressed to 40- minutes for weeks 5-8, and 50-minutes for weeks 9-12. HIT involved 10, 1-minute cycling intervals at 89% PPO separated by 1-minute intervals at 10% PPO (Hood et al. 2011). Intensity was increased every month to elicit the same pre-training absolute workloads.

Statistical Analysis

Statistical analyses were performed using Statistical Package for Social Science software, version 11.5 (SPSS, Chicago, IL, USA). Factorial (Group: END versus HIT) repeated-measures analyses of variance were used to compare pre- and post-training heart rate recoveries, mean and peak exercise heart rates, blood pressures, and RPE indices. Group comparisons of pre-training characteristics were compared using independent t-tests. Data are presented as mean ± SD, with $p \leq 0.05$ considered statistically significant.

Results

Participant characteristics, medical history and medications are presented in Table 1. There were no differences in pre-training age, height, weight, or BMI between exercise groups ($p \geq 0.05$). Heart rate, heart rate recovery, blood pressure and RPE are reported in

Table 2. Resting heart rate decreased following training with no differences between groups (p≤0.01). There were no group or training effects for resting brachial blood pressure. Heart rate recoveries at 1-minute and 2-minutes post-exercise were unchanged with training, with no differences between END and HIT. Mean exercise heart rate was decreased following 12-weeks of END and HIT, with no differences between exercise groups (p≤0.01). A training effect for RPE reported during the final sub-maximal exercise stage was also observed, with no differences between exercise groups (p≤0.01). There were no group differences or training effects observed for peak exercise heart rates or blood pressures.

Table 1 Participant characteristics

Variable	END n=7	HIT n=7
Age, yr	64 ± 6	63 ± 11
Height, m	1.76 ± 0.07	1.70 ± 0.04
Weight, kg	80.1 ± 12.6	89.1 ± 21.3
BMI, kg·m^{-2}	27.8 ± 3.9	28.6 ± 5.7
CAD criteria, number		
MI	5	5
PCI	5	4
CABG	2	3
Medication classification, number		
ACE inhibitors	5	3
Anti-Platelets	7	7
β-Blockers	6	6
Calcium channel blockers	1	0
Diuretics	0	2
Statins	7	6

Data are presented as mean ± SD. ACE, angiotensin converting enzyme; BMI, body mass index; CABG, coronary artery bypass graft; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table 2 Resting and sub-maximal heart rates and blood pressures, RPE, and heart rate recoveries

Variable	END		HIT	
	Pre-	Post	Pre-	Post-
Resting Values				
Resting HR, bpm	55 ± 4	53 ± 4*	58 ± 6	56 ± 5*
Resting systolic BP, mm Hg	128 ± 11	124 ± 10	133 ± 11	129 ± 16
Resting diastolic BP, mm Hg	53 ± 6	55 ± 3	52 ± 6	57 ± 8
Resting MAP, mm Hg	78 ± 7	78 ± 5	79 ± 8	81 ± 10
Exercise Values				
Mean exercise HR, bpm	91 ± 15	82 ± 6*	100 ± 19	88 ± 12*
Peak exercise HR, bpm	116 ± 26	109 ± 24	129 ± 25	121 ± 19
Peak systolic BP, mm Hg	175 ± 30	171 ± 25	196 ± 22	179 ± 39
Peak diastolic BP, mm Hg	62 ± 17	72 ± 10	76 ± 9	73 ± 15
Peak MAP, mm Hg	100 ± 17	105 ± 13	116 ± 12	108 ± 22
Peak RPE	15 ± 2	13 ± 2*	16 ± 2	13 ±2*
Heart Rate Recovery Values				
HRR-1 minute, bpm	40 ± 12	37 ± 19	31 ± 8	35 ± 8
HRR-2 minutes, bpm	44 ± 18	43 ± 19	42 ± 10	50 ± 6

Data are presented as mean ± SD. BP, blood pressure; HR, heart rate; HRR, heart rate recovery; MAP, mean arterial pressure. *p≤0.01 vs. pre-training.

Discussion

The main finding from this study was no change in sub-maximal exercise heart rate recovery responses following 12-weeks of exercise training in patients with CAD. While the findings do not support our hypothesis, they are still relevant and worthy of explanation.

Heart rate recovery was measured at 1-minute and 2-minutes post-exercise. Currently, there is no consensus on the mechanisms mediating heart rate responses at these two different time points (Lahiri et al. 2008). Savin and et al. (1982) previously demonstrated the role of sympathetic withdrawal immediately after exercise, whereas Imai et al. (1994) demonstrated the role of vagal reactivation within 30-seconds of

exercise cessation (Imai et al. 1994). Both time points show associations with mortality risk; however, heart rate recovery at 2-minutes has been shown to be a stronger predictor (Shetler et al. 2001). Additionally, there is no consensus on the clinical cut off for heart rate recovery. While a heart rate recovery < 12 bpm at 1-minute post-exercise is the most commonly used index (Cole et al. 1999), other investigations have demonstrated increased risk of mortality with values < 25 bpm (Jouven et al. 2005) after 1-minute, and < 22 bpm (Lahiri et al. 2008) or ≤ 42 bpm (Cole et al. 2000) after 2-minutes post-exercise.

Training induced increases in heart rate recovery at 1-minute have been observed in patients with MI (Giallauria et al. 2006a; Giallauria et al. 2006b; Hai et al. 2010; Hao et al. 2002), PCI(Hao et al. 2002), and CABG (Hao et al. 2002; Tsai et al. 2005; Wu et al. 2006). The exercise programs employed by these studies involved 30-60 minutes of moderate-intensity exercise for 12-weeks. The most commonly cited mechanisms for training induced improvements in heart rate recovery is improved parasympathetic tone. Laing et al. (2011) demonstrated increased post-exercise heart rate variability following 3-months of exercise training in patients with CAD. Therefore, it appears plausible that increased parasympathetic activation with exercise training may contribute to increased heart rate recovery following an acute exercise bout. We did not observe any change in heart rate recovery responses at 1 or 2-minutes following 12-weeks of END and HIT training in patients with CAD. Exercise training interventions showing improvements in heart rate recovery include populations with attenuated pre-training values of 4 (Tsai et al. 2005), 9 (Wu et al. 2006), 13 (Hao et al. 2002), 14 (Giallauria et al. 2006b) and 18 (Hai et

al. 2010) bpm. Both END (40 bpm) and HIT (31 bpm) demonstrated greater pre-training heart rate recovery values, which is likely to explain the non-significant findings. Additionally, the values observed in our sample are comparable to values reported in healthy populations (Ardic et al. 2011). Beta-blockade has been shown to enhance heart rate variability in patients with CAD (Niemela et al. 1994). Several investigations showing heart rate recovery improvements included patients on beta-blockers (Giallauria et al. 2006a; Giallauria et al. 2006b; Hai et al. 2010; Wu et al. 2006). Twelve of the 14 patients included in this study were receiving beta-blocker medication. Therefore, the higher than average pre-training heart rate recovery values reported by our patients may be attributed to increased heart rate variability due to their beta-blocker therapy. It is also worth noting that the pre-training averages at 1 and 2-minutes were well above the clinical cut off values listed above. Therefore, the absence of a training effect may be attributed to the low-risk, pre-training heart rate recovery values of our patients.

The absence of training induced improvements in heart rate recovery following isocaloric interval exercise training have been previously reported in patients with CAD (Moholdt et al. 2012). Similar to our sample, patients in this investigation reported higher than average pre-training heart rate recovery values, which provide further support that training induced improvements in patients with CAD may only be obtainable in individuals with attenuated values. Interval training has been shown to alter the autonomic nervous system, causing a shift towards increased parasympathetic activity and decreased sympathetic activation (Munk et al. 2010). While this investigation did not assess heart rate recovery, the adaptations suggest interval exercise has the capacity to

alter autonomic function, which could potentially contribute to increased heart rate recovery responses following training in patients with low pre-training values.

Our patients did report lower resting heart rates, and lower mean exercise heart rates and RPE during the sub-maximal exercise bout following 12-weeks of END and HIT, with no differences in the magnitude of change between exercise groups. Resting heart rate reductions have previously been reported by exercise training studies in CAD patients (Munk et al. 2009b; Wisloff et al. 2007), and are typically attributed to modifications in resting autonomic function. The improved exercise responses lend support to an improvement in patient fitness levels with exercise training. Peak exercise heart rates and blood pressure responses were unchanged with training. Previous studies examining heart rate recovery responses with exercise training employed maximal acute exercise bouts, resulting in unchanged (Hao et al. 2002) or increased (Dimopoulos et al. 2006; Giallauria et al. 2006b; Hai et al. 2010; Wu et al. 2006) peak exercise heart rates following training. Unchanged exercise blood pressure responses have been reported following continuous (Hao et al. 2002) and interval (Munk et al. 2009b) exercise training in patients with CAD. Resting blood pressure was also unchanged following training, which may be attributed to the use of anti-hypertensive medications by our patients, or the sample size.

The study had a few limitations. We attempted to recruit both men and women with CAD; however, we were only able to recruit men. Comparable increases in heart rate recovery have been reported in males and females following endurance exercise training (Kligfield et al. 2003). However, it remains possible that interval training may have an

alternative effect on women with CAD, and is worthy of examination. We had to exclude several participants due to medication changes and poor data quality; therefore our sample is small. It is possible that a larger sample may alter the results. Lastly, we did not measure heart rate variability; however, any additional information provided by these measures may help to explain our findings.

Conclusion

Unlike previous investigations in populations with CAD, we did not observe increases in heart rate recovery at 1-minute or 2-minutes following 12-weeks of END and HIT exercise training. Attenuated heart rate recovery responses following maximal and sub-maximal exercise bouts are associated with increased risk of mortality in healthy and clinical populations. While the finding of a significant increase in heart rate recovery following training would support an associated reduction in mortality risk, on average our patients reported low risk values for heart rate recovery at both the 1 and 2-minute time point. Training induced decreases in mean exercise heart rates and RPE suggest the exercise protocols were of sufficient intensity and duration to elicit improvements in patient fitness levels. Therefore, the absence of increases in heart rate recovery post-training are likely not attributed to the exercise programs, but rather the higher than average pre-training heart rate recovery values reported by our patients.

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8.0 CHAPTER 8: GENERAL DISCUSSION AND CONCLUSIONS

8.1 Discussion Overview

The four investigations contained in this thesis sought to: 1) examine the acute brachial artery endothelial responses and cardiovascular responses 60-minutes following a single bout of END and HIT exercise in habitually active patients with CAD, 2) examine the effect of 12-weeks of exercise training on the acute brachial artery endothelial responses to a single bout of sub-maximal exercise, 3) examine the effects of 12-weeks of END and HIT training on cardiorespiratory fitness and indices of resting cardiovascular health in patients with CAD, and 4) examine the effects of 12-weeks of END and HIT training on heart rate recovery and sub-maximal exercise responses in patients with CAD.

The first study (See chapter 4.0) of this thesis demonstrated no difference in the brachial artery endothelial responses and cardiovascular responses 60-minutes following a single bout of END and HIT exercise. The results suggest that despite involving a shorter exercise duration and lower total amount of work, the HIT bout elicited comparable acute post-exercise responses to the END bout. The second study (See chapter 5.0) examined the acute brachial artery endothelial responses to exercise before and following 12-weeks of exercise training to determine if training status would affect the acute post-exercise responses. The training period did not appear to alter the acute endothelial responses to sub-maximal exercise, as similar acute post-exercise changes in FMD and NTG-mediated dilation were observed pre- and post-training. However, the novel finding of this investigation was a reduction in endothelial-independent function immediately post-exercise at all training time points, which is likely explained by post-

exercise increases in arterial diameters. The chronic effects of HIT were examined in the last 2 studies. The third study (See chapter 6.0) demonstrated 12-weeks of END and HIT elicited comparable modifications in traditional and non-traditional CVD risk factors in patients with CAD. Contrary to previous interval exercise training investigations in patients with CAD, our low-volume HIT protocol involved less work and a shorter exercise duration than the END protocol, which suggests positive training adaptations are obtainable with a lower volume of exercise and therefore shorter time commitment for the participants. Finally, the fourth study (See chapter 7.0) observed no significant change in indices of heart rate recovery following 12-weeks of END and HIT training, which is in contrast to previous investigations. However, our patients had pre-training heart rate recovery values in the healthy, low risk range, which suggests training associated adaptations may only be achievable in populations with attenuated heart rate recovery values prior to initiating training.

The subsequent discussion will address the main findings of the studies, as well as provide directions for future research. The acute exercise investigations (chapters 4.0 & 5.0) will be discussed first, followed by a discussion of the findings observed with chronic training (chapters 6.0 & 7.0).

8.2 Acute Exercise and Endothelial Function

Examinations of the acute brachial artery endothelial responses to a single bout of exercise are plentiful, and have included a variety of populations including healthy individuals (Harvey et al. 2005; Jones et al. 2010; Llewellyn et al. 2012; Phillips et al.

2011; Rognmo et al. 2008; Silvestro et al. 2002; Tinken et al. 2010; Tyldum et al. 2009), athletes (Dawson et al. 2008; Phillips et al. 2011; Rognmo et al. 2008), post-menopausal women (Harvey et al. 2005), overweight individuals (Harris et al. 2008), medicated hypertensives (McGowan et al. 2006), and patients with peripheral arterial disease (Silvestro et al. 2002). The assessment of endothelial function following a single bout of exercise is relevant because it provides information about the exercise stimulus. It has been suggested that post-exercise impairments in endothelial-dependent function may be attributed to increased oxidative stress and/or decreased NO bioavailability, while enhanced endothelial-dependent function may be attributed to increased NO bioavailability and/or increased antioxidant capacity (Rognmo et al. 2008). No previous studies in this area have commented on the role of vascular smooth muscle function, as endothelial-independent assessments are either not performed, or unaffected by the acute exercise bout. Regardless of the mechanisms, post-exercise reductions in endothelial function may represent transient dysfunction, which may increase an individual's cardiovascular risk. Surprisingly, no studies have examined the acute brachial artery endothelial responses to exercise in patients with CAD, despite evidence of resting endothelial dysfunction (Lieberman et al. 1996; Zhang et al. 2000). The studies featured in chapters 4.0 and 5.0 of this thesis are the first to extend the acute exercise literature to a patient population with CAD.

8.2.1 The Role of Different Exercise Bouts

Investigations of the acute endothelial responses to a single bout of exercise have employed a variety of exercise interventions including endurance exercise (Dawson et al. 2008; Harris et al. 2008; Harvey et al. 2005; Jones et al. 2010; Llewellyn et al. 2012; Tyldum et al. 2009), interval exercise (Tyldum et al. 2009), sub-maximal and maximal exercise (Silvestro et al. 2002), isometric handgrip exercise (McGowan et al. 2006; Tinken et al. 2010), and resistance exercise (Phillips et al. 2011). Of these investigations, only 2 have compared the effect of different exercise bouts by employing within-subject study designs (Harris et al. 2008; Tyldum et al. 2009). The comparison of the acute physiological responses following different bouts can provide information about the relative vascular stress associated with each exercise stimulus. Harris et al. (2008) observed no difference in the FMD responses between 3 different bouts of low, moderate, and high-intensity endurance exercise in middle-aged overweight men, which suggests exercise intensity does not influence the acute brachial artery endothelial responses. Further support is provided by Tyldum et al. (2009) who observed similar increases in brachial artery FMD following endurance and isocaloric high-intensity interval exercise in middle-aged healthy men. It is important to note that the direction of the FMD change is not consistent between studies, as previous investigations have demonstrated increases (Harris et al. 2008; Harvey et al. 2005; Tinken et al. 2010; Tyldum et al. 2009), decreases (Harris et al. 2008; Llewellyn et al. 2012; McGowan et al. 2006; Rognmo et al. 2008; Silvestro et al. 2002), and no change (Dawson et al. 2008; Harvey et al. 2005; Rognmo et al. 2008; Silvestro et al. 2002) in FMD following an exercise bout. However, the evidence

from the 2 within-subject studies suggest exercise duration and intensity may not influence the magnitude of the post-exercise responses, as similar changes in endothelial-dependent function were observed within a given sample following different exercise bouts.

The primary objective of the first study described in chapter 4.0 was to compare the acute brachial artery endothelial responses to a single bout of END, which was modeled after the current exercise prescription in cardiac rehabilitation, and a novel time-efficient HIT prescription. While previous literature has documented improvements in resting brachial artery endothelial-dependent function following END (Walsh et al. 2003; Wisloff et al. 2007) and isocaloric interval (Moholdt et al. 2012; Wisloff et al. 2007) exercise training in patients with CAD, no studies have examined the effect of low-volume HIT training. It is important to first assess the feasibility of an exercise prescription prior to implementing it in a training program. Within-subject, acute exercise examinations provide an excellent method for comparing the cardiovascular impact of the exercise stimuli, as well as assessing the feasibility of implementing each exercise prescription in patients with CAD.

We observed improved endothelial-dependent function 60-minutes post-exercise in the face of unchanged endothelial-independent function, which suggests the improvements were attributed to endothelial-dependent pathways. More importantly, the magnitude of the post-exercise improvements in FMD was comparable between HIT and END. Additionally, post-exercise cardiovascular indices, including heart rate, blood pressure, blood flow, and vascular resistance, were similar between the END and HIT

bouts. The findings of this study suggest the HIT bout provided a comparable vascular stimulus to the END bout, despite differences in exercise duration and intensities, which aligns with the previous work by Tyldum et al. (2009) and Harris et al. (Harris et al. 2008). Overall, the data suggests transient improvements in endothelial-dependent function are obtainable with a smaller volume of exercise. This observation is of extreme importance, given that "lack of time" is one of the most commonly reported reasons for poor adherence to exercise programs (Barbour and Miller 2008; Evenson and Fleury 2000). Additionally, HIT appeared to be more feasible than END. All patients were able to complete the HIT protocol, while 20% of patients stopped the END protocol prematurely due to volitional fatigue. We concluded that in a population characterized by endothelial dysfunction, a single bout of either END or HIT exercise was capable of transiently improving endothelial function. In sum, the results of the first study provide support for the continued investigation of this novel, time-efficient HIT protocol in patients with CAD.

8.2.2 The Role of Training Status

In the first study, the average duration since the primary CAD event was 8.5 years, and all patients were habitually involved in weekly physical activity since their cardiac event. Consequently, the results of the first study represent the acute vascular responses to exercise in habitually active patients with CAD, as evidenced by their VO_2peak of 28.6 ml·kg^{-1}·min^{-1}. Training status, examined using cross-sectional study designs, has been shown to influence the acute endothelial responses to exercise. Phillips et al. (2011)

demonstrated no change in FMD immediately following resistance exercise in runners

and resistance trained and cross-trained athletes, while sedentary individuals experienced

post-exercise reductions in FMD. At 60-minutes post-exercise, active overweight males

experienced improvements in FMD compared to inactive overweight males who reported

reductions in FMD (Harris et al. 2008). Additionally, 2 longitudinal studies have

examined the effect of exercise training on the acute endothelial responses to exercise,

and demonstrate improvements (Tinken et al. 2010) or no change (McGowan et al. 2006)

in the acute FMD response to isometric handgrip exercise following 8-weeks of training.

Based on these investigations, it is plausible that inactive and habitually active patients

with CAD may experience different acute endothelial responses to exercise.

The second study featured in chapter 5.0 addresses the issue of the impact of

exercise training status on the acute brachial artery endothelial responses to a single bout

of sub-maximal exercise. We aimed to recruit patients who had a recent cardiac event. On

average, it was < 6 months since their CAD event before they began exercise training.

Additionally, pre-training VO$_2$peak values for the END and HIT groups were 18.7 ml·kg^{-1}·min^{-1} and 19.8 ml·kg^{-1}·min^{-1}, respectively, which suggests our patient population was at

a low fitness status at the initiation of their training programs. We hypothesized that

inactive patients with CAD would experience transient decreases in brachial artery FMD

after a single bout of exercise, and that these post-exercise decreases would be minimized

with 12-weeks of either HIT or END training. Our observations, however, did not support

our hypothesis. FMD was unchanged following sub-maximal exercise at both pre- and

post-training time points, and there was only a main effect for training suggesting the

post-training FMD values were larger than the pre-training values. The lack of change in FMD following an exercise bout is supported by previous cross-sectional investigations (Dawson et al. 2008; Harvey et al. 2005; Rognmo et al. 2008; Silvestro et al. 2002), and may suggest the sub-maximal exercise bout was not sufficient enough to elicit physiological perturbations to the endothelium. It could also be argued that the lack of change in acute FMD responses following training may be attributed to an insufficient training stimulus; however, this is likely not the case given evidence of improved fitness with training. Mean exercise heart rates and ratings of perceived exertion were lower during the post-training sub-maximal exercise bout, which provides evidence of improved fitness.

In spite of our FMD results, we did report a novel finding which has not been previously reported. At both pre- and post-training time points, we observed post-exercise reductions in endothelial-independent dilation. As previously described, few studies have examined endothelial-independent function in combination with endothelial-dependent function. In the previous studies that have included both assessments of endothelial function, no change in the independent assessment has been reported immediately (Silvestro et al. 2002; Tinken et al. 2010) and 1-hour following exercise (Harvey et al. 2005; Rognmo et al. 2008). Although it may appear that our novel finding of decreased NTG-mediated dilation is indicative of "impaired" vascular smooth muscle function, a more likely explanation may be post-training vasodilation. Brachial artery diameters were significantly larger following the sub-maximal exercise bout, resulting in a decreased dilatory range. Few acute exercise studies report NTG diameters, which limits our ability

to draw comparisons. However, the findings from this study highlight the necessity of performing both endothelial-dependent and –independent assessments, as a decreased dilatory capacity may influence endothelial-dependent dilation.

Our original intention was to investigate the role of training status on the acute endothelial responses to sub-maximal exercise. We concluded that training status has no effect on the acute endothelial-dependent or -independent responses in patients with CAD, which is supported by McGowan et al. (2006) who observed no change in endothelial responses to an acute bout of isometric handgrip exercise following 8-weeks of exercise training in medicated hypertensives. However, it remains possible that a longer training period may have elicited different responses. Individuals included in cross-sectional comparisons of active and inactive groups are habitually active (Harris et al. 2008; Phillips et al. 2011; Rognmo et al. 2008); therefore, a training period longer than 12-weeks may change the post-training acute endothelial responses.

8.2.3 Future Directions

There is no consensus on the acute brachial artery endothelial responses to exercise, which is likely attributed to differences in study design including the population examined, the acute exercise intervention, and the timing of measurements. Future investigations in this area should address these limitations by designing studies to fill in the gaps in the literature in their specific population of interest. The 2 studies included in this thesis are the first acute exercise investigations in patients with CAD; therefore, there are many areas in the literature that require further examination.

The first recommendation is to perform both endothelial-dependent and –

independent assessments, for a more comprehensive understanding of endothelial

function. While our post-exercise reductions in endothelial-independent dilation are likely

attributed to an increase in arterial diameter, we cannot rule out the possibility of reduced

vascular smooth muscle function. NTG assessments are performed as a control; thus

accurate interpretations of FMD results can only be made when a control measurement is

performed. Additionally, studies using multiple day trials need to report their day-to-day

reliability, to help determine if the differences observed were attributed to the

intervention rather than inherent variability.

Our 2 investigations also examined different time points. While our observations at

60-minutes post-exercise suggest a favorable transient adaptation, it is unknown how long

these responses will last, and whether they occur prior to the 60-minute time point. Post-

exercise impairments in endothelial responses, as well as cardiovascular indices,

immediately following exercise and throughout the recovery period, may indicate

elevated risk for cardiovascular events. Therefore, future investigations should focus on

the time course of endothelial responses following an exercise bout, focusing on

assessments within minutes of exercise cessation, and at time intervals throughout the

recovery. Prior research suggests endothelial responses have returned to baseline by 24

and 48 hours post-exercise (Rognmo et al. 2008), which provides a starting point for time

course investigations. Time course investigations should also consider the effect of

repeated endothelial assessments. There is no evidence that repeated FMD tests decrease

the accuracy of the subsequent tests (Harris et al. 2006). Additionally, current guidelines

support the assessment of endothelial-independent function 10-minutes following FMD cuff deflation (Corretti et al. 2002). However, repeated measures studies should consider the half life of NTG, and ensure the artery has returned to a baseline state prior to subsequent assessments by either adequately spacing the timing of measurements, or performing measurements across multiple days.

Lastly, acute exercise investigations need to examine possible mechanisms to explain their observations. Some studies have examined indices of antioxidant capacity (Rognmo et al. 2008), oxidative stress (Silvestro et al. 2002), and NO bioavailability (Rognmo et al. 2008) as possible sources of improved or reduced FMD. Future examinations should consider assessing these indices. As well, our evidence of post-exercise reductions in endothelial-independent dilation warrants the examination of its possible mechanisms. In conclusion, acute physiological responses to an exercise bout provide relevant information about the exercise stimulus. Since there is no consensus on the acute endothelial responses, results should be interpreted with caution. However, further research is necessary to examine the time course of acute endothelial responses, as well as the possible mechanisms.

8.3 Chronic Effects of Low-Volume HIT

The exercise training literature in populations with CAD is extensive, and has recently expanded to include investigations examining the effectiveness of interval exercise training. The consensus is that interval exercise training is capable of eliciting favorable improvements in physiological indices in patients with CAD. However, all

studies to date have employed isocaloric or isovolumetric interval exercise prescriptions, in an attempt to create an exercise stimulus that is comparable to the current endurance exercise prescription in cardiac rehabilitation. The studies described in chapters 6.0 and 7.0 of this thesis are the first to examine the effectiveness of low-volume interval exercise training (HIT) in patients with CAD. We observed favorable physiological adaptations following the HIT protocol, despite it involving less time and work than the current exercise prescription in cardiac rehabilitation.

8.3.1 Cardiorespiratory and Endothelial Adaptations

From a clinician's perspective, one of our most significant findings was an increase in cardiorespiratory fitness following 12-weeks of training. While previous studies have demonstrated superior improvements in fitness with isocaloric/isovolumetric interval exercise training (Rognmo et al. 2004; Warburton et al. 2005; Wisloff et al. 2007), we observed comparable improvements in VO_2peak following END and low-volume HIT. However, the magnitudes of improvement reported by our investigation are greater than the "superior" improvements reported by previous studies. We reported a 19% and 24% increase in fitness following END and HIT, respectively, while previous interval studies have reported improvements of 15% (Moholdt et al. 2012; Warburton et al. 2005), 17% (Munk et al. 2009), and 18% (Rognmo et al. 2004). Thus, while we cannot draw the conclusion that our low-volume HIT protocol elicited superior improvements in fitness, we can conclude that the magnitude of improvement is comparable to the improvements reported by previous higher-volume interval investigations, as well as the current exercise

prescription in cardiac rehabilitation. Additionally, our improvements are clinically relevant. Myers et al. (2002) reported an increase in fitness by 1 MET translated into a 12% improvement in survival. Both END and HIT groups improved their fitness by > 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$.

Another important finding from the study described in chapter 6.0 was an increase in resting endothelial-dependent function following 12-weeks of training. Similar to cardiorespiratory fitness, we did not observe a difference in the magnitude of improvement between the END and HIT groups, lending further support to the notion that positive training adaptations are obtainable with a lower volume of exercise. Patient with CAD are characterized as having endothelial dysfunction (Kaku et al. 1998; Lieberman et al. 1996); therefore, improved endothelial function would be desired in this population. Previous work suggests individuals with persistently impaired endothelial-dependent function (FMD ≤ 5.5%) following a 6-month intervention are at an increased risk of cardiovascular events and mortality, compared to individuals who positively responded to the intervention (Kitta et al. 2009). Our average FMD values reported in both the END and groups were < 5.5% at pre-training. However, 12-weeks of training significantly increased FMD in both groups, above 5.5%, suggesting our exercise intervention was capable of reducing their future cardiovascular risk.

8.3.2 Heart Rate Recovery Adaptations

In contrast to previous endurance exercise training studies in patients with CAD (Giallauria et al. 2006a; Giallauria et al. 2006b; Hai et al. 2010; Hao et al. 2002; Tsai et

al. 2005; Wu et al. 2006), the study described in chapter 7.0 did not report improvements in heart rate recovery following 12-weeks of END or HIT exercise. The lack of significant findings is supported by Moholdt et al. (2012) who observed no significant change in heart rate recovery following 12-weeks of endurance and isocaloric interval exercise training in patients with CAD, as well as Dimopoulos et al. (2006) who observed no heart rate recovery improvements in patients with heart failure following 12-weeks of interval training. While the evidence suggests interval exercise training is not effective at improving heart rate recovery, the average pre-training heart rate recovery values reported by our investigation, as well as these studies are, 1) greater than the pre-training values reported by studies demonstrated improved heart rate recoveries with training, and 2) above the clinical cut off values of 12 bpm (Cole et al. 1999) and 25 bpm (Jouven et al. 2005). Therefore, the lack of change in heart rate recovery may be attributed to the pre-training state of our patients, rather than the ineffectiveness of the training programs. In sum, we demonstrate that irrespective of their diseased state, individuals with normative heart rate recovery values at baseline are unable to undergo further improvements in this index with exercise training.

8.3.3 Future Directions

Our studies are the first to examine low-volume interval exercise training in a clinical population of patients with CAD. Therefore, the findings from our studies provide preliminary evidence, and justification for further investigation of the effectiveness of low-volume HIT in a cardiac rehabilitation setting.

One of our primary findings from the third study (chapter 6.0) was a significant improvement in resting brachial artery endothelial-dependent function in the face of unchanged endothelial-independent function, which suggests the improvements were attributed to endothelial-dependent pathways. Endothelial function is commonly assessed in exercise training studies in patients with CAD, since patients are characterized with dysfunction, and attenuated FMD values are associated with increased mortality risk. Future investigations need to examine possible mechanisms mediating the improvements with training. Endurance exercise training in patients with CAD has been shown to increase endothelial-dependent dilation and eNOS protein expression in the coronary arteries (Hambrecht et al. 2003). The examination of eNOS protein expression in the brachial artery could help to identify the mechanism for increased NO-mediated dilation following training. Similar to acute exercise investigations, additional indices of interest to explain the findings could include measures of antioxidant capacity and oxidative stress to see if the basal level of these indices change with exercise training. Additionally, it would be of interest to determine the associated risk reduction in mortality with training induced improvements in FMD. The main conclusion from this future direction is that exercise-training studies to date have demonstrated training is capable of improving brachial artery endothelial-dependent function in patients with CAD; however, few studies have examined the possible mechanisms mediating this adaptation, as well as the clinical significance of the improvements. Identifying the mechanisms of adaptation may help to optimize the exercise program to target these mechanisms.

We did not observe improvements in arterial stiffness, BMI, systolic blood pressure, or heart rate recovery with exercise training. As well, training induced reductions in carotid artery IMT, diastolic blood pressure, and resting heart rate were marginal, and therefore not likely clinically relevant. However, these findings should not deter future investigations from examining these indices. It remains possible that a larger sample size, or a sample with more clinically relevant pre-training states, such as hypertension, obesity, and elevated IMT, may experience more dramatic reductions in these indices with HIT training. Additionally, assessments of heart rate recovery with HIT should be performed in a CAD sample with clinically relevant pre-training heart rate recovery values, since previous interval exercise training investigations have used populations with non-clinical values, and therefore have not observed training induced improvements. Future investigations should also consider assessing additional physiological indices. Arterial stiffness assessments should include aortic pulse wave velocity because it is currently considered the non-invasive gold-standard method, and is associated with increased risk of mortality (Vlachopoulos et al. 2010). Additionally indices of interest could include cholesterol levels, left ventricular structure and function, quality of life and adherence. Little et al. (2011) previously reported improved glucose control following 6 sessions of HIT in individuals with type 2 diabetes. This type of assessment may be of relevance in diabetic CAD patients, and therefore should also be examined.

In addition to assessing additional physiological indices, future investigations should include a larger sample. Our study design stratified patients into the END or HIT

groups based on their pre-training FMD value, in an attempt to ensure an equal distribution of our primary outcome measure, FMD, between groups. Our stratification process was successful because there were no significant difference in pre-training values between the END and HIT groups. However, randomized controlled trials are considered the gold standard; therefore future examinations of the HIT protocol should employ a randomized control trial with a larger sample size. Future investigations should also consider including a broader spectrum of CAD. We focused our exclusion criteria to exclude conditions that may increase an individual's risk during high-intensity exercise. However, we also excluded conditions known to influence endothelial function, such as diabetes and pre-menopausal women. Since the end objective is to demonstrate the feasibility of HIT in populations with CAD, it is necessary to include higher-risk patients, as well as patients with co-morbidities such as diabetes.

The HIT bout investigated in these studies is considered a "practical" model, meaning the exercise intensities were not supra-maximal and therefore considered safe for clinical populations. We did not report any adverse events during the training period, and all patients were able to complete the HIT bout. We selected cycling as the mode of exercise because it was easy to control workload by adjusting the resistance or cycling cadence. However, stationary cycle ergometers may not be readily accessible; therefore future investigations should examine the effectiveness of HIT using other forms of training, such as walking or jogging independently or on a treadmill. Additionally, current cardiac rehabilitation exercise guidelines include resistance training. Only one previous study has examined the combination of aerobic and interval exercise training with

resistance training; however, this study employed an isovolumetric interval protocol (Warburton et al. 2005). Future examinations should also examine the effectiveness of HIT combined with resistance training.

As previously described, a "lack of time" is one of the most commonly cited reason for poor exercise compliance in cardiac rehabilitation program. We hypothesized low-volume HIT may increase compliance rates because it involves less time. However, we observed no significant difference in exercise compliance between the HIT and END groups, which suggests the exercise prescription does not influence compliance rates during the first few months of training. Exercise compliance declines as the duration of the program continues (Daly et al. 2002); therefore it remains plausible that a longer training period may have revealed different compliance rates. There is evidence to suggest adolescents who underwent 3-months of interval training report better outcomes at a 12-months follow-up compared to adolescents who do not receive interval training (Tjonna et al. 2009). Therefore, future examinations need to examine the long-term effect of low-volume HIT, to determine if its shorter duration increases long-term adherence. An optimal exercise prescription for cardiac rehabilitation programs has the capacity to both improve health outcomes in the short-term, as well as encourage life-long participation following the completion of a supervised cardiac rehabilitation program.

8.4 Conclusions

In conclusion, the main contribution of this thesis to the current literature is the observation that positive physiological responses in a clinical population with CAD are

obtainable with a smaller volume of exercise. The findings lend support to continued

investigation of practical, low-volume interval exercise prescriptions in clinical

populations. Exercise is a cost-effective secondary prevention strategy in patients with

CAD, yet current exercise programs report poor compliance due to a lack of time and

motivation. Our combined acute and training investigations report beneficial changes in

traditional and non-traditional cardiovascular risk factors with a protocol that involves

less time and less work than the current exercise prescription in cardiac rehabilitation.

Further investigations are needed, which should include a larger sample size and assess

additional physiological indices of interest. However, the preliminary data from this

thesis suggests patients with CAD can obtain positive health benefits by performing less

work, which may help to increase exercise compliance and promote secondary

prevention. The results of this thesis are summarized in the following conclusions:

1. In patients with CAD, a single bout of END and HIT improve brachial artery endothelial-dependent vasodilation 1-hour post-exercise to a similar extent, despite differences in exercise durations and intensities. The improvements observed are likely attributed to transient increases in NO bioavailability.

2. Endothelial-independent function appears to be transiently reduced immediately following exercise, but corrects itself by 1-hour of recovery. The attenuated responses are likely attributed to post-exercise increases in brachial artery diameters.

3. Training status does not appear to change the acute endothelial responses to an exercise bout, as similar post-exercise responses were observed before and following 12-weeks of END and HIT training.

4. Beneficial training adaptations are obtained with a lower volume of exercise. Despite involving less time and work, 12-weeks of HIT elicited comparable improvements in cardiorespiratory fitness, brachial artery FMD, resting heart rate, seated diastolic blood pressure, and carotid IMT as the current exercise prescription in cardiac rehabilitation.

5. Heart rate recovery did not improve following 12-weeks of END and HIT training. The lack of change is likely attributed to the pre-training low risk state of our patients, rather than an insufficient training stimulus.

9.0 CHAPTER 9: APPENDICES

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10.0 CHAPTER 10: REFERENCES

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