SHORT-TERM HIGH-INTENSITY INTERVAL TRAINING AND CONTINUOUS MODERATE-INTENSITY TRAINING IMPROVE PEAK AEROBIC CAPACITY AND DIASTOLIC FILLING DURING EXERCISE

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science
Graduate Department of Exercise Sciences
University of Toronto

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Short-term high-intensity interval training and continuous moderate-intensity training improve peak aerobic capacity and diastolic filling during exercise

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Abstract

This study examined the effects of short-term high-intensity interval training (HIT) and continuous moderate-intensity training (CMT) on left ventricular (LV) function in young, healthy men. Sixteen untrained men were randomly assigned to HIT (8-12 X 60:75 seconds cycling at 95-100%:10% $\dot{V}O_{2peak}$) and CMT (90-120 minutes cycling at 65% $\dot{V}O_{2peak}$) and assessed before and after six sessions of training. LV function was determined at rest and during submaximal exercise using two-dimensional and Doppler echocardiography. HIT and CMT improved $\dot{V}O_{2peak}$ and induced plasma volume expansion to a similar magnitude. Although resting LV function did not change, increased exercise stroke volume and cardiac output was observed, secondary to increases in end-diastolic volume. Numerous ECHO-derived indices of diastolic performance were similarly enhanced during exercise in both groups. Short-term HIT and CMT elicit rapid increases in $\dot{V}O_{2peak}$ and LV filling without global changes in systolic performance or cardiac morphology at rest.
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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>A</td>
<td>Peak late Doppler blood flow velocity during the late phase of diastole</td>
</tr>
<tr>
<td>A’</td>
<td>Peak late myocardial tissue velocity during the late phase of diastole</td>
</tr>
<tr>
<td>ATP</td>
<td>Adenosine triphosphate</td>
</tr>
<tr>
<td>AV</td>
<td>Atrioventricular</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>bpm</td>
<td>Beats per minute</td>
</tr>
<tr>
<td>BV</td>
<td>Blood volume</td>
</tr>
<tr>
<td>Ca&lt;sup&gt;2+&lt;/sup&gt;</td>
<td>Calcium</td>
</tr>
<tr>
<td>CMT</td>
<td>Continuous moderate-intensity training</td>
</tr>
<tr>
<td>CO</td>
<td>Cardiac output</td>
</tr>
<tr>
<td>COX</td>
<td>Cytochrome c oxidase</td>
</tr>
<tr>
<td>CS</td>
<td>Cirate synthase</td>
</tr>
<tr>
<td>dP/dt</td>
<td>Rate of rise of ventricular pressure; index of contractility</td>
</tr>
<tr>
<td>-dP/dt</td>
<td>Rate of decline in ventricular pressure; index of diastolic function</td>
</tr>
<tr>
<td>DT</td>
<td>E-wave deceleration time</td>
</tr>
<tr>
<td>E</td>
<td>Peak early Doppler blood flow velocity during the early phase of diastole</td>
</tr>
<tr>
<td>E’</td>
<td>Peak early myocardial tissue velocity during the early phase of diastole</td>
</tr>
</tbody>
</table>
**E:A**  Doppler-derived ratio describing LV filling pattern

**E/E’**  Doppler-derived measure used as a surrogate for left atrial pressure

**ECG**  Electrocardiogram

**EDV**  End-diastolic volume

**EF**  Ejection fraction

**ESV**  End-systolic volume

**FS**  Fractional shortening

**GLUT4**  Glucose transporter type 4

**Hct**  Hematocrit

**HF**  Heart failure

**HIT**  High-intensity interval training

**HR**  Heart rate

**125I-HSA**  Human serum albumin labeled with radioactive iodine

**IVRT**  Isovolumetric relaxation time

**IVS**  Interventricular septum

**LV**  Left ventricle or left ventricular

**LVIDd**  Internal diastolic diameter of the LV

**LVIDs**  Internal systolic diameter of the LV

**METs**  Metabolic equivalents

**MI**  Myocardial infarction
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺</td>
<td>Sodium</td>
</tr>
<tr>
<td>PAR-Q</td>
<td>Physical Activity Readiness Questionnaire</td>
</tr>
<tr>
<td>PGC-1∞</td>
<td>peroxisome proliferator-activated receptor y co-activator 1 alpha</td>
</tr>
<tr>
<td>PW</td>
<td>Pulsed wave</td>
</tr>
<tr>
<td>PWT</td>
<td>Posterior wall thickness</td>
</tr>
<tr>
<td>PV</td>
<td>Plasma volume</td>
</tr>
<tr>
<td>SBP/ESV</td>
<td>Ratio of systolic blood pressure to end-systolic volume; index of contractility</td>
</tr>
<tr>
<td>SIRT1</td>
<td>Silent mating-type information regulator 2 homolog 1</td>
</tr>
<tr>
<td>SPVR</td>
<td>End-systolic pressure volume ratio</td>
</tr>
<tr>
<td>STI</td>
<td>Speckle tracking imaging</td>
</tr>
<tr>
<td>SV</td>
<td>Stroke volume</td>
</tr>
<tr>
<td>τ</td>
<td>Tau; pressure decline in LV; index of diastolic function</td>
</tr>
<tr>
<td>TDI</td>
<td>Tissue Doppler imaging</td>
</tr>
<tr>
<td>˙VCO₂</td>
<td>Volume of carbon dioxide production</td>
</tr>
<tr>
<td>˙VO₂</td>
<td>Volume of oxygen consumption</td>
</tr>
<tr>
<td>˙VO₂max</td>
<td>Maximal oxygen consumption or maximal aerobic capacity</td>
</tr>
<tr>
<td>˙VO₂peak</td>
<td>Peak oxygen consumption or peak aerobic capacity</td>
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Chapter 1
Introduction

1.1 Rationale

Endurance exercise induces various physiological perturbations, which may act as triggers for long-term cardiovascular adaptations [1-3]. Much evidence regarding changes in cardiac function following exercise training has been drawn from models employing long-term training, ranging in duration from weeks to months [4]. The expansion of blood volume (BV), or hypervolemia, which has been observed during training [2, 5-10], appears to peak within approximately 10-14 days of training, and is explained almost completely by an expansion of blood plasma [2, 5]. However, the significance of an expanded plasma volume (PV) on cardiac function and structure during the early phase of training remains unclear. The evidence that inotropic function is improved with training is equivocal [1], and it appears that enhanced diastolic compliance contributes to a more pronounced utilization of the Frank-Starling mechanism during exercise after training [11]. This is in turn reflected by an increase in stroke volume (SV) and bradycardia during exercise following sustained aerobic training [12, 13]. Short-term training induces changes in left ventricular (LV) response to exercise [6]. Yet, sensitive and high-fidelity measures of LV contractility and diastolic function have not been studied following this type of training intervention.

Although most traditional training programs have involved continuous, moderate-intensity training (CMT) sessions of long durations, recent work demonstrated that high-intensity interval training (HIT) can stimulate similar, if not superior, changes in cardiovascular function in both
healthy [14] and clinical populations [15-18]. The stimulus provided by HIT is at a high intensity yet often at a reduced total exercise volume (duration x intensity); therefore, this form of training offers an efficacious alternative to CMT. In contrast to prolonged training, there are few data describing cardiovascular adaptations arising from short-term training interventions (e.g., ≤ 2 weeks), reflecting the early phase of the training process [6, 8, 9, 19-21]. Understanding the cardiac changes that occur with short-term training provides information about the early time-course of adaptations observed prior to prolonged training, before structural remodeling is likely to occur. Whereas short-term CMT has significant systemic and BV effects [19-21], short-term HIT induces rapid adaptations in skeletal muscle metabolism. [22-26]. However, the effects of HIT on cardiac morphology and function have not been thoroughly investigated during the early stages of training.
1.2 Objectives

I. To assess changes in peak aerobic capacity ($\dot{V}O_{2\text{peak}}$) and LV function following six sessions of endurance exercise training in healthy, young males (age range of 18-35 years), over a 2-week training period;

II. To compare the effects of short-term CMT vs. low-volume HIT on regional systolic and diastolic function and cardiac morphology at rest and during submaximal exercise; and

III. To examine whether changes in PV are associated with changes in $\dot{V}O_{2\text{peak}}$ and indices of LV filling following short-term CMT and HIT.

1.3 Hypotheses

I. Short-term HIT would be equally as effective as short-term CMT at producing similar improvements in $\dot{V}O_{2\text{peak}}$ and inducing a hypervolemic response;

II. Both short-term CMT and HIT would enhance LV filling at rest and during submaximal exercise without altering systolic performance; and

III. Changes in PV would be related to improvements in $\dot{V}O_{2\text{peak}}$ and indices of diastolic filling.
Chapter 2
Supplemental Review of Literature

2.1 Introduction

Long-term endurance exercise training is associated with well-established cardiovascular benefits [1, 3]. Endurance training elicits structural and regulatory adaptations in the heart and periphery, both of which contribute to increasing the maximal rate of oxygen delivery to the muscles (\(\dot{V}O_{2\text{max}}\)) [1]. A notable adaptation to sustained aerobic training involves a lowering of the heart rate (HR) at rest and during submaximal exercise, commonly referred to as training bradycardia [27]. Research has indicated that resting bradycardia is mediated by alterations in the autonomic nervous system, mainly increased parasympathetic (vagal) tone to the heart [28-30]. In the peripheral vasculature, an increased vasodilatory capacity coupled with decreased sympathetic vasoconstriction result in reduced vascular resistance [1]. Additional alterations in the skeletal muscle occur, leading to an improvement in oxygen delivery, the primary mechanism by which training induces improved oxygen uptake and performance [1, 31, 32]. Of particular importance are the specific structural and functional alterations of the heart that occur with aerobic training. In this regard, the increase in stroke volume (SV) is predominantly attributed to increases in left ventricular (LV) end-diastolic volume (EDV) and diastolic filling, secondary to plasma volume (PV) expansion [1, 2, 31-33]. The LV remodeling that increases both chamber size and mass accompanies these functional outcomes over the course of training [34, 35], referred to so-called ‘athletic heart’ [4, 36-40].
This chapter will extensively review what is known about myocardial adaptations to endurance exercise training. First, it describes LV systolic and diastolic function and their clinical measures. Next, it discusses both the structural and morphological cardiac adaptations in response to prolonged aerobic training. Subsequently, the importance of exercise intensity in health and disease and the utility of HIT are outlined. The chapter then introduces the short-term model of endurance training and the adaptations that occur following short-term CMT and HIT.

2.2 Left Ventricular Systolic Function

The systolic function of the LV, or systole, refers to the contraction of the myocardium, driving blood out of the cardiac chamber [41]. It begins as the action potential from the atrioventricular (AV) node enters the left ventricle, causing it to depolarize. On the electrocardiogram (ECG), systole corresponds to the beginning of the QRS complex [42]. Isovolumic contraction occurs when the AV valves are forced shut. During this brief period, the semilunar valves are still closed; thus, the volume of the ventricle remains unchanged. Ventricular ejection occurs as the continuing contraction increases the pressure in the ventricle and forces the semilunar valves open. At this point, blood is forced out of the ventricle. This interval ends as the ventricle begins to relax, the blood in the aorta and pulmonary trunk begin to flow backward, and the semilunar valves close [41].

LV systolic function is dependent on the loading conditions of the heart and intrinsic myocardial contractility [41]. The loading conditions include preload and afterload. The former refers to the magnitude of ventricular filling and stretch the heart undergoes with each beat. It represents all of the factors contributing to passive wall stress (or tension) at the end of diastole
Preload affects systolic function through the Frank-Starling mechanism where greater filling, and thus ventricular stretch, results in a greater ejection of blood. In contrast to preload, afterload reflects all the factors that contribute to total myocardial wall tension during systolic ejection (opposition to myocardial shortening) [43]. On the other hand, contractility is defined as the maximal velocity of the shortening myocardial fibre that can be measured and determines the load-independent force of contraction [41]. In clinical settings, direct measures of contractility are difficult to attain; therefore, various surrogate indices are used instead.

Combined excitation-contraction coupling and the activity of sodium (Na\(^+\)) and calcium (Ca\(^{2+}\)) ions govern contractility. In LV cells, the action potential fired by pacemaker cells in the sinoatrial node opens the voltage-induced opening of calcium L-type channels in the t-tubules. A series of intracellular mechanisms leads to the release of Ca\(^{2+}\) from the ryanodine receptors on the sarcoplasmic reticulum and into the cytosol. Ca\(^{2+}\) ions interact with Troponin-C (Tn-C) in the cytosol loosening the bond in the Tn-C and Troponin-I (Tn-I) complex and exposing the myosin binding sites on actin. Subsequently, cross-bridges are formed causing force generation [41].

### 2.2.1 Indices of Myocardial Contractility

Currently, direct quantification of changes in contractility in humans is impossible to achieve. Therefore, a number of indirect techniques have been established. Despite the rapid evolution of methods to assess LV function, alterations in loading conditions (i.e., preload and afterload) are important confounding factors in non-invasive assessments such as echocardiography. While the derivative of pressure over time (dP/dt) remains the gold standard
to examine LV contractility, this index is unattainable in most human studies given the invasive nature of its assessment [44]. Alternatively, the end-systolic pressure volume ratio (SPVR) has been reported as a relatively load-independent technique. However, this measure is limited by the estimation of the end-systolic arterial pressure as well as the variability of measures of LV end-systolic volume (ESV) [44]. Echocardiographic-derived measures such as dimensional fractional shortening (FS) and ejection fraction (EF) are also limited because of susceptibility to changes in loading conditions.

EF refers to the amount of blood that is pumped out of the LV chamber during each heartbeat [41]. Normal EFs at rest are variable; but generally, EF values greater than 50-55% are considered normal [41]. Although EF is the most widely used measure of LV contractility in research and clinical settings, it has a very low sensitivity [45]. In addition to being affected by factors such as HR, preload, and afterload, EF also fails to measure the force of myocardial contraction [45]. Nonetheless, it provides a non-invasive index of contractility that can be obtained through echocardiography. Recently, the novel techniques of myocardial strain and strain rate have become available for quantifying contractility in a relatively load-independent fashion.

### 2.3 Left Ventricular Diastolic Function

LV diastolic function represents the adequate filling of the LV in order to produce a cardiac output in proportion with the body’s metabolic needs [46]. The two major determinants of LV filling are ventricular relaxation and chamber compliance [47]. LV relaxation is an active, energy-dependent process during which the contractile elements are no longer activated and
return to their original length [47]. It corresponds to the rate and duration of decrease in LV pressure following systolic contraction. On the other hand, chamber compliance refers to the passive properties of the ventricle during blood flow from the left atrium, across the mitral valve, and into the LV [47]. It can be simplistically defined as the change in volume over the change in pressure during diastolic filling. Diastole of a normal cardiac cycle is characterized by four phases: isovolumic relaxation time (IVRT), the early or rapid filling phase, diastasis, and the late filling phase [48]. The IVRT corresponds to the time between aortic valve closure and mitral valve opening. During this phase, no changes in the volume of the LV occur [46]. This stage is reliant on both systolic function and LV relaxation, since it is a continuation of systole [48]. The early filling phase refers to the opening of the mitral valve, allowing blood to flow into the LV. This stage commences once the LV pressure falls below the pressure in the left atrium, causing the mitral valve to open [46]. Diastasis, or the slow filling phase, occurs near the end of diastole and is characterized by little ventricular filling. Finally, the late or active filling phase takes place at the end of diastole prior to the subsequent phase of atrial systole [46].

From a cellular perspective, relaxation occurs once Ca\(^{2+}\) is removed from Tn-C, thus leaving the myosin binding sites unexposed and preventing cross-bridge formation. The Sarco/Endoplasmic Reticulum Ca\(^{2+}\) ATPase (SERCA2a) of the sarcoplasmic reticulum wall pumps Ca\(^{2+}\) ions back into the sarcoplasmic reticulum. A Na\(^{+}\)-Ca\(^{2+}\) antiport protein also moves Ca\(^{2+}\) out of the cell while moving sodium into the cell. In addition, the protein calsequestrin binds to Ca\(^{2+}\) resulting in a lower Ca\(^{2+}\) concentration in the sarcoplasmic reticulum [41].
2.3.1 Indices of Left ventricular Diastolic Function

The gold standard measure of LV diastolic function, Tau (τ), refers to the time constant of the decline in LV pressure and is only minimally influenced by changes in ventricular loading [48]. The assessment of τ was originally described in an isolated canine LV preparation as the negative inverse of the slope of the LV pressure decay from maximum –dP/dt to the level of LV end-diastolic pressure [49]. However, this technique is highly invasive, as it requires catheterization and radiation. As a result, its applicability in research has been very limited. Nevertheless, the emergence and advancement of various non-invasive imaging tools such as echocardiography has allowed for relatively accurate measures of diastolic function in clinical settings and research involving healthy and athletic populations.

LV diastolic function can be quantified by echocardiography in several ways using indices of Pulsed-wave (PW) Doppler transmitral blood flow velocities. Similarly, in tissue Doppler Imaging (TDI), myocardial tissue velocities are measured at the septal and lateral mitral valve annulus and quantify the early and late filling phases of diastole. Furthermore, myocardial strain and strain rate and diastolic recoil (untwist) also allow for load-independent assessment of diastolic function. These indices are reviewed in the next section.

2.4 Non-invasive Assessment of the Left Ventricle: Echocardiography

Echocardiography has emerged as one of the most frequently used tests for detection of cardiac structure and function in clinical and research settings [46, 48, 50-52]. This tool provides
a comprehensive, non-invasive method of imaging the heart using ultra-high-frequency sound waves [52]. It is also associated with no known side effects and is overall, a painless procedure [53]. In addition, echocardiographic-derived data have been demonstrated to generally correlate well with invasive methods such as radionuclide angiography [54]. Therefore, the relatively low cost and real-time nature of echocardiography makes this technology a suitable alternative to invasive measurements. Several imaging modalities are used in echocardiography to assess LV morphology and hemodynamics.

2.4.1 Motion-mode Echocardiography

Motion-mode (M-mode) echocardiography provides a one-dimensional view of the heart and allows for assessment of cardiac size, structures, and their relationship to one another [55]. Determination of LV internal dimensions and wall thickness can be obtained throughout the cardiac cycle, which can then be used to estimate chamber volume and LV mass. A major advantage of M-mode lies in its high temporal resolution, which enhances timing for valve motion and improves the recognition of endocardial borders [51]. Due to operator dependency, possible disadvantages are underestimation or overestimation of dimensions [51]. Recently, anatomical M-mode (AM-mode), which is the use of a two-dimensional (2D) image as a basis for M-mode analysis at a defined line (independent of the transducer orientation), has been utilized in research and clinical settings. AM-mode allows for a more detailed assessment of cardiac chamber dimensions and regional wall motion [56].
2.4.2 Two-dimensional Echocardiography

Two-dimensional echocardiography, known as the “backbone” of echocardiography, displaces anatomic structures in real-time tomographic planes and generates 2D images of the heart from the data obtained [55]. Based on tracing along the endocardial border, it provides information regarding the spatial relationships between objects, such as global and regional cardiac function, LV volumes, and EFs [51, 55].

2.4.3 Doppler Echocardiography

Over the last 2 decades, the Doppler technique has been an extremely useful addition to echocardiography and has become a valuable clinical tool for the evaluation of systolic and diastolic function [47, 50, 55]. This method uses reflections from moving red blood cells to characterize blood flow [55] and compliments M-mode and 2D echocardiography by providing information about the direction and velocities of systolic and diastolic blood flow [47, 50, 55]. Doppler-derived interrogation has particularly become the cornerstone for evaluation of LV diastolic function [47, 48]. PW Doppler interrogation and TDI represent the main types of Doppler echocardiography [55].

2.4.3.1 Pulsed-wave Doppler Echocardiography

The PW Doppler mitral flow velocities are used to assess the LV filling patterns [47, 50]. The important variables that are used to assess diastolic function are peak early (E) diastolic
transmitral flow velocity (corresponding to the early or rapid phase of diastole) and peak late (A) diastolic transmitral flow velocity (corresponding to the late phase or ‘atrial’ kick of diastole) [48]. The other useful indices include the early filling deceleration time (DT) and the E:A ratio. DT reflects LV compliance in early diastole and is usually less than 220 milliseconds in healthy individuals [48]. The E:A ratio describes the filling pattern of the LV ventricle [48]. Normal values of E:A ratio have been challenging to define due to physiological factors and great variability amongst individuals [46]. The American Society of Echocardiography considers a normal E:A ratio to be between 0.75-1.5 [48]; but athletes and physically active populations typically present higher ratios (closer to 2) without the existence of diastolic dysfunction [57, 58]. Thus, a wide range of normal values exists and precise measurement is rather difficult. In a healthy heart, a greater proportion of filling occurs during the early phase of diastole and the DT and IVRT are relatively short because the ventricle is compliant and receives blood from the atria under low pressures. With stiffer ventricles, the IVRT and DT are prolonged and filling will have greater dependence on atrial contraction (45, 56). Since the E wave is attenuated and A amplified, the E/A ratio is reduced in diastolic dysfunction. Despite their utility, transmitral Doppler flow velocities are dependent on many factors such as HR, preload, and afterload [47, 48, 50]. TDI overcomes these limitations to an extent, since it is less affected by loading conditions and as a result, can compliment mitral valve flow velocity recordings [47, 50, 55].

2.4.3.2 Tissue Doppler Imaging

TDI is a recently developed imaging modality that measures the motion velocity of the myocardium in its longitudinal axis [47, 50, 55]. The velocities provided by TDI are typically high-amplitude and low-frequency [50]. The mitral annulus velocity represents the recorded
measure for examination of systolic and diastolic function [55]. Peak early diastolic myocardial velocity (E’) and late myocardial diastolic velocity (A’) are measured and reported [50, 55]. Under normal conditions, E’ and A’ occur coincidentally with the transmitral E and A velocities. Normal values of E’ are considered to be over 8-10 cm/s [48]. Because E’ is less sensitive to alterations in preload, it provides a helpful index in predicting diastolic function [48]. The integrated index of Doppler flow and TDI, the E/E’ ratio, provides a surrogate for left atrial pressure and correlates with pulmonary capillary wedge pressure [55]. The major limitation of TDI is the extrapolation of regional motion velocity to estimate global function [55].

2.4.4 Speckle Tracking Imaging: Strain and Strain Rate, Torsion and Recoil

In order to generate data for regional motion in multiple planes of movement, strain and strain rate analysis through speckle tracking imaging (STI) have been developed and are now routinely used in research and clinical settings. Myocardial strain and strain rate measure the absolute magnitude of myocardial motion (contraction / expansion) as well the velocity rate of that motion, providing an index of myocardial contractility and relaxation at a very high level of resolution and accuracy [55]. The indices of strain and strain rate are relatively load-independent, non-invasive measures of regional systolic and diastolic function [59, 60]. Strain, expressed as a percent, is defined as tissue deformity, whereas strain rate, the time derivative of strain, is expressed per second [59]. These measures are obtained through Doppler techniques from regions of interest placed along the lateral and septal walls of the LV [55]. Positive strain indicates myocardial lengthening (diastole) whereas negative strain represents myocardial shortening (systole) [60]. Unlike tissue velocities, these indices are not related to transducer
position and therefore, are not affected by tethering or cardiac translation. STI of 2D images can provide data with angle independency and is used to generate longitudinal, radial, and circumferential strain, and systolic and early diastolic strain rate measures [49]. Generation of rotational strain and strain rate at the base and apex of the LV has also allowed for assessment of LV torsion (twist) and recoil (untwist) [61]. These concepts refer to the net difference between basal and apical rotation (measured in degrees) during systole and diastole, respectively. The rate of torsion and recoil can also be obtained from STI and is referred to as torsional and recoil velocity [61].

In summary, developments in imaging techniques and echocardiography have illuminated the different components of ventricular function. The various indices obtained from M-mode and AM-mode, PW Doppler, TDI, and STI provide non-invasive assessments of LV systolic and diastolic function and were employed in the present study.

2.5 The Traditional Modality of Endurance Training

The vast majority of studies examining cardiac-specific adaptations to aerobic training have focused on continuous exercise (e.g., running, cycling, swimming) performed at moderate to high sub-maximal intensities (60-80% pre-training $\dot{V}O_2\text{max}$) for extended periods of time, ranging from 30 minutes to over 2 hours depending on the population and nature of the study. This form of training, referred to as CMT, is usually performed 3-5 days per week, requires a high volume of training and is therefore, time consuming. Nonetheless, CMT has consistently been shown to augment $\dot{V}O_2\text{max}$, an objective measure of aerobic exercise capacity and a useful index of the integrity of the cardiovascular system [62]. An improved $\dot{V}O_2\text{max}$ is largely due to
an increased maximal leg blood flow that is associated with a greater maximal cardiac output, capillarization, and ability to reduce total peripheral resistance in the skeletal muscle beds, which increases the maximum rate at which oxygen is delivered to and extracted by the skeletal muscles [1, 3].

Most of the evidence regarding changes in LV structure and function that will be discussed in this chapter has been derived from studies utilizing CMT as their primary mode of training. Indeed, public health guidelines have traditionally recommended the use of CMT as the appropriate modality of endurance training. Although the efficacy and safety of CMT in promoting health and reducing cardiovascular risk factors has been firmly established in the literature, data from recent investigations have indicated that training performed at higher intensities (i.e., HIT) may be just as beneficial and also more time-efficient.

2.6 Long-term Myocardial Adaptations to Endurance Training

In this section, structural and functional myocardial adaptations in response to chronic exercise training are described. It should be noted that when discussing longitudinal studies that specifically pertain to endurance training, the training protocol of the majority of trials has involved CMT.
2.6.1 Cardiac Structure

2.6.1.1 Physiological Left Ventricular Remodeling

A large body of evidence suggests that the hearts of individuals engaging in either endurance or strength training undergo typical structural and functional adaptations, provided that the training is of sufficient intensity and duration [34, 35, 37, 39, 58, 63-78]. The chief morphological aftereffect of training is an enlargement of the heart, more commonly known as cardiac remodeling [66]. Myocardial remodeling in highly trained athletes has been termed the “athlete’s heart” and its recognition dates back to the early 19th century [79, 80]. Swedish physician Henschen first coined the term back in 1899 following percussion of the chest of cross-country skiers and proposed that there is a physiologic enlargement of the heart in athletes, due to repetitive athletic activity [80]. His pioneering work was remarkable given that his theory has been supported by echocardiography studies in recent years [79].

Physical training is associated with hemodynamic changes and alters the loading conditions of the heart [36]. In endurance training, chronic exposures to volume overload occur in response to increased HR and SV, the primary determinants of cardiac output [33, 36, 40, 81]. In addition, systemic vascular resistance is reduced resulting in a slight-to-moderate rise in blood pressure (BP). The chronic overloading conditions and hemodynamic changes, in the long run, lead to ventricular remodeling.
2.6.1.2 Effect of Training Type on Left Ventricular Remodeling

Studies have shown that cardiac remodeling varies depending upon the specific type of training [12, 36, 40, 57, 73, 82-84]. Strength training is primarily associated with pressure overload inducing the thickening of LV wall with little or no changes in internal dimensions. The ensuing adaptation is generally known as concentric LV hypertrophy [33, 36, 85]. On the other hand, chronic volume load in endurance training increases the internal diastolic diameter of the LV (LVIDd) with proportional increases in posterior wall thickness (PWT), leading to eccentric LV hypertrophy [33, 36, 40, 85]. Morganroth and colleagues [83] were the first to demonstrate different patterns of LV hypertrophy in hearts of highly trained athletes. Although such differences in hypertrophy have been reported in the literature, one should not view these cardiac adaptations as a dichotomous and absolute phenomenon, but rather, as a relative concept [40, 85]. Athletic activities are rarely purely static (i.e., strength/power) or dynamic (i.e., endurance) and there is often an overlap in the training programs of individuals [40]. Therefore, endurance-training-induced adaptations in the structure of the heart are due to a combination of volume and pressure loads. This is particularly evident if we take into consideration HR and BP responses during exercise [40]. The cardiac output of an endurance-trained heart increases from 5 to 6 L·min⁻¹ at rest and up to 40 L·min⁻¹ during maximal exercise [86, 87]. An increase in internal diameter reflects an adaptation to this volume load. Furthermore, BP also rises during aerobic activity, although to a lesser extent than during strength exercise [87]. Therefore, the heart has to adapt to both volume and pressure loads by increasing wall thickness and internal diameter. Regardless, the physiological significance of such adaptations is presumably to compensate for the increased LV wall stress [40].
2.6.1.3 Chamber Dimensions and Posterior Wall Thickness

The majority of studies evaluating the structural adaptations to endurance training have been cross-sectional in nature, matching for sedentary controls of the same age, gender, and body mass index (BMI) [39, 63, 68, 69, 88-90]. The major findings of these investigations have overall indicated that the LV mass of endurance athletes are greater than their non-athletic counterparts. This difference is attributed to greater LV internal dimensions, LV volumes, and thickening of the LV wall. An increased interventricular septum (IVS) has also been reported in some studies [40, 63, 88, 91]. Relatively few longitudinal studies have investigated endurance training-induced adaptations in cardiac structure and morphology [57, 64, 67, 75, 77, 92]. Nonetheless, their findings have been similar to cross-sectional data.

It is important to note that the feature distinguishing physiological enlargement of the athlete’s heart from pathological conditions (i.e., hypertrophic cardiomyopathy) is the “symmetrical” dilatation and hypertrophy associated with training [38] (Figure 1). Recreational athletes typically present cardiac dimensions within the normal healthy range (LVIDd < 55 mm, LVPWT < 12 mm) [85]. However, the accepted normal ranges are well exceeded in many elite-level athletes (LVIDd > 55-60 mm, LVPWT > 13 mm) [39]. These numbers correspond to a 10% and 15% greater than normal values for LVIDd and LV PWT, respectively [93].
Figure 1. Interaction between left ventricular dimensions and wall stress.

(a) Normal left ventricle (untrained); (b) After chamber enlargement without LV hypertrophy (i.e., cardiomyopathy); (c) After endurance training (increased ventricular chamber volume and modest hypertrophy). From Goodman [38], with permission.

2.6.2 Cardiac Function

2.6.2.1 Systolic Function

LV systolic function, as measured by echocardiography, is typically expressed as dimensional FS or EF [55]. Evidence regarding the effects of prolonged endurance training on systolic function and LV contractility remains highly ambiguous. Whereas many investigators have detected no changes in systolic function [64, 68, 73, 77], others have reported enhanced
or even depressed systolic performance [96] following sustained aerobic training.

### 2.6.2.1.1 Cross-Sectional Data

Douglas and colleagues [68] evaluated changes in cardiac function by comparing highly trained endurance athletes to their matched counterparts. Using echocardiography and Doppler ultrasound, authors reported normal systolic function in ultra-endurance athletes, similar to sedentary subjects. MacFarlane et al. [73] evaluated the effects of training on LV functional adaptations in an endurance-trained group, a strength-trained group, and age-matched controls. LV systolic function, as indicated by percentage of FS, did not differ between the groups. Similarly, Brandao et al. [97] failed to demonstrate significant changes in LV contractile reserve of 13 moderately trained athletes compared to 12 sedentary sex- and age-matched controls.

In contrast, Seals et al. [94] evaluated LV systolic performance of 9 older endurance-trained athletes and matched sedentary controls. They found that LV systolic function at peak exercise was higher in the athletic group than in sedentary controls as evidenced by a greater LV contractile functional reserve, and significantly higher LV FS. Moreover, maximal SV was higher in the trained group than in the sedentary controls and changes in SV correlated with changes in EF in the trained group but not in sedentary controls. More importantly, for a given increase in EDV, the rise in SV during exercise was significantly larger in the athletes than in controls, which, in the absence of differences in mean BP, indicated that enhanced LV systolic function played a large role in maintaining a higher SV at peak exercise, independent of preload. They concluded that cardiac adaptations in older endurance-trained men are characterized by volume-overload LV hypertrophy and enhancement of LV systolic performance at peak exercise.
In another study, Fisman et al. [70] compared 47 long-distance male runners with 24 sedentary controls at rest and during exercise. Doppler aortic flow velocity and acceleration were used as indices for assessment of LV systolic function. Echocardiographic-derived data revealed increased peak aortic flow velocity in athletes under basal conditions as well as during exercise. Similarly, resting and exercise mean acceleration values were also higher in athletes than in sedentary subjects. The authors suggested that these observations are indicative of improved LV systolic parameters in the athletic population. They also proposed that the lack of similar findings in the literature is due to the moderately active state of athletic groups. However, this notion is not completely supported given that the subjects of the investigations by Douglas et al. [68] and MacFarlane et al. [73] were previously untrained. A more recent study by Pela et al. [74] also did not support improved systolic performance in athletes.

2.6.2.1.2 Longitudinal Data

Adams and colleagues [64] did not observe a significant change in the EF of sedentary young men following 11 weeks of CMT, indicative of no alterations in LV contractile function. Sadanianzt et al. [77] assessed six previously inactive middle-aged men (39 ± 7 years) before and after one year of training (cycling) for 4 hours per week. Measurements of resting EF and FS failed to demonstrate significant alterations in LV systolic function. Spina et al. [98] evaluated LV contractile function in response to beta-adrenergic stimulation. They studied 10 women and 6 men prior to and after 12 weeks of a combined running and cycling exercise training protocol. Whereas FS remained unchanged under resting conditions, it significantly increased in response to an isoproterenol challenge post-training. The investigators concluded that the training regimen induced improved systolic function in both groups compared with baseline. In a subsequent
investigation, Spina et al. [95] evaluated changes in cardiac function of healthy older men (63-67 years) by inducing an afterload stress. Following 9 months of endurance training, FS significantly reduced in response to a cardiac muscarinic receptor blocker. Changes in FS were significantly higher after training than before, suggestive of enhanced LV contractile function.

Even though it appears that there is modest evidence to support improvement of myocardial contractility, the subject groups of the studies have primarily consisted of older men [32, 94, 95]. Other published reports examining younger populations have failed to demonstrate any significant training-induced changes in systolic function [64, 68, 73, 77, 97]. The recent large-scale meta-analysis by Pluim et al. [40] found no significant differences between endurance athletes (runners) and control subjects with respect to LV EF and FS. These findings are in agreement with two previous meta-analyses by Fagard [36, 81].

2.6.2.2 Diastolic Function

In contrast to LV adaptations in contractility and systolic function, a number of investigators have detected training-induced enhanced LV diastolic function in both young and older groups [37, 65, 71, 73, 99].

2.6.2.2.1 Cross-sectional Data

MacFarlane and colleagues [73] determined the diastolic filling pattern of weightlifters, endurance-trained, and physically inactive subjects at rest and during exercise. Whereas no differences were found between the strength-trained and control group, endurance athletes
exhibited augmented diastolic function both at rest and during exercise, as evidenced by a significantly higher E:A ratio. Similarly, Forman et al. [71] obtained PW Doppler inflow measurements in three different healthy male and female groups: (i) young adults; (ii) sedentary elderly, and (iii) endurance-trained elderly. In comparison to the sedentary old subjects, early diastolic filling at rest was significantly improved in the athletic elderly group. The early diastolic filing pattern of older athletes was reported to resemble that of healthy, young adults. In another study, Caso et al. [65] investigated the effects of endurance training on myocardial regional diastolic function. Using standard PW Doppler-derived blood flow velocities and TDI, they assessed 20 male water polo players and 20 matched sedentary subjects. Compared to controls, athletes exhibited a significantly higher peak E flow velocity of the inferior wall even after adjusting for HR, body size, and SV. This finding further points to the beneficial effects of endurance training in improving myocardial diastolic filling properties.

Takemoto et al. [99] compared 20 older long-distance runners to 20 untrained individuals matched for age and BP. In addition to finding a higher resting E:A ratio in the trained subjects, they also detected a significantly reduced late diastolic peak velocity in this group. The investigators suggested that endurance training has the potential to attenuate the diastolic dysfunction associated with normal aging. These findings were consistent with those observed by previous reports [71, 99]. However, Fleg and coworkers [100] demonstrated a lack of lifelong training effect on peak E/A ratios at rest in male endurance athletes aged 52 to 76 years, compared with sedentary and young controls. However, their attempt to uncover the effects of physical activity on aging from Doppler measures of diastolic function was limited by participant selection as well as pitfalls of Doppler measurements. In addition to being male, the age of the participants recruited was between 52 to 76 years of age. This rather wide age range may fail to precisely delineate the effects associated with lifelong endurance training. Also, only PW
Doppler measures of transmitral flow velocity profiles were used as indices of diastolic function. These variables, although valuable, only reflect partial aspects of diastolic filling properties when used alone [47, 50]. As described previously, utilization of TDI technology in addition to PW Doppler measures would provide a much better assessment of LV diastolic function [50]. Nonetheless, Gates et al. [89] also did not identify a positive modulation of age-associated diastolic dysfunction with regular aerobic activity in older men. In line with this evidence, Galetta et al. [37] examined the LV diastolic function of 20 normotensive elderly with a lifelong history of endurance training (competitive running) and compared it to that of 20 matched healthy volunteers. Using PW Doppler echocardiography and TDI methods, they evaluated diastolic velocities of the basal lateral segment and basal IVS of the subjects. With respect to controls, athletes showed a higher E’, a reduced A’, and thus, an increased E’:A’ ratio. Furthermore, the IVRT was significantly reduced in the trained population, as compared to inactive individuals. It is noteworthy that the indices of interest were all within the normal range in the trained subjects. The investigators concluded that highly trained elderly athletes exhibit augmented LV diastolic filling, as compared to their matched controls. Therefore, chronic aerobic training may act to slow down the diastolic dysfunction associated with normal aging. However, a study by Baldi et al. [58] did not support the training-induced attenuation of age-related deterioration of LV diastolic function. Nineteen older male athletes (60-80 years), 20 older untrained men, 13 young athletes (20-30 years), and 13 young sedentary men underwent PW Doppler echocardiography and TDI evaluation. There was a clear age effect when comparing the Doppler-derived indices of diastolic function in the four groups. This was evidenced by a significantly higher Peak E, lower Peak A, higher E:A ratio, as well as a shorter IVRT in the younger group compared to the older subjects. However, no significant training effect was observed in these indices. Only IVRT was found to be markedly shorter in trained
older men as compared to older inactive males. These findings do not support the role of exercise training as means of preserving the diastolic filling properties associated with ageing.

More recently, Prasad et al. [101] showed minimal improvement of LV diastolic filling and relaxation in elderly athletes (66-74 years). Comparison of young healthy subjects to older athletes confirmed that aging is associated with diastolic dysfunction. However, endurance training did not alter the age-related changes of diastolic function, as measured by PW Doppler measures. Only E’ was found to be higher in older athletes, but not in sedentary elderly individuals. The investigators suggested that lifelong physical activity may have minimal positive effects on the age-associated diastolic dysfunction and that the benefits may be more related to changes in LV compliance, as shown previously [102], rather than LV relaxation.

2.6.2.2.2 Longitudinal Data

Few longitudinal studies have evaluated the effects of endurance training on diastolic function [57, 95]. Brandao and coworkers [97] observed a more pronounced rise in the peak diastolic filling rate during exercise in the endurance-trained group, as measured by radionuclide angiography. Spina et al. [95] implemented a CMT intervention for 8 older men and conducted follow-up measures after 9 months. CMT resulted in a higher E:A transmitral diastolic flow velocity ratio at similar HRs, indicating improved diastolic filling in the subjects. More recently, Baggish et al. [57] conducted a prospective, longitudinal evaluation of training in 40 competitive endurance athletes. Following 90 days of team training, they observed enhanced diastolic function, as indicated by increased early peak diastolic tissue velocities, measured at both the lateral wall and the IVS.
Whereas data with regards to resting diastolic filling parameters are equivocal, several lines of evidence provide strong support that LV diastolic function in endurance-trained athletes is markedly enhanced during exercise in both young and older populations [73, 91, 95, 99, 103]. The meta-analysis by Pluim and colleagues [40] did not find any significant differences in the E/A ratio of endurance athletes compared to non-athletic populations. Nevertheless, the authors suggested that most data point to a significant augmentation of diastolic function during exercise as a result of sustained aerobic training. Therefore, it appears that enhanced diastolic compliance contributes to a more pronounced utilization of the Frank-Starling mechanism during exercise following training. This is in turn reflected by an increase in SV and bradycardia during exercise following sustained aerobic training. In addition, several investigators have reported augmented LV diastolic filling at rest in endurance-trained athletes [37, 57, 65, 71, 73], suggesting that global diastolic function may become favourably modulated with aerobic training.

The cellular alterations associated with enhanced LV filling following exercise training have yet to be elucidated, but several mechanisms have been proposed. Intrinsic adaptations in the cardiomyocyte may explain enhanced relaxation in trained hearts. Studies in animal models have shown training improves the rate of -dP/dt and Tau [104], while increasing Ca$^{2+}$ reuptake by the sarcoplasmic reticulum [105] and Ca$^{2+}$ stimulated myosin ATPase activity [106]. Adaptations may also be related to changes within myocardial collagen metabolism. An experiment comparing endurance-trained rats with an experimental rat model of hypertension demonstrated a substantial increase in LV collagen in hypertensive rats, but not in the trained rats [107]. Hypertensive rats had a lesser collagen type III:I ratio and a reduced -dP/dt. Because a low type III:I collagen ratio is indicative of noncompliant and stiff tissue, these changes can at least partially explain the increased diastolic stiffness observed in hypertensive hearts.
2.6.3 Blood Volume

There is compelling evidence in the scientific literature that exercise and physical training significantly affect the regulation of BV [2, 6-8, 10, 20, 31, 108, 109]. Repeated exposure to physical activity has been consistently demonstrated to increase total BV [7, 20, 108, 110, 111]. Indeed, athletes have greater BVs and extracellular fluid compartments compared to sedentary populations [110, 112]. Also, the expansion of BV, termed hypervolemia, has been observed following acute exercise and is primarily attributed to PV expansion [7, 113, 114]. In addition, hypervolemia is positively correlated with aerobic capacity [2] (Figure 2). Thus, it appears that BV and its training-associated adaptations play an important role in the mechanisms that control cardiovascular function. The remarkable rate at which exercise induces hypervolemia is demonstrated by the observations that only a single bout of exercise increases BV by as much as 10-20% within 24 hours [8, 114]. The expansion of BV continues to rise until it peaks around 10-14 days of exercise training. Up to this point, hypervolemia can be explained almost completely by an expansion of blood plasma with little or no changes in red blood cell (erythrocyte) mass. Further training (>2-4 weeks) results in a more equal distribution of increased PV and red blood cell volume [2, 10, 45] (Figure 3).
Figure 2. Cross-sectional relation between total blood volume and maximal exercise performance. From Convertino [2], with permission.
2.6.3.1 Underlying Mechanisms Responsible for Training-induced Hypervolemia

Several inter-related mechanisms are responsible for promoting the expansion of PV and BV concomitant with increased physical activity. A key factor in regulation of BV involves increased water and sodium retention [5]. During an acute bout of exercise, PV is reduced commensurate to the thermal and metabolic demands. This loss of volume results in increased circulating electrolyte concentrations that activate the renin-angiotensin-aldosterone system as well as the antidiuretic hormone vasopressin. These endocrine responses are associated with
increased renal water and sodium retention, and accompany a decrease in urine output up to 24 hours following recovery from exercise [2, 5]. Coupled with reduced water output is increased water intake (due to thirst), which exceeds the sweat loss brought upon during exercise. Thus, increased body water and sodium retention represent an important mechanism that contributes to the BV expansion associated with exercise and training [2, 5, 10]. Furthermore, increased total circulating protein levels (e.g., albumin) allows for compartmentalization of fluid volume in the vascular space by increasing the pressure across the capillary membranes. Since each gram of circulating protein binds to approximately 14-15 millilitres of water, elevated protein levels would serve to hold water in the vascular space and consequently, increase intravascular volume [2, 5]. The proportional increases in circulating protein levels associated with training occur without changes in plasma protein concentrations [2, 5, 20]. Hence, the primary mechanisms underlying exercise- and training-induced hypervolemia include increased fluid intake, reduced electrolyte and water excretion, and chronic elevation of total circulating plasma proteins.

2.6.3.2 Relation to Central Hemodynamics

Numerous reports have associated training-induced hypervolemia with a reduction in HR and increased SV during the same exercise intensity [9, 115, 116]. This was eloquently demonstrated by Mier et al. [9], who observed a marked rise in SV and subsequently, cardiac output following 10 days of cycling. Convertino et al. [115] demonstrated that a 1% increase in PV corresponds to a 1% decrease in exercise HR, signifying the close relationship between the two. An enhanced Frank-Starling mechanism, through increased EDV, has been proposed as the most likely explanation for the effects of PV and BV expansion on exercise HR and SV [6, 9, 20, 115]. The importance of this effect was shown by Coyle et al. [116], who reported increased
exercise HR and reduced SV associated with lowered BV following a 2-week detraining period. In addition, research has indicated that hypervolemia and elevated SV are associated with increased central venous pressure at rest as well as during exercise [2, 10, 111]. Hence, a greater venous return may partially account for the rise in SV during exercise following endurance training. With respect to exercise bradycardia, the interaction between hypervolemia and the cardiac response more likely reflects the optimal availability of BV and the time allowed for cardiac filling, although autonomic factors also play an important role [10]. Regardless, training-induced hypervolemia clearly enhances cardiovascular stability during exercise by increasing SV.

In order to establish the significance of PV expansion on cardiovascular adaptations independent of other changes that might occur, investigators have artificially induced an acute hypervolemic response using serum albumin or high molecular weight compounds such as Dextran, diluted in saline [117-119]. Similar to exercise training, acute PV expansion has been shown to increase SV and cardiac output through the use of the Frank-Starling mechanism, leading to improvements in \( \dot{\text{VO}}_{2\text{max}} \) [120, 121]. However, these adaptations are only evident in untrained individuals, as minimal changes in exercise performance and cardiovascular function have been observed in endurance athletes [122, 123]. It appears that endurance athletes are already at an optimal BV that places their myocardium near the limits of it ability to fill and further expansion of BV would not increase cardiac function or exercise capacity [122].

Over time, our understanding of the mechanisms underlying BV alterations in response to physical exercise has drastically improved; yet, several areas are subject to further investigation and many questions remain unanswered. Approximately, 30% of the variance in changes in LV function can be explained by changes in PV [2]. Thus, improvements in LV function following
endurance training are not solely the passive result of training-induced hypervolemia. Hypervolemia then, by itself, is insufficient to explain the training-induced central adaptations associated with prolonged aerobic training.

2.7 The Importance of Exercise Intensity

Research in exercise science has established that the mode, intensity, frequency, and duration of exercise are essential determinants of the magnitude of training benefits in athletes and healthy sedentary individuals [124]. The same variables are of importance for the outcome of exercise training in prevention and treatment of cardiovascular disease [106, 125]. A working hypothesis that has gathered interest in the past decade is that training at a high intensity results in greater cardiovascular benefits compared to training performed at a moderate or low intensity [18, 106, 125-127]. A large body of evidence derived from experimental models and clinical settings has supported the notion that high-intensity training induces greater effects on the myocardium as well as important health outcomes such as $\dot{V}O_2^{\text{peak}}$.

2.7.1 Association Between Exercise Intensity and $\dot{V}O_2^{\text{peak}}$

Until recently, most public health recommendations concerning exercise had focused on the efficacy of CMT for improving cardiovascular health. However, data from training studies have consistently shown that the higher the exercise intensity, the greater the increase in $\dot{V}O_2^{\text{peak}}$ and hence, the greater the health benefit [17, 18, 126, 128]. This concept is in fact not new and has been proposed for several decades [124, 129]. Recently, it has been demonstrated that
improvements in $\dot{V}O_{2\text{peak}}$ and SV are intensity-dependent in healthy men, with the highest response corresponding with the highest exercise intensity (90% $\dot{V}O_{2\text{peak}}$) [128]. Helgerud and colleagues compared the effects of aerobic endurance training at different intensities. The investigators examined responses in $\dot{V}O_{2\text{max}}$, SV, BV, lactate threshold, and running economy of 40 healthy, moderately trained male individuals. The participants were allocated to one of the following training programs: long slow distance running (70% peak HR); lactate threshold (85% peak HR); 15/15 HIT (15 seconds of running at 90-95% peak HR separated by 15 seconds of active resting at 70% peak HR); and 4/4 HIT (4 minutes of running at 90-95% peak HR followed by 3 minutes of active resting at 70% peak HR). An objective of the study was to match for the total training volume of work across the groups. All protocols were followed for 3 sessions per week for a total of 8 weeks. The investigators demonstrated that the HIT protocols resulted in significantly increased $\dot{V}O_{2\text{max}}$ compared with long slow distance and lactate-threshold training intensities. The percentage increases for the 15/15 and 4/4 HIT groups were 5.5% and 7.2%, respectively, while no changes occurred in the long slow distance running and lactate threshold groups. They concluded that high-intensity training was significantly more effective at improving exercise capacity than performing the same total work at lower exercise intensities. In line with this observation, other studies that have employed high-intensity with shorter durations have reported greater enhancements of $\dot{V}O_{2\text{peak}}$ compared to moderate-intensity training in healthy [128, 130, 131] and clinical populations [16-18]. Duffield et al. [130] examined the effect of HIT on the $\dot{V}O_2$ response. Training involved high-intensity intervals (2 minute work, 1 minute rest) performed for 8 weeks, 3 times per week. Results demonstrated that training resulted in significant improvements in $\dot{V}O_{2\text{max}}$, power at $\dot{V}O_{2\text{max}}$, and power at lactate threshold.
In a recent meta-analysis comparing the cardioprotective benefits of high- and moderate-intensity exercise, Swain and Franklin [126] concluded that exercise performed at vigorous intensities yields greater gains in VO$_{2}$peak, given equal energy expenditure. Since VO$_{2}$peak has been established as a key prognostic factor for cardiovascular disease [62], its close association with exercise intensity further points to the importance of intensity in promoting health and reducing cardiovascular risk factors.

### 2.7.2 Cardioprotective Benefits of High-intensity Training

Numerous epidemiological studies have reported greater cardioprotective benefits of endurance training performed at a higher intensity compared to low or moderate training while controlling for total energy expenditure [126, 127, 132-135]. In a study of health professionals, high exercise intensity was associated with significantly reduced all-cause mortality, independent of physical activity duration [132]. This finding was complemented by a subsequent report, which linked higher exercise intensity with greater reduction in risk of coronary heart disease in old men [133]. In a 16-year follow-up study, Wisloff et al. [127] showed that a singly weekly bout of high intensity exercise significantly reduced the risk of cardiovascular death in men and women compared to their sedentary counterparts. An interesting finding from this study was that increased frequency of exercise sessions or duration of physical activity did not provide additional benefits. Altogether, these data indicate that exercise intensity, rather than its duration, may be more important in achieving cardiac benefits associated with regular endurance training.
2.8 High-intensity Interval Training

HIT, a training modality that requires repeated bouts of short and intense activity, has been demonstrated to induce significant improvements in both aerobic and anaerobic exercise performance in trained athletes [136, 137] as well as healthy individuals [128, 130, 138] and patients with cardiac disease [15, 17, 18, 139]. This mode of training is characterized by repeated efforts of short (15 seconds–4 minutes) bursts of intense activity (85-100% \( \dot{V}O_2 \)peak), interspersed with periods of relief or active recovery (low-intensity exercise at 10-50% \( \dot{V}O_2 \)peak for 15 seconds-4 minutes) [14, 26, 106, 125]. The stimulus provided by HIT is at a high intensity but reduced volume per week; therefore, this form of training offers an alternative to the more time-consuming CMT (although not all HIT protocols result in time savings compared to CMT). HIT also poses a considerable metabolic challenge to skeletal muscle as large reductions in muscle glycogen and pH, and increases in blood lactate as well as whole body carbohydrate and fat oxidation have been observed following HIT [140]. One of the most attractive features of HIT is that it resembles the activity patterns that individuals typically experience in their activities of daily living such as climbing the stairs [141]. Furthermore, HIT provides an alternative option for individuals who cannot or would rather not sustain extensive, continuous periods of physical activity. Although this type of exercise is at a level below or near maximal \( \dot{V}O_2 \)peak and is thus “aerobic”, it is nevertheless above the intensity thresholds at which intramuscular adenosine triphosphate (ATP) levels deplete, lactate and metabolites start to accumulate, the slow component of \( \dot{V}O_2 \) kinetics becomes steeper, and as a result, fatigue occurs within minutes of exercise [106]. Hence, continuous exercise at such high intensities cannot be sustained for prolonged periods. In order to accumulate time in the high-intensity bouts, which confer the
greatest benefit, periods of lower intensity exercise are employed to allow the individual to re-
engage in high-intensity intervals.

The relative intensities and durations of exercise intervals depend upon the population and should be tailored to the individual’s goals and needs. There are significant differences in design of HIT interventions. Whereas some protocols involve as little as 10 minutes per week of sprint interval training (SIT), others are designed to be isocaloric to the energy expenditure of comparable CMT programs [141]. It is noteworthy that anecdotal evidence from studies has indicated that HIT is more motivating than CMT, mainly due to the short, yet vigorous stress it places on the participants as well as its typically time efficient nature [14, 106, 141].

Although HIT has been frequently employed in athletic populations, it has traditionally been viewed as unsafe and unfeasible for sedentary individuals and those with health-related disorders. However, this perception is now being strongly challenged by evidence-based research, which suggests that HIT is a safe training modality and can induce similar, if not superior, changes in exercise and work performance, skeletal muscle metabolism, and cardiovascular function, compared to traditional CMT [14, 106, 125, 141].

2.9 Long-term Myocardial Adaptations to HIT

2.9.1 Evidence from Experimental Models

Several investigations by Wisloff, Kemi, and co-workers have examined HIT-induced myocardial adaptations in rats and mice [142-145]. Overall, these data have reported cardiac changes that are also observed in humans in response to chronic CMT. Such adaptations include
increased VO_{2peak}, reduced resting HR, increased LV size, as well as improved systolic and diastolic function. In addition, their findings have established that the improvement in VO_{2peak} and contractile and relaxation rates are intensity-dependent [125]. Regular HIT at 85-90% VO_{2peak} improved VO_{2peak} and maximal extent of shortening in unloaded cardiomyocytes twice those induced by CMT at 65-70% VO_{2peak} [142, 144]. The experiments also indicate that contraction and relaxation rates enhance by 20-40% [142-145], with the improvement more consistently observed in relaxation rates. Kemi et al. [143] showed that HIT results in significant improvements in contractility during the first 2 months of training, after which a plateau is reached. These changes correlated with improvements in VO_{2peak} and cardiomyocyte hypertrophy. The extent of cardiomyocyte hypertrophy depended on the exercise intensity as HIT induced a 14% increase in longitudinal cell growth compared to 5% increase in response to CMT.

2.9.1.1 Cellular Basis for Intensity-Dependence of Cardiac Benefits

Experimental models using rodents have studied cardiomyocyte hypertrophy in response to HIT by assessing various contractile variables including FS, intracellular Ca^{2+} handling, and myofilament responsiveness to Ca^{2+} [143]. The repetitive contractions of the cardiomyocytes stimulated through intracellular Ca^{2+} encompass the cardiac pump function. These plastic cells respond to both short-term and long-term stress. With regards to endurance exercise training, they acutely and chronically adapt through increased frequency, amplitude, force of contractions, as well as rate of relaxation [146]. Prolonged endurance training augments the contractile capacity of the isolated cardiomyocyte by increasing the rates of shortening during systole and
lengthening during diastole and by improving its ability to generate force [106]. This contributes to the Frank-Starling mechanism as the heart adapts to higher stress (increased load) by performing more work. Adaptations may be partially due to training-induced activation of the Ca\(^{2+}\) calmodulin-dependent protein kinase II and phosphorylation of the threonine-17 residue of phospholamban, increasing the activity of the SERCA2a during diastole and upregulating the SERCA2a:phospholamban ratio. In turn, these changes increase the rate of Ca\(^{2+}\) reuptake into the sarcoplasmic reticulum and improve the SERCA2a component of free Ca\(^{2+}\) removal in the cytosol. This not only improves relaxation, but also enhances Ca\(^{2+}\) loading of the sarcoplasmic reticulum [125].

2.9.2 Evidence from Healthy Humans

Much of the HIT research in the literature has been conducted on high-performance athletes [136, 137]. Overall, this training modality has shown to be effective in enhancing exercise performance and cardiovascular regulation in endurance athletes. However, very few longitudinal studies have thoroughly evaluated the long-term cardiac adaptations induced by HIT in healthy individuals. One of the earliest studies employing an intense interval training approach was conducted by Cox et al. [147]. The training protocol consisted of running 6 alternating days per week (40 minutes) and five 5-minute intervals at 85-90% \(\dot{V}O_2\text{peak}\). Adaptive changes in LV dimensions occurred following 7 weeks of endurance training in previously untrained individuals. Training-induced increases in IVS occurred during both systole and diastole and in LVIDd. The absolute values of LV EDV, SV, EF, and LV mass significantly increased after training. In a more recent investigation, Slordahl et al. [138] employed 8 weeks of HIT performed at four 4-minute intervals and at 90-95% of maximal HR in 12 young, previously
untrained women. They demonstrated that HIT increased LV mass, LV contractility during exercise, and \( \dot{VO}_{2\text{max}} \) by 12%, 13%, and 18%, respectively [138].

### 2.9.3 Clinical Utility of High-intensity Interval Training in Heart Disease

Endurance training-induced adaptations in heart disease are primarily attributed to improved skeletal muscle function and peripheral circulation. Numerous recent trials, however, have demonstrated that HIT may indeed reduce cardiac dysfunction and improve the intrinsic function of the myocardium by enhancing contractility and relaxation. Consequently, it has been suggested that aerobic training needs to be of sufficient intensity to exert its beneficial effects on the myocardium [106, 125].

#### 2.9.3.1 Experimental Models of Heart Disease

One of the most commonly used models of heart disease is the post-myocardial infarction (MI) heart failure (HF) rodent [125, 148]. These animals are characterized by LV remodeling and pathological hypertrophy and reduced cardiac pump function [148]. The molecular and cellular changes underlying these adaptations include abnormal excitation-contraction patterns and \( \text{Ca}^{2+} \) handling. Yet, the post-MI rodent is also susceptible to positive modulation by aerobic exercise training, which can reverse or partially correct pathological alterations of the cardiomyocyte. Furthermore, the magnitude of the training effect is associated with exercise intensity; the reversal of pathology in response to training at 85-90% \( \dot{VO}_{2\text{peak}} \) is superior to that at moderate or lower intensities [106, 125]. In post-MI HF rats, HIT induced marked
improvements in $\dot{V}O_{\text{peak}}$, LV dimensions, and LV mass. Of note, $\dot{V}O_{\text{peak}}$ increased by 10% every week until it approached a plateau after 5-6 weeks. This study controlled the intensity and extent of exercise and employed a higher intensity program than earlier models. In the same study, HIT also corrected FS and the rate of relaxation in cardiomyocytes towards levels observed in healthy sedentary rats. Importantly, the improvement in the rate of relaxation was closely associated with enhanced rates of intracellular Ca$^{2+}$ handling, which were near normal levels following training. While the intensity-dependence of endurance training is not firmly established in post-MI HF rats, accumulated evidence suggests that the cardiomyocyte undergoes more favourable adaptations following HIT compared to CMT [106].

Historically, exercise training has been utilized as a therapeutic approach in humans with heart disease for some time. However, most interventions have employed CMT and thus, their exercise intensity has been considerably lower than HIT protocols. Since findings from experimental work suggested that training intensity must be of sufficient intensity to elicit improvements in cardiac function, several investigations applied HIT to clinical populations, including HF [18], coronary artery disease (CAD) [15, 17, 139], and those at increased risk of developing heart disease [16, 149].

### 2.9.3.2 Heart Failure

Perhaps the most well-known and widely cited study regarding the utility of HIT in cardiac patients is the recent work by Wisloff and colleagues [18]. In this study, post-MI HF patients with LV systolic dysfunction were randomized into a control group, CMT, and HIT interventions lasting 9 weeks and 3 days per week (1 day per week was home-based), and the
training protocols were held isocaloric. Each training group consisted of nine patients, with the average of 75.5 years old. Patients were classified with New York Heart Association classes I-III, had a mean EF of 29%, and were on optimal medical therapy. The HIT protocol involved running 4 intervals at 90-95% peak HR (~85-90% \( \dot{V}O_{2peak} \)), interspersed with 3-minute period recovery at 50-60% peak HR. In contrast, CMT comprised of continuous walking or running at 50-70% \( \dot{V}O_{2peak} \) for 47 minutes. Compared to controls, both training groups showed marked improvements in several measures of exercise capacity and cardiovascular function. However, the beneficial effects were substantially greater in the HIT group. HIT increased \( \dot{V}O_{2peak} \) by 46% compared to a 14% increase induced by CMT. HIT also increased EF and SV, and reduced LV dilatation, whereas these cardiac variables were unchanged in response to CMT (Figure 4). In addition, plasma levels of pro-brain natriuretic peptides (a marker of LV remodeling) were reduced by 40%, implying that reversal of remodeling occurred in these patients. Furthermore, quality of life was improved in the HIT group only. This was the first study to eloquently demonstrate that aerobic training, if performed at a sufficiently high intensity, could lead to marked adaptations in the hearts of HF patients. It also clearly showed that HIT could be safely applied to patients with severely comprised cardiac function. A striking aspect of this report was the average age of the patients (75.5 years of age), which was much higher that the typical age of HF patients enrolled in other endurance training studies.
2.9.3.3 Coronary Artery Disease

Three small single-centre trials have employed HIT in patients with stable CAD and an average age of 60 years old [15, 17, 139]. Although these studies are statistically underpowered to evaluate safety and efficacy, they nonetheless provide evidence for the utility of HIT in this clinical population. Warburton et al. [17] reported that HIT results in similar benefits in aerobic capacity and a greater tolerance to an anaerobic challenge compared to CMT in 14 men with CAD. Whereas the CMT group exercised continuously at 65% of HR reserve for 30 minutes, the HIT protocol consisted of 2-minute intervals at 90% HR reserve followed by 2 minutes of recovery (at 40% HR reserve). Both interventions were matched for total work and required training 30 minutes per day, 2 days a week, for a total of 16 weeks. In the other two reports, patients were allocated into CMT or HIT and underwent 10 weeks of aerobic training. Relative to CMT, the training-induced increase in $\dot{V}O_2$peak was significantly higher in the HIT group.

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<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Baseline</th>
<th>Control Follow-Up</th>
<th>MCT Baseline</th>
<th>MCT Follow-Up</th>
<th>AIT Baseline</th>
<th>AIT Follow-Up</th>
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<tr>
<td>LVDD, mm</td>
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<td>67.8 ± 12.5</td>
<td>69.1 ± 8.8</td>
<td>68.2 ± 6.5</td>
<td>66.7 ± 6.8</td>
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<tr>
<td>LVSD, mm</td>
<td>56.2 ± 9.2</td>
<td>56.7 ± 13.7</td>
<td>56.6 ± 8.8</td>
<td>53.9 ± 7.4</td>
<td>53.9 ± 6.7</td>
<td>46.1 ± 8.2*†</td>
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<tr>
<td>LVEDV, mL</td>
<td>250.5 ± 64.4</td>
<td>242.1 ± 62.3</td>
<td>245.5 ± 53.1</td>
<td>230.3 ± 41.0</td>
<td>248.1 ± 79.6</td>
<td>202.9 ± 72.0*†</td>
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<tr>
<td>LVESV, mL</td>
<td>187.8 ± 53.0</td>
<td>186.6 ± 58.6</td>
<td>172.9 ± 48.7</td>
<td>160.6 ± 34.3</td>
<td>177.4 ± 72.1</td>
<td>133.9 ± 57.8*†</td>
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<tr>
<td>HR at rest, bpm</td>
<td>60 ± 11</td>
<td>59 ± 11</td>
<td>55 ± 10</td>
<td>54 ± 12</td>
<td>65 ± 14</td>
<td>61 ± 13</td>
</tr>
<tr>
<td>SV, mL</td>
<td>53.4 ± 15.3</td>
<td>55.0 ± 13.7</td>
<td>63.5 ± 12.7</td>
<td>63.1 ± 15.7</td>
<td>57.1 ± 14.3</td>
<td>67.0 ± 19.9*</td>
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<td>CO, L/min</td>
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<td>3.5 ± 0.9</td>
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<td>3.9 ± 0.6*</td>
</tr>
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<td>EF, %</td>
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<td>32.8 ± 4.8</td>
<td>33.5 ± 5.7</td>
<td>28.0 ± 7.3</td>
<td>38.0 ± 9.8*†</td>
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</tbody>
</table>

Data are mean ± SD. LVDD indicates LV diastolic diameter; LVSD, LV systolic diameter; LVEDV, LV end-diastolic volume; LVESV, LV end-systolic diameter; HR, heart rate; SV, stroke volume; CO, cardiac output; and EF, ejection fraction.

*Different from baseline, \( P < 0.01 \); †different from controls and moderately trained, \( P < 0.02 \).
(18% vs. 8%), indicating an intensity-dependence effect. In Amundsen’s study [15], resting TDI and strain rate echocardiographic measures were also obtained before and after training. While early transmitral Doppler velocities were increased in both groups, LV early diastolic strain rate increased in the HIT group only, suggesting that regular high intensity exercise is more effective at enhancing diastolic function in these patients.

2.9.3.4 Patients at Risk of Developing Heart Disease

Two recent investigations by Tjonna et al. [16, 149] have focused on the effects of HIT in patients without cardiac disease, but who are at an increased risk of developing heart disease due to the metabolic syndrome and obesity. The results from these studies also confirm that the beneficial effects of HIT on exercise performance and health parameters are superior relative to CMT and other multi-treatment strategies. In one study comparing the fitness and health outcomes of 16 weeks of HIT to CMT and controls in 32 patients with the metabolic syndrome, the authors showed that HIT increased \( \dot{VO}_{2\text{peak}} \) by 35% compared to 16% in MCT [16]. In addition, endothelial function improved more after HIT relative to CMT (9% vs. 5%). More importantly, whereas both interventions were equally efficacious at reducing body weight and mean arterial BP, HIT was associated with removal of more risk factors that constitute the metabolic syndrome. These include reducing blood glucose and lipogenesis in adipose tissue, improving insulin signaling in fat and skeletal muscle, and augmenting skeletal muscle biogenesis. In a subsequent trial, Tjonna et al. [149] showed the marked ability of HIT to decrease several cardiovascular risk factors in 62 overweight and obese adolescents. Participants were randomized to either HIT (4 x 4 minute intervals at 90% of peak HR, each interval interspersed with 3 minute at 70% peak HR, twice a week for 3 months) or to a multi-treatment
approach involving exercise, dietary, and psychological advice (twice a month for 12 months). Intriguingly, the superior effect of HIT was observed not just at the end of the 3 months, but even at 12 months, 8 months after the formal training had been completed. Compared to the multi-treatment strategy, \( \dot{V}O_2 \text{max} \) and endothelial function enhanced more after HIT, both at 3 months and 12 months. Moreover, HIT was more beneficial in reducing BMI, body fat percentage, and mean arterial BP. In addition, HIT induced a more favourable effect on blood glucose and insulin regulation. The novel findings from these two studies provide compelling evidence that HIT can reduce cardiovascular risk factors associated with the metabolic syndrome and obesity more than CMT or another multi-treatment strategy.

It is important to acknowledge that the majority of trials utilizing HIT in different patient cohorts have been small and lack adequate statistical power to fully establish the benefits and safety of this intervention. The efficacy of HIT should be investigated by larger studies with greater power and more sensitive measures. With respect to patient groups, the clinical applicability of this training modality is currently unknown. The recent large-scale, multi-centre HF-ACTION trial [150] did not find significant exercise training-induced benefits with respect to the primary and secondary endpoints of all-cause mortality and all-cause hospitalization. However, the training modality employed was primarily of moderate intensity and it may be that higher exercise intensity has the potential to confer greater benefits in heart disease patients such as HF.
2.10 The Short-term Endurance Training Model

Examining the effects of short-term training is of particular importance as it can help elucidate the mechanisms and initial triggers of adaptations that take place with long-term training. It has been suggested that modifications in response to physical training in a relatively short period of time are primarily attributed to functional adaptations such as improvements in muscle oxidative capacity [24, 25]. In this regard, structural modifications appear unlikely to occur with short-term training. Nevertheless, very little research has been conducted on the effects of short-term training on cardiovascular function.

2.11 Short-term Adaptations in Response to Continuous Moderate-intensity Training

2.11.1 Blood Volume

Training-induced hypervolemia has been investigated in several studies employing short-term CMT interventions [6-9, 20, 21, 108, 114, 151, 152]. These data firmly indicate that hypervolemia represents the primary adaptation to acute exercise and short-term CMT in individuals, independent of age and sex. Convertino et al. [108] evaluated the mechanisms and time-course of BV expansion in response to endurance training. They examined 8 young men (20-22 years) before, during, and after 8 consecutive days of CMT, which consisted of cycling for 2 hours a day at 65% $\dot{V}O_{2\text{max}}$. Measurements of hematocrit (Hct), PV, hemoglobin, circulating proteins, as well as renin and vasopressin activity were obtained throughout the study. During training, increased plasma albumin levels accompanied PV expansion. Following
training, BV expanded by 8%, due to a 12% rise in PV, suggestive of training-induced hypervolemia. BV expansion was also associated with significant elevations in renin and vasopressin activity, leading to electrolyte and sodium retention. In another study, Luetkemeier and colleagues [151] reported CMT-induced hypervolemia in 22 healthy young men following cycling for 3 consecutive days at 65% pre-training \( \dot{VO}_2\)max values. Mier et al. [152] also demonstrated that 10 days of cycling results in similar changes in BV expansion of men and women. The intriguing finding from this study was that with the training-induced elevated BV, \( \dot{VO}_2\)max during maximal testing and SV during submaximal testing increased nearly identically in both men and women. Katyal et al. [153] examined adaptations in young, old (post-menopausal) women undergoing hormone replacement therapy, and old non-medicated women following 10 sessions of CMT. Interestingly, whereas \( VO_2\)peak improved in all groups, only the young females underwent significant PV expansion, suggesting that age in women may have an effect on the magnitude of PV expansion. More recent investigations in young individuals have confirmed these earlier findings and clearly suggest that hypervolemia represents the most notable adaptation to short-term training [6, 9, 21].

2.11.2 Cardiac Structure and Function

Previous research on the influence of short-term training on cardiac morphology and function is rather scarce. Investigators have only recently begun to examine the mechanisms and early time-course of central adaptations in response to short-term endurance training.

Ehsani and colleagues [92] provided the very first evidence into the effects of short-term training on LV structure and function. They assessed 8 swimmers over a nine-week training
period and obtained echocardiographic measurements throughout the study. By the end of the first week, significant changes in LV structural variables were already taking place, as indicated by an increased LVIDd. No alterations in systolic function, as evaluated by changes in EF were reported. Although such findings were rather intriguing at the time, it took twelve years to exclusively examine the cardiac adaptations in response to short-term CMT. Green et al. [20] evaluated the effects of 3 days of cycling on LV hemodynamics during prolonged exercise. Eight male university students cycled for 120 minutes at approximately 65% \( \dot{V}O_{2\text{max}} \) on day 1. Measures of respiratory gas exchange, cardiac function, blood, and muscle substrates were obtained before and at 30, 60, 90, and 120 minutes during exercise. The training protocol on days 2 and 3 were identical except that no measurements were taken on these days. Follow-up assessments similar to day 1 were then performed after 48 hours of recovery. PV and BV elevated by 20% and 12%, respectively, after training, but hypervolemia did not alter resting or exercise \( \dot{V}O_{2\text{peak}} \), volume of carbon dioxide production (\( \dot{V}CO_2 \)), and respiratory exchange ratio. In terms of cardiac function, however, hypervolemia resulted in a substantial rise in cardiac output at all exercise intensities. This was accompanied by a 25% increase in mean SV and a significant reduction in HR at rest and during exercise. The authors concluded that the training-induced hypervolemia led to an increased exercise cardiac output, which in turn was associated with elevated SV and depressed HR. They also suggested that these early physiological adaptations are associated with improved LV filling and increased filling time, leading to a greater cardiac reserve. Yet, the major limitation of this study was that sensitive measures of LV functional and structural indices were not performed. Goodman and colleagues [6] overcame this shortcoming when they assessed the effects of a short-term CMT intervention on the LV functional response during exercise. Eight previously untrained university students (19-20 years) were evaluated before and after 6 days of training at rest and during 60 minutes of exercise at
intensities corresponding to 53%, 68%, and 83% pre-training \( \dot{\text{VO}_2} \text{max} \). Each training session consisted of 2 full hours of cycling at 65% baseline \( \dot{\text{VO}_2} \text{max} \) values. Cardiac function was assessed using cardiac images obtained through portable radionuclide angiography. Following the training regimen, calculated PV expanded by 11.4%, accompanied by a significant increase in \( \dot{\text{VO}_2} \text{max} \), a reduction of 5.6% in maximal HR, an elevated cardiac output at the same exercise intensity, and an increased EF at the highest intensity. Resting LV function was unaltered, although there was a trend for enhanced early filling phase of diastole after training. The investigators concluded that training-induced hypervolemia elicited an enhanced SV and LV filling during exercise, secondary to a Frank-Starling effect, with minor improvements in systolic function. These results were similar to those of Mier et al. [9], who observed the same pattern of changes in LV functional response to exercise following 10 days of cycling.

Most recently, Currie and colleagues [19] examined the effects of 6 consecutive days of CMT on vascular function in young, healthy males. Measures of \( \dot{\text{VO}_2 \text{peak}} \), arterial stiffness, calf vascular conductance, and HR variability were obtained before and after training. Each participant completed 2 hours of cycling at 65% baseline \( \dot{\text{VO}_2 \text{peak}} \) during exercise sessions. Following the intervention, arterial stiffness was significantly reduced, as indicated by lower values of central and peripheral pulse wave velocity. This adaptation occurred independent of measures of vascular conductance and HR variability, which remained unchanged.

Whereas short-term CMT has been demonstrated to affect vascular function and LV hemodynamics during exercise, its effects on cardiac morphology and function have not been thoroughly investigated. Two studies have reported enhanced rapid diastolic filling and increased E:A ratio (due to both elevated peak E and depressed A) at rest in healthy elderly [21] and seniors with LV diastolic dysfunction [154]. Yet, very little data exist on the cardiac adaptations
in response to short-term training in healthy and younger populations. One previous study reported increased LVIDs with minimal changes in systolic function and diastolic filling patterns in young men and women after 10 days of training [9]. Nonetheless, sensitive measures of LV contractility and relaxation have not been studied following this type of training intervention.

2.12 Short-term Adaptations in Response to High-intensity Interval Training

Much of the evidence regarding adaptations to short-term HIT has focused on metabolic adaptations in the skeletal muscle and has been derived from the work of Gibala, and Burgomaster, and co-workers from McMaster University. The type of training used in most of this work involves supramaximal, anaerobic-interval exercise (or SIT), where participants exert “all-out” supramaximal efforts corresponding to >150% \( \dot{V}O_{2\text{peak}} \). In a series of studies, Burgomaster et al. [22, 24] evaluated young, recreationally active individuals before and after 6 sessions of HIT over a 2-week training period. Each session consisted of 4-7 Wingate tests (30 seconds of cycling at 250-300% \( \dot{V}O_{2\text{peak}} \)), followed by 4-minute recovery periods. Following training, cycling performance, measured by time trial or time to exhaustion, increased significantly. Interestingly, there was an increase in fat use and a reduction in carbohydrate consumption after only 16 minutes of exercise post-training [22]. Additionally, there was a 38% increase in maximal citrate synthase (CS) activity and 26% increase in resting muscle glycogen content following HIT [24]. Subsequently, Gibala et al. [25] compared the effects of two weeks of CMT and HIT protocols in 16 moderately active men. The CMT program involved 90-120 minutes of cycling at 65% \( \dot{V}O_{2\text{peak}} \), whereas the HIT protocol consisted of 4-6 repeated efforts of maximal cycling for 30 seconds, interspersed with 4 minutes of recovery (cycling at 30W).
Following the interventions, exercise performance and the maximal activity and content of cytochrome c oxidase (COX) increased similarly in both groups. Interestingly, the total volume of work performed by the HIT group was only ~10% of that by the CMT group. Yet, both training protocols elicited similar adaptations in skeletal muscle oxidative capacity.

It should be mentioned that repeated Wingate tests often lead to severe headaches, dizziness, nausea, and vomiting [26]. As a result, the practicality of this training modality and its applicability to sedentary populations in the long run has been questioned. Most recently, Little et al. [26] implemented a more practical model of low-volume HIT and sought to examine its effects on skeletal muscle metabolism. Seven young, recreationally active men trained for six sessions over a 2-week training period. The HIT protocol involved 8-12 intervals of cycling for repeated 60-second efforts at 100% pre-training peak power output (95-100% \( \dot{V}O_{2\text{peak}} \)), interspersed by 75 seconds of cycling at a workload corresponding to 30 Watts. Participants completed 8 intervals on the first and second training sessions, 10 intervals on the third and fourth sessions, and 12 intervals on the last two sessions. Biopsies of vastus lateralis were obtained prior to and following training. HIT induced marked improvements in exercise performance as measured by cycling time trials. Furthermore, Compared to baseline, maximal activity of CS and COX as well as nuclear abundance of peroxisome proliferator-activated receptor y co-activator 1alpha (PGC-1alpha) were significantly increased after training. Total silent mating-type information regulator 2 homolog 1 (SIRT1), a proposed activator of mitochondrial biogenesis, resting muscle glycogen, and total Glucose transporter type 4 (GLUT4) protein content was also significantly elevated post-training. This study has eloquently demonstrated that a practical low-volume HIT intervention can stimulate rapid adaptations in
exercise performance and skeletal muscle mitochondrial capacity after only 6 sessions of exercise.

It has been suggested that future research should assess the short-term effects of low-volume, time-efficient HIT on other physiological changes typically associated with high-volume CMT [25]. Such adjustments include changes in blood markers of health status, maximal capacity for lipid oxidation, and cardiovascular function. With respect to changes in PV and BV, Green et al. [8] examined 4 young male participants (19-23 years) following 3 consecutive days of supramaximal exercise at 120% \( \dot{V}O_2 \text{max} \) (1-minute intervals followed by 4-minute recovery). PV, as estimated from serum albumin levels, increased by 12% after training. Changes in total BV, determined based on PV and Hct levels, were increased by 5%. Thus, it was clearly shown that only 3 days of intensive regular exercise results in significant changes/expansions in PV and BV. In a follow-up study, Green and coworkers [7] investigated the hypervolemic effects of 4 days of CMT (70% \( \dot{V}O_2 \text{max} \)) on 8 young, healthy males. PV and BV increased by 20% and 12%, respectively, while red blood cell mass remained unchanged. Interestingly, these alterations were not accompanied by any changes in submaximal or maximal aerobic capacity, leading the authors to propose that 4 days of training is not sufficient enough to affect aerobic capacity. However, this discrepancy between the two studies can be explained by the difference in the training intensities. The intensity of exercise in the first study was greater than that used in the second investigation (120% vs. 70% \( \dot{V}O_2 \text{max} \)) and most likely accounted for the observed improvements in maximal exercise performance.

Despite these data, it is currently unknown whether low-volume, short-term HIT would induce rapid changes in myocardial function, a literature gap which has driven the rationale and hypotheses associated with this thesis.
Conclusions

Long-term aerobic endurance training is associated with LV remodeling and improvements in LV filling, particularly during exercise. The majority of evidence surrounding myocardial adaptations in response to endurance training has been derived from traditional CMT models. Emerging data over the last two decades have indicated that the cardiac benefits of exercise training depend on the intensity of exercise. Thus, there has been a growing appreciation for the applicability and efficacy of HIT as an alternative training modality in healthy and clinical populations. Taken together, current data from experimental and human studies suggest that given equal total work, HIT results in more favourable modifications in aerobic capacity and myocardial function compared to CMT. Training-induced hypervolemia represents the most prominent adaptation to short-term training. However, it is not known whether low-volume HIT can stimulate PV expansion, similar to traditional CMT. Finally, changes in central hemodynamics and LV filling have not been meticulously examined following short-term CMT and HIT.
Chapter 3
Manuscript for Journal Submission

This chapter contains a modified version of a manuscript to be submitted for publication.

3.1 Introduction

Long-term endurance training elicits numerous cardiac [1, 36, 38, 40, 155] and peripheral vascular adaptations [1, 3, 156], both of which contribute to increasing the maximal rate of oxygen delivery to the muscles (\( \dot{V}O_{2\text{max}} \)) [1]. Structural and functional adaptations of the heart secondary to exercise training have been well described [1, 2, 31-33]. While evidence of improved inotropic function secondary to training in humans remains equivocal [1, 6], cardiac adaptations to sustained aerobic training include bradycardia [27] and increased stroke volume (SV) at rest and during exercise [1, 2, 32, 33]. Training-induced bradycardia is mediated by increased parasympathetic (vagal) tone to the heart [28-30]. The increase in resting and exercise SV is predominantly attributed to increases in left ventricular (LV) end-diastolic volume (EDV) and diastolic filling, in part attributed to plasma volume (PV) expansion [1, 2, 31-33]. Left ventricular remodeling that increases both chamber size and mass accompany these functional outcomes over the course of training [34, 35], referred to so-called ‘athletic heart’ [4, 36-40].

Although most traditional training programs have involved continuous, moderate-intensity training (CMT) sessions of long durations, recent work demonstrated that high-intensity interval training (HIT) can stimulate similar, if not superior, changes in cardiovascular function in both healthy [14] and clinical populations [15-18]. The stimulus provided by HIT is at a high intensity yet often at a reduced total exercise volume (e.g., duration x intensity); therefore, this form of
training offers an efficacious alternative to CMT. In contrast to prolonged training, there are few data describing cardiovascular adaptations arising from short-term training interventions (e.g., ≤ 2 weeks), reflecting the early phase of the training process. The cardiac changes that occur with short-term training provide information about the early time-course of adaptations, before structural remodeling is likely to occur.

Whereas short-term CMT has significant systemic and BV effects [6, 20, 21], short-term HIT induces rapid adaptations in skeletal muscle metabolism. [22-26]. A limited number of studies have assessed the influence of short-term endurance training on cardiovascular function [6, 8, 9, 19-21]. However, the effects of HIT on cardiac morphology and function have not been investigated during the early stages of training. Therefore, we examined the effects of short-term CMT and HIT on cardiac function at rest and during exercise in young, healthy, previously untrained men. We hypothesized that HIT would be equally effective as CMT at inducing a hypervolemic response and producing similar improvements in peak exercise performance (\(\dot{V}O_{2peak}\)). In addition, we expected short-term CMT and HIT to enhance LV filling at rest and during submaximal exercise.

3.2 Methods

3.2.1 Participants

We recruited 16 young, previously untrained males from the general community with an age range of 19 to 31 years. Individuals who were more than recreationally active, defined as participating in more than two hours of low to moderate (> 6 METs) physical activity per week,
were excluded. Physical activity was considered any unorganized or routine activity that requires the body to expend more energy compared to resting conditions [157]. All participants were normotensive (blood pressure <140/90 mmHg), non-obese (BMI <30 kg·m$^{-2}$), non-diabetic, non-smokers, and had no prior history of cardiovascular, pulmonary, or other metabolic or musculo-skeletal disease. In addition, they were excluded if they possessed any other health conditions that would preclude vigorous exercise, or were taking any medications related to the treatment of cardiovascular conditions. Informed written consent was obtained from all participants and the Physical Activity Readiness Questionnaire (PAR-Q) was completed successfully prior to participation. All study procedures were reviewed and approved by the hospital and the university’s research ethics board, in full conformity with the Helsinki Declaration on the use of human participants.

3.2.2 General Experimental Design

All participants underwent an initial graded exercise test on a cycle ergometer in a to determine baseline $\dot{V}O_2^{\text{peak}}$. These results were later used to establish training intensities for each participant according to their training group. On a separate occasion separated by at least 1 day but not exceeding 2 weeks of baseline testing $\dot{V}O_2^{\text{peak}}$, participants underwent baseline testing of cardiac function. Doppler and 2-dimensional (2D) echocardiography (ECHO) was performed at rest and during submaximal exercise at a HR corresponding to ~105 beats per minute (bpm) on a cycle ergometer in a semi-upright position. Participants were then randomly assigned to either HIT or CMT groups. Following baseline assessments of peak aerobic capacity and LV function, participants were given at least 24 hours to rest, after which they began the supervised training
Each training protocol consisted of 6 sessions over a 12-day period with 1-2 days of rest in between. Peripheral blood samples were obtained at the beginning and at the end of training to determine hematocrit (Hct) and changes in PV. Following the cessation of the training program, participants returned for post-training assessments, which mirrored baseline testing. Post-training tests were performed no earlier than 48 hours and no later than 72 hours of the cessation of the training intervention (Figure 1). Participants were asked to avoid alcohol and caffeine consumption 12 hours prior to their baseline and follow-up assessments.

**Figure 5.** Overview of experimental protocol. $\dot{V}O_2\text{peak}$, peak oxygen consumption; ECHO, two-dimensional and Doppler echocardiography.

### 3.2.3 Peak Oxygen Consumption

$\dot{V}O_2\text{peak}$ was measured using a standard progressive exercise test to exhaustion on a Lode Examiner electrically braked cycle ergometer (Lode B.V. Groningen-Holland Medical
Technology) as previously described [19]. Following a 3-minute warm-up at 25 Watts (W), workrate was increased by 50W every two minutes until 200W, after which workload increased by 25W every minute until exhaustion. Breath-by-breath expired gases were collected using a metabolic cart (Moxus Modular System, Applied Electrochemistry Incorporated, Pittsburgh, PA) and recorded as 20-second averages. HR was recorded each minute using a Polar heart rate monitor (Polar 810i) and recorded electronically (HRTrak II Heart Rate Tracker, Equilibrated Bio Systems Inc., New York, USA). \( \dot{V}O_2 \text{peak} \) was determined based on attainment of a plateau in oxygen consumption despite an increase in workload (intensity) or secondary endpoints including attainment of age-predicted maximal HR, and achievement of a respiratory exchange ratio that is \( \geq 1.15 \). If none of the criteria were reached, the highest \( \dot{V}O_2 \) obtained during the assessment was recorded as \( \dot{V}O_2 \text{peak} \).

### 3.2.4 Blood Sampling

Resting blood samples (~3.3-3.6 mL) were drawn prior to and after training using microhematocrit capillary tubes in triplicate. Hct was determined on site using a microhematocrit scale and reported in %. Raw Hct values were multiplied by 0.8736 (0.96 X 0.91) to correct for trapped plasma (0.96) and to convert venous Hct to whole body Hct (0.91) [158]. The percent change in PV following training was calculated from the corrected Hct readings, as described previously [158].
3.2.5  Left Ventricular Function

Resting and submaximal exercise (corresponding to HR of ~105 bpm) ECHO images were acquired on an imaging table with the participants placed in a semi-upright position (60-degree table elevation), oriented in the left lateral decubitas position. Heart rate was monitored by a 3-lead ECG (Case 16 Exercise Testing System, Marquette Medical Systems, Milwaukee, WI, USA). ECHO was performed on a commercial system (GE Vivid 7 Imaging System, version BT03-5; GE Healthcare, Canada) using an M4S probe. Exercise was performed on an electrically braked echocardiography exercise cycle ergometer (Supine Ergometer, model AE2, American Echo, Kansas City, MO) that was secured to the echo-imaging table (Model 96039, American Echo). Three cardiac cycles were captured and averaged for all analyses, performed subsequently offline using a proprietary workstation (GE Healthcare, EchoPac, Version 7) by a single trained observer, with analyses performed in accordance with the American Society of Echocardiography guidelines [55]. Anatomical M-mode (AM-mode) and Two-dimensional (2D) ECHO images were obtained from the standard parasternal and apical windows. All system settings were adjusted to produce optimal signal-to-noise ratio and endocardial delineation. AM-mode image acquisition and measurements were used to determine the LV internal dimension during diastole (LVIDd) and systole (LVIDs), the interventricular septum during diastole (IVSd), and the LV posterior wall thickness during diastole (LVPWDd). Measures of LV mass and LV mass index were then automatically derived using standard equations. LV end diastolic (EDV) and end systolic (ESV) volumes were measured and used to determine ejection fraction (EF) in apical two chamber and four chamber views, using a modified bi-plane Simpson’s method [159]. Myocardial strain (S) and strain rate (SR) were measured from apical four chamber views using 2D ECHO speckle tracking analysis acquired with a frame rate of 70 frames per second.
Regional systolic and diastolic longitudinal S and SR analysis involved six segments of the LV wall (basal septum, mid septum, apical septum, apical lateral, mid lateral, and basal lateral). Global longitudinal S and SR were derived based on the calculated average of the six LV segments from three cardiac cycles. Peak longitudinal S was defined as the greatest value on the strain curve (S-curve). Measures of LV S are reported as the percentage change (%) in deformation from the initial value, whereas SR is the rate of deformation change per second (s\(^{-1}\)). Early (peak E) diastolic SR (SRe) and late (Peak A) diastolic SR (SRa) were assessed with 2D ECHO speckle tracking and the resulting SRe/SRa was calculated. LV diastolic function was evaluated by Pulsed-wave (PW) Doppler interrogation of mitral inflow velocity spectral, and Tissue Doppler imaging (TDI) in the apical four chamber view. PW Doppler recordings were performed to examine diastolic transmitral blood flow velocities for peak early (E) and peak late (A) filling and the ratio of early to late diastolic filling velocities (E/A). LV diastolic performance was then evaluated using E/A ratios, as well as their absolute values. TDI measures of peak early (E’) and late atrial (A’) myocardial tissue velocities were acquired at the septal and lateral mitral annular sites for the determination of E’/A’ values and were averaged over 3 consecutive cardiac cycles. PW Doppler and TDI data were combined to calculate E/E’ (ratio of early diastolic filling to peak early tissue velocity), a non-invasive estimate of left atrial pressure [55].

3.2.6 Exercise Training

Training interventions were modified based upon previous short-term models in the literature [6, 19, 25, 26]. Each training regimen consisted of 6 sessions completed over 12 days. Thus, a minimum of 24 hours of rest was given to each participant in between training days to
minimize fatigue. The time of the training session each day varied slightly according to subject scheduling but was within a similar 3-4 hour window. Each session included a 3-minute, low-intensity warm-up (10% pre-training \( \dot{VO}_{2\text{peak}} \)). Water was provided to the participants \textit{ad libitum}. HR and fluid intake were recorded throughout to ensure that participants were working at their specified intensity and maintained hydration.

3.2.6.1 Continuous Moderate-intensity Training

The CMT program required the participants to cycle for 90-120 minutes (1.5-2 hours) during six sessions at 65% of their pre-training \( \dot{VO}_{2\text{peak}} \) values. Training consisted of cycling for 90 minutes on the first and second training sessions, 105 minutes on the third and fourth sessions, and 120 minutes on the final two sessions. It was expected that during the earlier phases of the training program, some participants would not have the capacity to cycle continuously for 90-105 minutes at their given training intensity. Therefore, participants were allowed to take intermittent rests as required; however, they had to complete the required number of hours of exercise during each training session. Previous studies have reported that subjects were able to complete 2 hours of exercise without interruption by the end of a six-day exercise training session [6, 19].

3.2.6.2 High-intensity Interval Training

The HIT intervention was modified from Little et al. [26], who reported high tolerance and no complications in young, healthy, recreationally active males in a low-volume and time-
efficient manner [26]. This involved 8-12 intervals of cycling for repeated efforts of 60 seconds at a high intensity corresponding to 95-100% pre-training \( \dot{V}O_2\text{peak} \) (peak power output achieved during baseline testing), interspersed by 75 seconds of cycling at a workload corresponding to 10% pre-training \( \dot{V}O_2\text{peak} \). Participants completed 8 intervals on the first and second training sessions, 10 intervals on the third and fourth sessions, and 12 intervals on the last two sessions. The protocol is unique in that unlike previous studies comparing HIT to CMT where the total volume of work had been similar between the two groups, the total training volume for the HIT group was only \(~24\%\) of the CMT group (1,565 kJ vs. 6,500 kJ). Furthermore, the total training time commitment over 2 weeks was \(~2\) hours (including recovery periods) for the HIT intervention, whereas participants in the CMT group performed a total of \(~10.5\) hours of continuous exercise.

3.2.7 Statistical analysis

Statistical analysis was performed using a mixed model repeated measures of Analysis of Variance (ANOVA) with 2 factors to determine the significance of the main effect: group (CMT/HIT) and time (Pre- and Post-training). Independent t-tests using Bonferroni post hoc analysis were used to assess differences in main effect between groups. Pearson’s simple correlation was used to study the association between changes in PV and changes in \( \dot{V}O_2\text{peak} \), SV, EDV, E, E’, as well the relation between changes in \( SR_e \) and changes in EDV. All comparisons were based on a 95% confidence limit \((P < 0.05)\). All data were analyzed using the statistical software PASW (Predictive Analytics SoftWare) Statistics, version 18.0.
3.3 Results

3.3.1 Subjects

Subject characteristics are presented in Table 1. All participants (25.1 ± 4.1 years of age) successfully completed the study with no adverse events. At baseline, there were no significant differences in age, height, body mass, body mass index (BMI), peak HR, \(\dot{V}O_2\text{peak}\) and peak power output between the two groups. All participants presented with normal \(\dot{V}O_2\text{peak}\), typical of young, previously untrained males. There were no significant changes in height, body mass, BMI, and peak HR following training in either group compared to baseline.
Table 1. Participant characteristics before and after training

<table>
<thead>
<tr>
<th>Variable</th>
<th>HIT</th>
<th>CMT</th>
<th>HIT</th>
<th>CMT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-training</td>
<td>Post-training</td>
<td>Pre-training</td>
<td>Post-training</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>178.6 (6.3)</td>
<td>178.6 (6.3)</td>
<td>182.0 (2.0)</td>
<td>182.0 (2.0)</td>
</tr>
<tr>
<td>Body Mass (kg)</td>
<td>82.6 (13.8)</td>
<td>82.5 (12.8)</td>
<td>85.1 (10.5)</td>
<td>85.2 (10.7)</td>
</tr>
<tr>
<td>BMI (kg·m(^{-2}))</td>
<td>26.0 (5.5)</td>
<td>26.0 (95.3)</td>
<td>25.7 (2.8)</td>
<td>25.7 (2.8)</td>
</tr>
<tr>
<td>Peak HR (bpm)</td>
<td>186 (10)</td>
<td>188 (9)</td>
<td>184 (11)</td>
<td>186 (9)</td>
</tr>
<tr>
<td>( \dot{V}O_2\text{peak} ) (L·min(^{-1}))</td>
<td>3.22 (0.55)</td>
<td>3.60 (0.50)*</td>
<td>3.38 (0.61)</td>
<td>3.55 (0.65)*</td>
</tr>
<tr>
<td>( \dot{V}O_2\text{peak} ) (mL·kg(^{-1})·min(^{-1}))</td>
<td>39.5 (7.1)</td>
<td>43.9 (5.5)*</td>
<td>39.9 (5.9)</td>
<td>41.7 (5.3)*</td>
</tr>
<tr>
<td>Peak Power Output (W)</td>
<td>234 (27)</td>
<td>269 (32)*</td>
<td>241 (35)</td>
<td>269 (37)*</td>
</tr>
</tbody>
</table>

Values are means (SD).

* \( P < 0.05 \) for within-group comparison of pre- vs. post-training

HIT, high-intensity interval training; CMT, continuous moderate-intensity training; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; \( \dot{V}O_2\text{peak} \), peak oxygen consumption.

### 3.3.2 Hematocrit and Changes in Plasma Volume

Following training, Hct was significantly reduced in both HIT (from 45.5 ± 2.4 % to 43.0 ± 3.4 %, \( P < 0.001 \)) (Figure 6) and CMT (from 46.1 ± 2.3 % to 43.8 ± 3.3 %, \( P < 0.001 \)) (Figure 7). The calculated changes in PV were 10.8% and 9.7 % in the HIT and CMT groups, respectively.
Figure 6. Hematocrit among HIT participants before and after training.

* $P < 0.05$ for within-group comparison of pre- vs. post-training.

HIT, high-intensity interval training.
Figure 7. Hematocrit among CMT participants before and after training. 

* $P < 0.05$ for within-group comparison of pre- vs. post-training.

CMT, continuous moderate-intensity training.

3.3.3 Peak Oxygen Consumption

$\dot{V}O_{2\text{max}}$ increased from $3.22 \pm 0.55 \text{ L} \cdot \text{min}^{-1}$ at baseline to $3.6 \pm 0.50 \text{ L} \cdot \text{min}^{-1}$ after training (from $39.5 \pm 7.1$ to $43.9 \pm 5.5 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) in HIT ($P < 0.001$) and from $3.38 \pm 0.61$ to $3.55 \pm 0.65 \text{ L} \cdot \text{min}^{-1}$ (from $39.9 \pm 5.3$ to $41.7 \pm 5.3 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) in CMT ($P = 0.022$) (Table 1; Figures 8 and 9), reflecting improvements of 9% and 5% in HIT and CMT, respectively. No significant differences were observed in the magnitude of increase between the two groups. There was a significant correlation between the percent change ($\% \Delta$) in PV and $\% \Delta \dot{V}O_{2\text{peak}}$ ($r =$
0.71, $P < 0.01$; Figure 10). In addition, peak power output was significantly increased in HIT (from $234 \pm 27$ W to $272 \pm 32$ W, $P < 0.001$) and CMT (from $241 \pm 35$ W to $269 \pm 37$ W, $P = 0.001$) compared to baseline (Table 1).

![Graph](image)

**Figure 8.** Peak aerobic capacity among HIT participants before and after training.

* $P < 0.05$ for within-group comparison of pre- vs. post-training.

$\dot{V}O_2^{\text{peak}}$, peak oxygen consumption; HIT, high-intensity interval training.
**Figure 9.** Peak aerobic capacity among CMT participants before and after training.

* $P < 0.05$ for within-group comparison of pre- vs. post-training.

$\dot{V}O_2\text{peak}$, peak oxygen consumption; CMT, continuous moderate-intensity training.
Figure 10. Relation between percent change in PV and percent change in $\dot{V}O_2_{peak}$.

$r = 0.71, P < 0.01$.

$\%\Delta$, percent change; PV, plasma volume; $\dot{V}O_2_{peak}$, peak oxygen consumption; HIT, high-intensity interval training; CMT, continuous moderate-intensity training.

3.3.4 Left Ventricular Morphology

AM-mode data for LV morphology are shown in Table 2. Ventricular morphology was similar between HIT and CMT groups at baseline and did not significantly change following training.
Table 2. AM-mode data for left ventricular morphology before and after training

<table>
<thead>
<tr>
<th>Variable</th>
<th>HIT</th>
<th></th>
<th>CMT</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-training</td>
<td>Post-training</td>
<td>Pre-training</td>
<td>Post-training</td>
</tr>
<tr>
<td>LVIDd (mm)</td>
<td>4.89 (0.43)</td>
<td>5.00 (0.55)</td>
<td>4.91 (0.37)</td>
<td>4.94 (0.34)</td>
</tr>
<tr>
<td>LVIDs (mm)</td>
<td>3.37 (0.33)</td>
<td>3.35 (0.33)</td>
<td>3.45 (0.45)</td>
<td>3.42 (0.42)</td>
</tr>
<tr>
<td>LVPWd (mm)</td>
<td>1.09 (0.17)</td>
<td>1.06 (0.18)</td>
<td>0.96 (0.11)</td>
<td>0.98 (0.15)</td>
</tr>
<tr>
<td>IVSd (mm)</td>
<td>0.99 (0.15)</td>
<td>1.00 (0.17)</td>
<td>0.99 (0.16)</td>
<td>0.97 (0.23)</td>
</tr>
<tr>
<td>LV Mass (g)</td>
<td>182.4 (49.1)</td>
<td>191.2 (58.2)</td>
<td>186.7 (36.2)</td>
<td>187.7 (29.7)</td>
</tr>
<tr>
<td>LV Mass Index (g·m⁻²)</td>
<td>92.3 (30.3)</td>
<td>96.3 (33.9)</td>
<td>90.6 (17.8)</td>
<td>91.3 (15.9)</td>
</tr>
</tbody>
</table>

Values are means (SD).

HIT, high-intensity interval training; CMT, continuous moderate-intensity training; LVIDd, left ventricular internal dimension during diastole; LVIDs, left ventricular internal dimension during systole; LVPWd, left ventricular posterior wall thickness during diastole; IVSd, interventricular septum dimension during diastole; LV mass, left ventricular mass; LV mass index, LV mass divided by body surface area.
3.3.5 Hemodynamic Responses to Training

Hemodynamic data at rest and during submaximal exercise are shown in Tables 3 and 4, respectively. At rest, baseline measures of systolic blood pressure (SBP), diastolic blood pressure (DBP), HR, SV, cardiac output (CO), EDV, ESV, EF, and systolic blood pressure to end-systolic volume (SBP/ESV) did not significantly differ between the groups, nor were changes observed following either training intervention.

Measures of EDV and SV were significantly elevated during exercise under comparable HRs after training (HIT vs. CMT; EDV: $P < 0.001$ vs. $P = 0.037$; SV: $P < 0.001$ vs. $P = 0.034$), with the magnitude of increase being similar between the two training groups. These changes resulted in significantly higher CO values in both groups after training relative to baseline (HIT vs. CMT; $P < 0.001$ vs. $P = 0.034$). There was a modest, yet significant association between $\%\Delta$PV and $\%\Delta$SV ($r = 0.52$, $P < 0.05$; Figure 11), although there was no significant relation between $\%\Delta$PV and $\%\Delta$EDV ($P > 0.05$, Figure 12). Exercise measures of ESV, EF, and SBP/ESV were unaltered following training in both groups.
Table 3. Resting hemodynamic data before and after training

<table>
<thead>
<tr>
<th>Variable</th>
<th>HIT Pre-training</th>
<th>HIT Post-training</th>
<th>CMT Pre-training</th>
<th>CMT Post-training</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td>66 (13)</td>
<td>64 (13)</td>
<td>63 (6)</td>
<td>62 (5)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>124 (10)</td>
<td>123 (9)</td>
<td>125 (9)</td>
<td>125 (7)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>76 (9)</td>
<td>77 (8)</td>
<td>75 (7)</td>
<td>74 (6)</td>
</tr>
<tr>
<td>CO (L·min⁻¹)</td>
<td>4.7 (0.8)</td>
<td>4.6 (0.9)</td>
<td>4.5 (0.9)</td>
<td>4.5 (0.4)</td>
</tr>
<tr>
<td>SV (mL)</td>
<td>72 (8)</td>
<td>73 (8)</td>
<td>72 (7)</td>
<td>73 (7)</td>
</tr>
<tr>
<td>EDV (mL)</td>
<td>126 (11)</td>
<td>128 (10)</td>
<td>127 (10)</td>
<td>127 (9)</td>
</tr>
<tr>
<td>ESV (mL)</td>
<td>54 (6)</td>
<td>55 (5)</td>
<td>55 (5)</td>
<td>56 (4)</td>
</tr>
<tr>
<td>EF (%)</td>
<td>57 (3)</td>
<td>57 (3)</td>
<td>57 (3)</td>
<td>58 (4)</td>
</tr>
<tr>
<td>SBP/ESV</td>
<td>2.32 (0.63)</td>
<td>2.26 (0.61)</td>
<td>2.30 (0.52)</td>
<td>2.32 (0.50)</td>
</tr>
</tbody>
</table>

Values are means (SD).

HIT, high-intensity interval training; CMT, continuous moderate-intensity training; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; CO, cardiac output; SV, stroke volume; EDV, left ventricular end-diastolic volume; ESV, left ventricular end-systolic volume; EF, ejection fraction; SBP/ESV, systolic blood pressure to end-systolic volume ratio.
Table 4. Submaximal exercise hemodynamic data before and after training

<table>
<thead>
<tr>
<th>Variable</th>
<th>HIT</th>
<th>CMT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-training</td>
<td>Post-training</td>
</tr>
<tr>
<td>Workrate (W)</td>
<td>88 (33)</td>
<td>91 (23)</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>105 (1.7)</td>
<td>106 (2)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>162 (42)</td>
<td>160 (41)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>84 (21)</td>
<td>85 (22)</td>
</tr>
<tr>
<td>CO (L·min⁻¹)</td>
<td>10.1 (1.1)</td>
<td>11.4 (0.9)*</td>
</tr>
<tr>
<td>SV (mL)</td>
<td>96 (11)</td>
<td>108 (9)*</td>
</tr>
<tr>
<td>EDV (mL)</td>
<td>145 (10)</td>
<td>157 (10)*</td>
</tr>
<tr>
<td>ESV (mL)</td>
<td>49 (5)</td>
<td>49 (5)</td>
</tr>
<tr>
<td>EF (%)</td>
<td>66 (4)</td>
<td>69 (3)</td>
</tr>
<tr>
<td>SBP/ESV</td>
<td>3.32 (0.47)</td>
<td>3.30 (0.40)</td>
</tr>
</tbody>
</table>

Values are means (SD).

* P < 0.05 for within-group comparison of pre- vs. post-training.

HIT, high-intensity interval training; CMT, continuous moderate-intensity training; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; EDV, left ventricular end-diastolic volume; ESV, left ventricular end-systolic volume; EF, ejection fraction; SBP/ESV, systolic blood pressure to end-systolic volume ratio.
Figure 11. Relation between percent change in PV and percent change in SV.

$r = 0.52, P < 0.05.$

$\%\Delta$, percent change; PV, plasma volume; SV, stroke volume; HIT, high-intensity interval training; CMT, continuous moderate-intensity training.
Figure 12. Relation between percent change in PV and percent change in EDV.

$r = 0.37; P > 0.05$.

$\% \Delta$, percent change; PV, plasma volume; EDV, end-diastolic volume; HIT, high-intensity interval training; CMT, continuous moderate-intensity training.
3.3.6  Diastolic function at rest and during submaximal exercise

Indices of transmitral Doppler blood flow velocities and myocardial tissue velocities at rest and during submaximal exercise are presented in Tables 5 and 6, respectively. The E/A ratio under resting conditions was significantly increased after training compared to baseline in the HIT group only ($P = 0.02$). There were no differences observed for other resting PW Doppler flow and myocardial tissue velocities before and after training. E/E’ ratio at rest was significantly higher at baseline ($P = 0.013$) and following training ($P = 0.018$) in the HIT group compared to CMT, although this index was unaltered by either training program. However, during submaximal exercise, short-term HIT and CMT resulted in increased velocities for A ($P = 0.001$ and $P = 0.036$, respectively), E’ septal ($P = 0.006$, $P = 0.01$), E'/A’ septal ($P = 0.007$, $P = 0.019$) and E'/A’ lateral ($P = 0.001$, $P = 0.033$), with reduced velocity of A’ lateral ($P = 0.021$, $P = 0.019$). Furthermore, E, E/A ratio, and E’ lateral were augmented ($P = 0.002$, $P = 0.001$, and $P = 0.004$, respectively), with a reduction in septal A’ ($P = 0.025$) in the HIT group only. Training-induced $\%\Delta PV$ was related to changes in E ($r = 0.53$, $P < 0.05$; Figure 13), while $\%\Delta PV$ was also significantly correlated with $\%\Delta E’$ along both septal ($r = 0.89$, $P < 0.01$; Figure 14A) and lateral ($r = 0.72$, $P < 0.01$; Figure 14B) walls.
Table 5. Resting Pulsed-wave Doppler and tissue Doppler indices of diastolic function before and after training

<table>
<thead>
<tr>
<th>Variable</th>
<th>HIT</th>
<th>CMT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-training</td>
<td>Post-training</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>66 (13)</td>
<td>64 (13)</td>
</tr>
<tr>
<td>E (m·s(^{-1}))</td>
<td>0.83 (0.10)</td>
<td>0.85 (0.08)</td>
</tr>
<tr>
<td>A (m·s(^{-1}))</td>
<td>0.50 (0.04)</td>
<td>0.48 (0.05)</td>
</tr>
<tr>
<td>E/A</td>
<td>1.67 (0.27)</td>
<td>1.77 (0.28)*</td>
</tr>
<tr>
<td>E DecelT (ms)</td>
<td>247 (31)</td>
<td>244 (24)</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>66 (10)</td>
<td>64 (9)</td>
</tr>
<tr>
<td>E’ septal (cm·s(^{-1}))</td>
<td>-12.90 (1.88)</td>
<td>-12.45 (1.44)</td>
</tr>
<tr>
<td>A’ septal (cm·s(^{-1}))</td>
<td>-7.05 (1.02)</td>
<td>-6.85 (1.12)</td>
</tr>
<tr>
<td>E’/A’ septal</td>
<td>1.89 (0.52)</td>
<td>1.88 (0.48)</td>
</tr>
<tr>
<td>E’ lateral (cm·s(^{-1}))</td>
<td>-12.64 (1.61)</td>
<td>-12.95 (1.76)</td>
</tr>
<tr>
<td>A’ lateral (cm·s(^{-1}))</td>
<td>-6.91 (1.07)</td>
<td>-6.64 (0.77)</td>
</tr>
<tr>
<td>E’/A’ lateral</td>
<td>1.90 (0.55)</td>
<td>2.00 (0.46)</td>
</tr>
<tr>
<td>E/E’</td>
<td>6.56 (0.37)†</td>
<td>6.75 (0.73)†</td>
</tr>
</tbody>
</table>

Values are means (SD).

* P < 0.05 for within-group comparison of pre- vs. post-training.
† P < 0.05 for between-group comparison of pre- vs. post-training

HIT, high-intensity interval training; CMT, continuous moderate-intensity training; HR, heart rate; E, peak early diastolic blood flow velocity across the mitral valve; A, peak late atrial
diastolic blood flow velocity across the mitral valve; E/A ratio, Doppler blood flow derived ratio describing diastolic function; E DecelT, E-wave deceleration time; IVRT, Isovolumetric relaxation time; E’ septal, peak early myocardial tissue velocity at the septal wall; A’ septal, peak late myocardial tissue velocity at the septal wall; E’/A’ septal, Tissue Doppler derived ratio at the septal wall describing diastolic function; E’ lateral, peak early myocardial tissue velocity at the lateral wall; A’ lateral, peak late myocardial tissue velocity at the lateral wall; E’/A’ lateral, Tissue Doppler derived ratio at the lateral wall describing diastolic function; E/E’, ratio of early diastolic filling to peak early tissue velocity used as a surrogate for left atrial pressure.
Table 6. Submaximal exercise Pulsed-wave Doppler and tissue Doppler indices of diastolic function before and after training

<table>
<thead>
<tr>
<th>Variable</th>
<th>HIT Pre-training</th>
<th>HIT Post-training</th>
<th>CMT Pre-training</th>
<th>CMT Post-training</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td>105 (1.7)</td>
<td>106 (2)</td>
<td>106 (1.8)</td>
<td>106 (1.1)</td>
</tr>
<tr>
<td>E (m·s⁻¹)</td>
<td>1.13 (0.29)</td>
<td>1.20 (0.32)*</td>
<td>1.11 (0.36)</td>
<td>1.14 (0.35)</td>
</tr>
<tr>
<td>A (m·s⁻¹)</td>
<td>0.65 (0.08)</td>
<td>0.59 (0.07)*</td>
<td>0.65 (0.10)</td>
<td>0.61 (0.07)*</td>
</tr>
<tr>
<td>E/A</td>
<td>1.78 (0.57)</td>
<td>2.07 (0.72)*</td>
<td>1.81 (0.83)</td>
<td>1.94 (0.83)</td>
</tr>
<tr>
<td>E DecelT (ms)</td>
<td>185 (29)</td>
<td>183 (27)</td>
<td>181 (29)</td>
<td>181 (25)</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>45 (9)</td>
<td>44 (7)</td>
<td>44 (10)</td>
<td>43 (8)</td>
</tr>
<tr>
<td>E’ septal (cm·s⁻¹)</td>
<td>-16.29 (2.14)</td>
<td>-17.35 (1.64)*</td>
<td>-15.65 (2.86)</td>
<td>-16.63 (2.50)*</td>
</tr>
<tr>
<td>A’ septal (cm·s⁻¹)</td>
<td>-8.10 (0.94)</td>
<td>-7.72 (0.73)*</td>
<td>-7.91 (1.08)</td>
<td>-7.63 (0.99)</td>
</tr>
<tr>
<td>E’/A’ septal</td>
<td>2.06 (0.48)</td>
<td>2.28 (0.42)*</td>
<td>2.05 (0.66)</td>
<td>2.23 (0.57)*</td>
</tr>
<tr>
<td>E’ lateral (cm·s⁻¹)</td>
<td>-16.31 (2.80)</td>
<td>-17.39 (2.26)*</td>
<td>-15.52 (2.67)</td>
<td>-16.00 (2.14)</td>
</tr>
<tr>
<td>A’ lateral (cm·s⁻¹)</td>
<td>-8.07 (0.98)</td>
<td>-7.64 (0.82)*</td>
<td>-8.01 (0.94)</td>
<td>-7.58 (0.59)*</td>
</tr>
<tr>
<td>E’/A’ lateral</td>
<td>2.08 (0.57)</td>
<td>2.32 (0.53)*</td>
<td>1.99 (0.57)</td>
<td>2.13 (0.42)*</td>
</tr>
<tr>
<td>E/E’</td>
<td>6.89 (1.03)</td>
<td>6.84 (1.20)</td>
<td>7.05 (1.29)</td>
<td>6.94 (1.19)</td>
</tr>
</tbody>
</table>

Values are means (SD).

* P < 0.05 for within-group comparison of pre- vs. post-training.

HIT, high-intensity interval training; CMT, continuous moderate-intensity training; HR, heart rate; E, peak early diastolic blood flow velocity across the mitral valve; A, peak late atrial diastolic blood flow velocity across the mitral valve; E/A ratio, Doppler blood flow derived ratio.
describing diastolic function; E DecelT, E-wave deceleration time; IVRT, Isovolumetric relaxation time; E’ septal, peak early myocardial tissue velocity at the septal wall; A’ septal, peak late myocardial tissue velocity at the septal wall; E’/A’ septal, Tissue Doppler derived ratio at the septal wall describing diastolic function; E’ lateral, peak early myocardial tissue velocity at the lateral wall; A’ lateral, peak late myocardial tissue velocity at the lateral wall; E’/A’ lateral, Tissue Doppler derived ratio at the lateral wall describing diastolic function; E/E’, ratio of early diastolic filling to peak early tissue velocity used as a surrogate for left atrial pressure.

Figure 13. Relation between percent change in PV and percent change in E.

$r = 0.53, P < 0.05$

%Δ, percent change; PV, plasma volume; E, peak early filling flow velocity; HIT, high-intensity interval training; CMT, continuous moderate-intensity training.
Figure 14. Relation between percent change in PV and percent change in A) E’ at the septal wall (r = 0.89, P < 0.01); B) E’ at the lateral wall (r = 0.72, P < 0.01).

%Δ, percent change; PV, plasma volume; E’ Septal, peak early myocardial tissue velocity at the septal wall; E’ Lateral, peak early myocardial tissue velocity at the lateral wall; PV, plasma volume; HIT, high-intensity interval training; CMT, continuous moderate-intensity training.
3.3.7 Myocardial strain and strain rate at rest and during submaximal exercise

Table 7 depicts speckle tracking imaging indices of myocardial strain and strain rate at rest and during exercise. There were no changes in resting measures of S, SR, SR_e, SR_a, and SR_e/a in either group ($P > 0.05$). SR_e during exercise was significantly elevated in the HIT group only after training ($P = 0.002$). Furthermore, there was a significant association between $\%\Delta SR_e$ and $\%\Delta EDV$ in both groups ($r = 0.54; P < 0.05$; Figure 15). Other exercise measures of S and SR remained unchanged in both groups following training.
Table 7. Systolic strain and strain rate, early and late diastolic strain rate, and early to late diastolic strain rate ratio at rest before and after training

<table>
<thead>
<tr>
<th>Variable</th>
<th>HIT</th>
<th>CMT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-training</td>
<td>Post-training</td>
</tr>
<tr>
<td><strong>REST</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S (%)</td>
<td>-21.4 (3.9)</td>
<td>-20.2 (7.5)</td>
</tr>
<tr>
<td>SR (s⁻¹)</td>
<td>-1.15 (0.27)</td>
<td>-1.18 (0.30)</td>
</tr>
<tr>
<td>SRe (s⁻¹)</td>
<td>2.01 (0.64)</td>
<td>2.10 (0.65)</td>
</tr>
<tr>
<td>SRa (s⁻¹)</td>
<td>0.81 (0.24)</td>
<td>0.83 (0.22)</td>
</tr>
<tr>
<td>SRe/a</td>
<td>2.77 (1.43)</td>
<td>2.73 (1.13)</td>
</tr>
<tr>
<td><strong>EXERCISE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S (%)</td>
<td>-30.2 (5.8)</td>
<td>-30.5 (5.1)</td>
</tr>
<tr>
<td>SR (s⁻¹)</td>
<td>-1.51 (0.39)</td>
<td>-1.53 (0.39)</td>
</tr>
<tr>
<td>SRe (s⁻¹)</td>
<td>3.13 (0.73)</td>
<td>3.47 (0.70)*†</td>
</tr>
<tr>
<td>SRa (s⁻¹)</td>
<td>1.31 (0.40)</td>
<td>1.27 (0.40)</td>
</tr>
<tr>
<td>SRe/a</td>
<td>2.64 (1.13)</td>
<td>2.97 (1.04)</td>
</tr>
</tbody>
</table>

Values are means (SD).

* P < 0.05 for within-group comparison of pre- vs. post-training.

† P < 0.05 for between-group comparison of pre- vs. post-training.

HIT, high-intensity interval training; CMT, continuous moderate-intensity training; S, systolic strain; SR, systolic strain rate; SRe, early diastolic strain rate; SRa, late diastolic strain rate; SRe/a, early to late diastolic strain rate ratio.
Figure 15. Relation between percent change in SR<sub>e</sub> and percent change in EDV.

\[ r = 0.54, \ P < 0.05. \]

%Δ, percent change; SR<sub>e</sub>, early diastolic strain rate; EDV, end-diastolic volume; HIT, high-intensity interval training; CMT, continuous moderate-intensity training.

3.4 Discussion

We have demonstrated that six sessions of HIT and CMT produce a similar extent of PV expansion, improvements in \( \dot{V}O_2 \text{peak} \), and LV diastolic function during submaximal exercise. To our knowledge, this is the first study to compare the influence of short-term HIT and CMT on LV function at rest and during submaximal exercise. Our findings of enhanced \( \dot{V}O_2 \text{peak} \) and PV expansion are congruent with previous studies of short periods of training [6, 9, 20, 21] and
support observations that low-volume HIT induces rapid adaptations in exercise performance with a relatively low time commitment [22-26]. We also report a novel finding of improved diastolic function during exercise after short-term HIT. A key observation was that the similarity in training adaptations occurred despite significant differences in total work performed and total training time. The HIT group performed approximately 1,565 kilojoules (kJ) of work including the recovery periods, whereas the CMT group performed close to 6,500 kJ, almost four times the total work of HIT. Furthermore, participants in the HIT group cycled for a total duration of ~120-174 minutes, considerably less than the CMT group (~630 minutes).

### 3.4.1 Peak Aerobic Capacity

We have shown that short-term HIT and CMT result in comparably marked improvements in peak aerobic capacity, in agreement with others using short-term CMT [9, 19-21, 92, 152]. Our group has previously reported significant augmentations in \( \dot{V}O_2 \) peak following 6 consecutive days of CMT [6]. However, others have failed to demonstrate changes in \( \dot{V}O_2 \) peak following CMT protocols [19, 21]. The discrepancy is likely due to differences in experimental protocols, training interventions, and participant characteristics. All post-training \( \dot{V}O_2 \) peak measures occurred after 2 days and before 3 days of recovery to avoid detraining effects and ensure optimal recovery before post-training assessments. Although an increase in \( \dot{V}O_2 \) peak following interval training has been reported in athletes [136, 137], healthy sedentary individuals [128, 130, 138], and clinical populations [16-18], the training period for the majority of these reports has been longer than the current study. Several recent investigations have observed improvements in cycling time trial performance as a measure of functional exercise capacity following HIT interventions [22, 25, 26]. Using a similar HIT protocol as the one employed in
the present study, Little et al. [26] reported significant enhancements in 50kJ and 750kJ cycling time trial performance, concomitant with increased mean power output, in recreationally active males. To our knowledge, the present study is the first study to demonstrate the effectiveness of a low-volume HIT model to elicit pronounced responses in $\dot{V}O_2$peak within two weeks of training. It is noteworthy that prior reports evaluating adaptations to short-term HIT [22-26] have primarily employed recreationally active individuals as study participants, which may limit improvements.

3.4.2 Plasma Volume Expansion

An expansion of PV following both CMT and HIT is consistent with prior studies using CMT [6-9, 20, 21, 152] and similar to the effects of acute PV expansion in untrained individuals [116, 118, 120, 160, 161]. Hypervolemia, mostly through PV expansion [2, 10], is the most pronounced adaptation to short-term training and has been consistently observed in previous training studies [2, 5, 10]. BV expansion peaks within approximately 10-14 days of training; therefore, it has been suggested that the early enhancement of cardiovascular performance is associated and possibly triggered by hypervolemia [2, 6, 8, 21, 162]. Rapid PV expansion is likely secondary to increased total circulating protein levels (e.g., albumin) that promotes compartmentalization of fluid volume in the vascular space by increasing the pressure across the capillary membranes. This subsequently helps bind additional water, holding it in the vascular space and thereby, increases intravascular volume [2, 5, 163]. Early increases in BV, and thus PV, are directly related to the intensity of the exercise stimulus as well as its duration [2, 162]. In our study, the total number of training sessions was similar between the two groups, yet the average intensity and duration greatly differed. Since the degree of PV expansion was similar
between the groups, both exercise intensity and volume may act independently to trigger this response. Data from a randomized controlled study [162] comparing longer-term (12 weeks) interval and continuous training reported a similar increase in PV and BV, mostly observed within the first week of training, which supports our observation of an early and rapid PV expansion after both CMT and HIT regardless of total work output.

As expected, there was a significant correlation between the changes in PV and changes in $\dot{V}O_{2}\text{peak}$ ($r = 0.71, P < 0.01$), which has been reported previously [2, 5, 121, 161, 162]. Interestingly, changes in EDV were not related to PV expansion, which is contrary to previous data [2]. Nonetheless, changes in PV were also significantly related to changes in SV, although this association was rather modest ($r = 0.52, P < 0.05$). Training-induced hypervolemia is associated with increased central venous pressure at rest and particularly during exercise, augmenting EDV [6, 111]. Thus, a greater venous return may partially account for the elevation in SV during exercise following short-term training.

3.4.3 Systolic Function

Evidence surrounding the effects of short-term endurance training on cardiac contractile function is mixed. Goodman et al. [6] did not report changes in EF following 6 consecutive days of CMT, yet EF is influenced significantly by loading conditions and inferences to contractile function based on EF are limited [45]. Similar data to EF were shown when changes in SBP/ESV ratio, a more sensitive index of contractility, were calculated [6]. Using similar indices, no changes in systolic function were documented after 6 weeks of CMT and HIT [162]. However, exercise LV EF, SBP/ESV, and fractional shortening ratio have been shown to increase
following short-term endurance training [9, 164]. Contrary to these findings, we failed to detect changes in any of these indices, particularly with less load-dependent measures of systolic performance obtained from speckle tracking imaging, such as LV S and SR. These findings support the notion that short-term endurance training generally does not alter LV contractile performance in healthy young individuals [1, 32].

3.4.4 Diastolic Function

A consistent finding for both CMT and HIT groups was increased LV filling (i.e., EDV) during exercise. It appears that enhancements in SV evident with sustained endurance training are secondary to enhanced ventricular preload [32, 97] and recruitment of the Frank-Starling mechanism; these changes were associated with enhanced diastolic filling indices. It has been postulated that this adaptation may be related to the intensity of training and independent of training duration [6, 32]. Due to the significant influence of HR on LV loading conditions (particularly diastolic function), we assessed all subjects at a target heart rate of ~105 bpm so that early and late phases of diastole could be delineated. Of particular interest was the finding that under comparable HRs, SV and CO were augmented in both groups following training, whereas LV EF, ESV, SBP/ESV, S, and SR were unchanged. Interestingly, E/E’, an index of left atrial pressure, was also not affected by training, suggesting that a key adaptation was an increase in SV and CO despite both a similar filling pressure and time in diastasis. This is supported by numerous reports indicating that the primary difference between trained individuals and their sedentary counterparts is the improved ability of the trained to recruit the Frank-Starling mechanism [121, 161, 162, 165], possibly through remodeling that enhances LV compliance. This may be due to improved beta-adregenic stimulation in association with
increased rate of calcium uptake from the myocellular cytosol into the sarcoplasmic reticulum induced by phosphorylation of phospholamban [166]. In addition, alterations in BV have a large impact on LV diastolic filling, as the elevated myocardial performance of endurance-trained individuals may be partly due to the training-induced expansion of BV [121, 123, 161, 162]. The improved LV filling observed in our study was associated with training-induced hypervolemia as changes in indices of diastolic function (i.e., E and E’) were related to changes in PV that induce a hemodilution/expansion effect early in the training program. PV expansion may induce longer-term structural remodeling [6], while acutely enhancing the Frank-Starling mechanism during exercise.

We were surprised to observe that SRₑ increased significantly in the HIT group only. In addition, while there was a significant association between changes in SRₑ and changes in EDV, this observation was largely confined to the HIT group. Although the significance of these particular findings are unclear at this point and require further investigation, they nonetheless provide further support for the effectiveness of HIT as a potent stimulus to mediate rapid improvements in diastolic performance. We also did not observe a training-induced bradycardia in either group after short-term training. This finding is not surprising given that the training period required to stimulate neural changes in HR are typically longer in duration [6], yet indicates the changes in EDV were independent of filling time and unrelated to changes sino-atrial function. Longer-term training appears to induce LV remodeling and changes in vagal-sympathetic drive that induces more substantial changes in cardiac function [1, 21].
3.4.5 Limitations

Our study had certain limitations. We did not include a sedentary control group in the present study, yet a small number of controlled studies reported no training effects in a control group [22, 24, 152, 167]. It is unclear whether our results can be generalized to a broader age-range or in females who may have a differential training response [155, 168]. In addition, we estimated changes in PV and did so without determining hemoglobin content; notwithstanding, the van Beaumont equation has been previously used to report changes in PV in short-term training studies [6, 21]. Finally, the failure to detect significant changes in certain indices of diastolic function may be a function of our sample size.

3.4.6 Conclusion

Short-term HIT and CMT elicit improvements in peak exercise performance and LV diastolic filling during submaximal exercise. These adaptations are dependent on a significant PV expansion that increases LV filling without global changes in systolic performance or cardiac morphology at rest. These enhancements were similar in HIT and CMT groups, despite the fact that the latter intervention entailed almost four times the total work and training, suggesting HIT is an efficacious intervention for inducing rapid adaptations in LV function and aerobic exercise performance.
Chapter 4
Limitations, Future Perspectives, and Conclusions

4.1 Study Limitations

4.1.1 Echocardiography

Indices of echocardiography are associated with inherent limitations that may lead to potential variability in ECHO-derived measures. The use of PW Doppler blood flow indices to assess diastolic function remains somewhat load-dependent, yet the use of S and SR mitigates this limitation to an extent. In addition, having standard uniform protocols and techniques within a single laboratory using the same personnel minimized the variability in ECHO measures. Since a single trained observer analyzed all ECHO data, the possibility of inter-observer variability was abolished. The frame rate for acquisition of speckle tracking imaging for determination of S and SR during submaximal exercise was reduced, which may have limited analysis in some frames. In line with this, we could not evaluate the LV response to exercise at higher HRs during exercise. As a result, cycling was performed at a relatively low intensity as HR was slightly elevated (~105 bpm); thus, the analysis of the majority of data was feasible despite the lower sector size of the captured frames. Imaging at higher HRs would also lead to the fusion of the mitral E and A curves in Doppler mode, making the analysis less feasible.

Our study assessed the regional response of normal myocardium to physical exercise in the longitudinal direction only, and we did not assess the radial and circumferential myocardial function. Further study of LV rotational mechanics with enhanced speckle tracking echocardiographic techniques (i.e., LV torsion and untwist) is currently ongoing in our
laboratory and has the potential to better elucidate myocardial systolic and diastolic adaptations to physiological perturbations such as exercise training. Ultimately, this will help provide a framework for better understanding of the role of exercise in human performance and cardiac function.

4.1.2 Participants

Although we could not control for participants’ engagement in physical activity between training sessions and assessments, we asked each participant to maintain their daily activity levels and refrain from structured exercise outside the laboratory environment. Further, we could not monitor participants’ diet and nutrition outside the laboratory, which may have influenced the measures; nonetheless, we controlled for alcohol and caffeine consumption 12 hours prior to each assessment and training session. This period of abstention was likely sufficient to eradicate the potential effects of the two substances on the outcome variables.

An objective of this study was to examine cardiac adaptations in response to short-term HIT and CMT in young, healthy men. Thus, efforts were made to recruit a homogenous sample based on age, sex, and activity level. A limitation of this homogeneity is that the results are specific to this group and caution should be taken in interpretation of results for different populations. Our sample did not include females, which precluded the investigation of potential sex differences. Previous research has shown that adaptations to endurance exercise training, particularly the SV response to exercise, may differ between males and females, although the mechanisms responsible for this difference have yet to be fully elucidated [155, 168]. The sample populations of previous short-term training studies have predominantly comprised of
males and excluded females. Thus, there remains a wide gap in the literature with respect to short-term training outcomes in women and examining the cardiac response to short periods of training in females is necessary and should be addressed in future studies.

4.1.3 Plasma Volume

We estimated changes in PV indirectly based on percentage shifts in Hct alone and without measuring hemoglobin, which reduces the reliability of data. Several methods are available for determining PV, most of which involve the principles of dilution analysis. According to the International Committee for Standardization in Hematology, the recommended technique for measuring PV is human serum albumin labeled with radioactive iodine (\(^{125}\)I-HSA) [169]. Where the use of radio-labeled compounds is not possible, the Evans blue dye method is appropriate for operation in research and clinical environments [170]. Notwithstanding, our findings are in congruent with previous studies examining changes in PV in response to short-term aerobic training.

4.2 Future Perspectives and Clinical Implication

As stated in Chapter 2 (section 2.7), data from several investigations indicate that the benefits associated with prolonged training are intensity-dependent [17, 18, 126, 128]. Given the findings from this study and the significance of \(\dot{VO}_2\text{peak}\) as a key prognostic factor for cardiovascular disease [62], its close association with exercise intensity further points to the importance of intensity in promoting health and reducing cardiovascular risk factors. Lack of time has often been cited as a primary barrier to regular exercise participation [26, 171]. Thus,
low-volume HIT may be a practical and time-efficient intervention for inducing rapid adaptations in LV function and aerobic exercise performance, both of which are associated with improved health benefits and longevity. Nevertheless, prescription of HIT to the general population is currently limited, as it requires monitoring of training sessions (e.g., HR, adjustment of workload) in addition to initial exercise testing. Future work should be aimed towards identification of relatively easier ways to introduce HIT to the physically inactive population.

While low-volume HIT may be a useful strategy to induce physiological adaptations that are comparable to traditional CMT, the minimum volume of training required for stimulating beneficial adaptations (i.e., how little exercise and at what intensity) remains unknown. Furthermore, the effectiveness of HIT and the nature and magnitude of adaptations that can be sustained over the long-term are currently unclear and should be subject to future investigation.

The particular sequence and time-course of adaptations that occur in response to endurance training are of considerable scientific interest. With respect to the cardiovascular system, the initial response appears to involve hypervolemia and an increased capacity for central circulation. Yet, Hct is normalized with sustained training [1] and an excess loss of PV results in regression of BV towards pre-training levels [2, 21]. Regardless, augmented SV and enhanced LV filling coupled with bradycardia are consistently observed following prolonged training. Therefore, it appears that there is a shift from the mechanisms controlling BV regulation early during the training stage to other factors governing cardiac function later on. What constitutes these factors has yet to be fully elucidated, but alterations to the myocardial tissue underlying LV remodeling and changes in vagal-sympathetic drive have been speculated [1, 21].
The cellular and molecular mechanisms responsible for enhanced relaxation following exercise training are primarily attributed to improved beta-adrenergic stimulation and increased reuptake of Ca\(^{2+}\) due to activation of the Ca\(^{2+}\) calmodulin-dependent protein kinase II and phosphorylation of the threonine-17 residue of phospholamban [125, 166]. Yet, the specific mechanisms underlying improved LV filling secondary to endurance training have not been elucidated. In addition, it remains to be determined whether these mechanisms differ between different training stimuli (i.e., HIT and CMT). These areas warrant future research.

Although the comparative effects of short-term endurance training and acute PV expansion on cardiac response to prolonged exercise has been addressed in a previous report [119], future studies should investigate the association between PV expansion and enhanced cardiovascular regulation using both HIT- and CMT-induced hypervolemia as well as acute PV expansion alone. In doing so, recommended and standardized techniques for measuring PV and BV (e.g., Evans blue dye) and cardiac function (e.g., ECHO) should be employed.

Aerobic exercise training has been established as an effective intervention in the rehabilitation of patients with cardiovascular disease including patients with congestive HF [172-175], patients who have undergone coronary bypass surgery [176], and patients who received a heart transplant [177, 178]. The majority of training studies in these populations has involved CMT and has shown to result in beneficial adaptations. However, due to emerging data on the efficacy of HIT, several experimental models and clinical investigations have focused on the effects of this modality of training and reported favourable outcomes (Chapter 2, section 2.9.3). Although findings have been encouraging to date, there is a need for larger multicenter studies employing HIT and examining the safety and efficacy of this type of aerobic training in the population of patients with established cardiovascular disease. Further, HF patients typically
undergo chronic volume overload in order to maintain circulatory perfusion pressures, a hallmark feature of this condition [179]. The available data indicate that PV is expanded in the untreated edematous HF patients [180]. However, patients with stable HF (treated with conventional therapy) appear to have a contracted PV [181], a concept that is in contrast to the widely held belief that CHF is associated with long-term hypervolemia [170] It has been suggested that the contracted PV and BV may contribute to exercise intolerance and chronic fatigue, secondary to reduced cardiac output and peripheral blood flow [181]. Future research should focus on how changes in PV relate to HF symptoms or how modification of therapy affects PV in patients. In addition, it is important to examine the role of exercise training on the PV and BV response of these patients over time, a research area that is currently under-investigated.

4.3 Study Conclusions

This study sought to compare the effects of short-term HIT and CMT on cardiac function and exercise performance in young, healthy men. To our knowledge, this is the first study to demonstrate the effectiveness of a low-volume HIT model to elicit pronounced responses in $\dot{V}O_{2\text{peak}}$ within two weeks of training. The benefits obtained were similar to a continuous protocol at a lower intensity, yet significantly higher total work and training volume. We have also provided evidence for similar magnitude of PV expansion following these modalities of training. In line with previous data, there was a strong association between changes in $\dot{V}O_{2\text{peak}}$ and changes in PV.
To our knowledge, there have been no reports on the impact of short-term HIT on ventricular performance to date. We did not observe changes in the traditionally studied indices of systolic function (i.e., EF and SBP/ESV) following the two forms of training. Additionally, we have provided corroborating evidence to confirm existing data on the effects of short-term endurance training on LV systolic performance using the less load-dependent speckle tracking echocardiographic measures (i.e., S and SR). These findings support previous reports and suggest that short-term aerobic training does not alter systolic measures of LV function.

In the present study, EDV, SV, and CO during submaximal exercise were significantly improved in both training groups under similar HRs, which supports the notion that short-term training results in volume-mediated alterations in LV function. Changes in SV were correlated with changes in PV, while there was no relation between changes in PV and changes in EDV. Since contractile function was unaltered, the mechanism allowing for augmentation of SV and CO was likely an enhanced ability to utilize the Frank-Starling mechanism. The results of the present study also showed that short-term CMT and HIT stimulate similar improvements in LV filling during exercise, without altering function at rest. Several ECHO-derived indices for evaluation of diastolic function (i.e., Doppler flow, TDI, and STI) were significantly improved during exercise following both training interventions. Changes in PV were significantly related to changes in E, E’ septal, and E’ lateral. Thus, it is likely that improved cardiac performance during the initial phase of training is associated with early and rapid PV expansion.

Taken together, the current study supports the utility of short-term interval-based training as a potent stimulus for enhancing functional exercise performance and LV diastolic filling, similar to traditional continuous training with much higher training volume.
References


159. Lang, R.M., et al., *Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology*. J Am Soc Echocardiogr, 2005. 18(12): p. 1440-63.


Appendices

Appendix 1. Informed Consent Form

Consent Form for Participation in a Research Study

TITLE: Effects of short-term endurance training on cardiac function in young, healthy males: continuous moderate vs. high-intensity interval training

PRINCIPAL INVESTIGATOR: Dr. J. Goodman, PhD, University of Toronto
Faculty of Physical Education and Health, 416-978-6095

CO-INVESTIGATORS: Dr. Z. Sasson, MD, FRCPC, Mount Sinai Hospital
Mr. Sam Esfandiari, BPHE, University of Toronto
Department of Exercise Sciences
Faculty of Physical Education and Health, 416-554-3614

I. INTRODUCTION

You are being asked to take part in a research study. Before agreeing to participate in this study, it is important that you read and understand the following explanation of the proposed study procedures. It describes the purpose, procedures, benefits, discomforts, risks and precautions associated with this study. It also describes your right to refuse to participate or withdraw from the study at any time, the time commitment and the risks and benefits, so that you can make an informed decision. This is known as the informed consent process. Please ask the study investigators to explain anything you do not understand before signing this consent form.

II. PURPOSE

The purpose of this study is to examine the effects of six sessions (2 weeks) of two different types of endurance exercise training programs on cardiac (heart) function in young, healthy males.
III. PROCEDURES

Eight laboratory visits and two visits to Mount Sinai Hospital will be required. On the first visit, you will come to the Cardiovascular Regulation Laboratory for a fitness assessment, and on the second visit, you will come to Mount Sinai Hospital where you will undergo assessments of heart function. Following baseline testing, you will begin your endurance exercise training program. You will perform this program for six sessions (Visits 3-8) over 2 weeks (e.g., Monday, Wednesday, Friday). Following the cessation of the training program, you will return to the Cardiovascular Regulation Laboratory (Visit 9) and Mount Sinai Hospital (Visit 10) within 2-3 days for follow-up tests of fitness and heart function that will be identical to baseline assessments. Please refer to the attached “Detailed Information Study” sheet for a detailed explanation of the tests.

Fitness Assessment

Your fitness will be measured using a maximal exercise test. You will be asked to cycle while the resistance on the bike is gradually increased until you reach exhaustion and can no longer continue.

Heart Function

Your heat function will be assessed by an echocardiogram, which takes images of your heart non-invasively while you rest on a bed in a slightly elevated position. Resting and exercise measures will be obtained.

Changes in Blood Volume

Two small blood samples will be taken before and after training on the first training session (visit 3) and before and after training on the last day (visit 8) using the finger-prick technique.

Short-term Endurance Exercise Training (visits 3-8)

Following baseline assessments of your fitness and heart function, you will return to the Cardiovascular Regulation Laboratory to begin your training program. You will be randomly allocated to either the moderate, continuous training (CMT) group or the high-intensity interval training (HIT) group. Please refer to the attached “Detailed Information Study” sheet for a detailed description of each training program.

IV. ELIGIBILITY

We are looking for young (18-35 years of age) healthy males. Given that the experimental condition of the study is an exercise training program, the study will recruit individuals who do not regularly participate in physical activity or competitive sports. Therefore, if you are more
than recreationally active, defined as participating in more than two hours of physical activity per week, you cannot be recruited as a participant. Physical activity is considered any movement or activity that requires the body to expend more energy compared to resting conditions. You must have normal blood pressure (blood pressure <140/90 mmHg), must have a body mass index of <30kg/m2), must be non-diabetic, non-smoker, and have no prior history of cardiovascular, pulmonary, or other metabolic or musculo-skeletal disease. In addition, you will be excluded if you are not within the specified age range, or possess any other health conditions that would preclude vigorous exercise, or on any medications related to the treatment of cardiovascular conditions.

V. RISKS

The risks associated with these procedures are small. There are no known risks associated with heart rate monitoring. You may experience cramping or fatigue in your legs from the exercise testing and/or training but these feelings should subside within a few days. Exercise alone briefly increases your risk of a cardiovascular complication including a fatal heart attack; these risks are extremely low, about 1 in 500,000 or less for participating in any endurance exercise training program. The risk of a non-fatal event is much less. The risks associated with blood sampling via the finger prick method may include minor skin irritation, bruising and/or infection at the site. However, these risks will be minimized by having a trained and experienced student investigator conducting the sampling and applying appropriate sanitary and sterile techniques.

In the unlikely event that we note an atypical finding on your electrocardiogram (ECG) or heart images, we will contact you to help arrange medical follow-up to interpret the significance of findings, if any. We may also ask a cardiologist or other health care professional to examine your test results. By signing this consent form, you agree to the release of the result for review. It is possible that you could become unnecessarily worried if a problem were suspected, but not actually found.

In Case You are Harmed in the Study:

If you become ill, injured, or harmed as a result of participating in this study, you will receive care. The reasonable costs of such care will be covered for any injury, illness, or harm that is directly a result of taking part in the study. In no way does signing this consent form waive your legal rights nor does it relieve the investigators, sponsors, or involved institutions from their legal and professional responsibilities. You do not give up any of your legal rights by signing this consent form.

VI. BENEFITS

The only direct benefit of participation is an increased knowledge of your fitness and health status. However, your participation may help increase our understanding of the effects of short-term training on cardiovascular function in healthy individuals, with potential implications in individuals with heart disease.
VII. COMPENSATION

If you desire, we will provide you with interpretation on your exercise testing results as well as arranging further counseling regarding your fitness. We will also reimburse you with public transportation costs to the laboratory and the hospital. In addition, we will provide you with a 1-month membership to the athletic centre, which gives you access to all its facilities.

VIII. CONFIDENTIALITY

Any personal information revealed and experimental data collected will be treated as confidential and will not be revealed to anyone other than the investigators. You will be identified only by a study number with no identifying information in any publication or presentations. All data from this study will be secured in a locked filing cabinet in the Cardiovascular Regulation Laboratory and will be destroyed after 7 years.

IX. VOLUNTARY PARTICIPATION AND WITHDRAWAL

Your participation in this study is voluntary. You have the right to refuse to participate in any component of the study and may also withdraw your consent to participate without prejudice or consequence to any other interactions that you may have with the study investigators. You may refuse to answer any question you do not want to answer, or not an answer an interview question by saying “pass”. We will provide you with any new information learned during the study that might affect your decision to continue participation in the study.

X. INQUIRIES

If you have any questions about the study please feel free to contact any of the investigators listed above. If you have any questions about your rights as a research participant, please contact Dr. R. Heslegrave, Chair of Mount Sinai Hospital Research Ethics Board (REB) or the Research Ethics office number at (416) 586-4875. The REB consists of a group of people who oversee the ethical conduct of research studies. These individuals are not part of the research study. Everything that you discuss will be kept strictly confidential.

XI. CONSENT

I have read the information letter and the detailed study information sheet that has been provided to me and I fully understand the risks associated with the testing and exercise procedures. I have been able to discuss this study and my questions have been answered to my satisfaction. I consent to take part in the study with the understanding that I may withdraw at any time without affecting me in anyway. I have received a signed copy of this consent form.
I voluntarily consent to participate in this study.

__________________________  ________________________  ____________
Subject Name (Please Print)  Subject Signature          Date

I confirm that I have explained the nature and purpose of the study to the subject named above. I have answered all questions.

__________________________  ________________________  ____________
Name of Person              Signature                  Date
Obtaining Consent
DETAILED STUDY INFORMATION

This information sheet will provide you with a detailed explanation of the tests, procedures, as well as the exercise training intervention you will undergo as a participant in our study.

Study Tests and Assessments

Upon arrival to the laboratory, you will be asked to complete the Physical Activity Readiness Questionnaire (PAR-Q), which will help us screen you for participation in our study. On your first two visits, your exercise capacity and heart function will be assessed (each requiring 1 hour). These measures will also be taken at the end of your training program (visits 9 and 10). Please refrain from caffeine and alcohol intake 12 hours before testing. You will then undergo the following assessments:

Height and Weight

Measurements of height and weight will be taken in exercise clothing with shoes removed. These measurements will be repeated once you have completed the training program (visit 9).

Exercise Capacity

During your first visit, your exercise capacity will be measured using a maximal exercise test. You will be asked to cycle on a cycle ergometer while the pedal resistance is gradually increased until you reach exhaustion (about 8-10 minutes). You will also breathe into a tube while your nose is plugged, and your expired air will be measured. In addition, your heart rate will be measured by wearing a transmitter and watch.

Heart Function

Measures of heart function will be made by echocardiography, a non-invasive technique which obtains high-resolution images of the heart. The heart function is measured in addition to its size. You will be resting on a bed in a slightly elevated position. Gel is placed on your chest and a probe is placed on your skin and pictures are taken of your heart. Following this, you will exercise by cycling on the bed at an intensity eliciting a heart rate of 110-115 beats per minute.
for 5 minutes, and pictures of your heart will be taken again. This will complete the heart function assessment.

**Changes in Blood Volume**

In order to examine changes in blood volume, two small blood samples (using the finger-prick method) will be taken before and after training on the first training session (visit 3) and before and after training on the last day (visit 8). This technique involves lancing (“pricking”) one of your finger tips using a lancet device. A small capillary tube will then be used to draw a small amount of blood from your fingertip.

**Short-term Exercise Training Intervention (Visits 3-8)**

Each training program consists of 6 sessions and will be completed over 12 days (e.g., Monday, Wednesday, Friday). Thus, you will have a minimum of 24 hours of rest in between training days to minimize fatigue. The time of the training session each day will depend upon your availability; therefore, training sessions may not necessarily occur at the same time each training day. You will perform a 3-minute warm-up at a very low intensity (10% of your baseline maximal exercise capacity) each session prior to training. Throughout the training session, water will be provided to you at your convenience. Also, your heart rate and water intake will be recorded throughout to ensure you are working at your specified intensity and that you are staying hydrated. All training sessions will be directly supervised by the student investigator.

**Continuous Moderate Training**

If you are randomly allocated to the CMT group, you will be asked to cycle for 90-120 minutes (1.5-2 hours) a day for six sessions at a resistance that is equivalent to 65% of your baseline maximal exercise capacity (to be determined by investigators). Training will consist of cycling for 90 minutes on the first and second training sessions, 105 minutes on the third and fourth sessions, and 120 minutes on the final two sessions. It is anticipated that during the earlier phases of the training program (visits 3-5), you may not have the capacity to cycle continuously for 90-105 minutes at your given training intensity. Therefore, you will be allowed to take intermittent rests as required; however, you have to complete the required number of hours of exercise during each training session. Previous studies have reported that subjects were able to complete 2 hours of exercise without interruption by the end of a six-day exercise training program.

**High-intensity Interval Training**

If you are randomly allocated to the HIT group, you will be asked to cycle for repeated efforts of 60 seconds at a high intensity that is equivalent to 95-100% of your baseline maximal exercise capacity (to be determined by investigators), interspersed by 75 seconds of cycling at a workload corresponding to 10% of your maximal exercise capacity. The 60-second high-intensity effort followed by the 75-second recovery period forms a high-intensity exercise bout or 1 “interval”. You will complete 8 intervals on the first and second training sessions, 10 intervals on the third and fourth sessions, and 12 intervals on the last two sessions. In a recent study, it was reported that this training program was well tolerated by young, healthy males and they all completed the training phase without any complications.
Appendix 2. Recruitment Poster

GET FIT FAST
Participants needed for a Research Study

STUDY PURPOSE:
Our study is attempting to evaluate how the heart responds to two different short-term training programs (six sessions) over 2 weeks.

WHO IS ELIGIBLE?
• Healthy men aged 18-35
• Not undergoing exercise training
• Free from any history of cardiovascular disease, pulmonary or metabolic diseases, or any musculo-skeletal condition that will limit you during intense exercise

WHAT THE STUDY REQUIRES:
• Six sessions of supervised training program
• Significant time commitment (on-site training and laboratory assessments)
• Assessment of changes in blood volume by finger-prick blood sampling before and after the training program (3 samples in total)
• Maximal exercise testing (VO2max)
• Echocardiography measurements (non-invasive pictures of your heart)
• Training program consists of cycling for 1-2 hours at 65-100% of your maximum effort

THE BENEFITS TO PARTICIPATING:
• Measures of cardiac function will be taken before and after the training program.
• You will be given the opportunity to increase physical activity levels during supervised training sessions and will gain knowledge about your fitness levels and the condition of your cardiovascular systems.
• You will also make a large contribution to exercise science.

PLEASE CONTACT:
sam.esfandiaris@utoronto.ca
Cardiovascular Regulation Laboratory
416-978-0762

MOUNT SINAI HOSPITAL
 eject and Wolf Living Health Complex

UNIVERSITY OF TORONTO
Appendix 3. Physical Activity Readiness Questionnaire (PAR-Q)

**PAR-Q & YOU**

*(A Questionnaire for People Aged 15 to 69)*

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. However, some people should check with their doctor before they start becoming much more physically active.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below. If you are between the ages of 15 and 69, the PAR-Q will tell you if you should check with your doctor before you start. If you are over 69 years of age, and you are not used to being very active, check with your doctor.

Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly: check YES or NO.

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
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1. Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?
2. Do you feel pain in your chest when you do physical activity?
3. In the past month, have you had chest pain when you were not doing physical activity?
4. Do you lose your balance because of dizziness or do you ever lose consciousness?
5. Do you have a bone or joint problem (for example, back, knee or hip) that could be made worse by a change in your physical activity?
6. Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?
7. Do you know of any other reason why you should not do physical activity?

---

**YES to one or more questions**

Talk with your doctor by phone or in person BEFORE you start becoming much more physically active or BEFORE you have a fitness appraisal. Tell your doctor about the PAR-Q and which questions you answered YES.

- You may be able to do any activity you want — as long as you start slowly and build up gradually. Or, you may need to restrict your activities to those which are safe for you. Talk with your doctor about the kinds of activities you wish to participate in and follow his/her advice.
- Find out which community programs are safe and helpful for you.

**NO to all questions**

If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can:
- start becoming much more physically active — begin slowly and build up gradually. This is the safest and easiest way to go.
- take part in a fitness appraisal — this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively. It is also highly recommended that you have your blood pressure evaluated. If your reading is over 144/94, talk with your doctor before you start becoming much more physically active.

---

**DELAY BECOMING MUCH MORE ACTIVE:**

- If you are not feeling well because of a temporary illness such as a cold or a fever — wait until you feel better;
- If you are or may be pregnant — talk to your doctor before you start becoming more active.

**PLEASE NOTE:** If your health changes so that you then answer YES to any of the above questions, tell your fitness or health professional. Ask whether you should change your physical activity plan.

---

**Informed Use of the PAR-Q** The Canadian Society for Exercise Physiology, Health Canada, and their agents assume no liability for persons who undertake physical activity and if in doubt after completing this questionnaire, consult your doctor prior to physical activity.

**No changes permitted. You are encouraged to photocopy the PAR-Q but only if you use the entire form.**

---

**NOTE:** If the PAR-Q is being given to a person before he or she participates in a physical activity program or a fitness appraisal, this section may be used for legal or administrative purposes.

"I have read, understood and completed this questionnaire. Any questions I had were answered to my full satisfaction."

---

**NAME**

**SIGNATURE OF PARENT** or GUARDIAN (for participants under the age of majority)

**DATE**

**WITNESS**

---

**Note:** This physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if your condition changes so that you would answer YES to any of the seven questions.
...continued from other side

PAR-Q & YOU

Physical activity improves health.

Every little bit counts, but more is even better—everyone can do it! Get active your way—build physical activity into your daily life...

- at home
- at school
- at work
- at play
- on the way
- that’s active living!

Increase Endurance Activities
Increase Flexibility Activities
Increase Strength Activities
Reduce Fatigue by Sleep

You Can Be It—Getting started is easier than you think

Physical activity doesn’t have to be very hard. Build physical activities into your daily routine:

- Walk whenever you can—get off the bus early, use the stairs instead of the elevator.
- Reduce inactivity for long periods, like watching TV. Get up from the couch and walk around the house.
- Play activities safely.
- Choose to walk, walk or cycle for short trips.

Start with a 10-minute walk—gradually increase the time. Find an activity that you enjoy. Be active every day, if you can. If you want to try it. Try one day a week—start small. Try to make it a long-term commitment.

The activities you are doing now, more often.

Health risks of immobility:
- functional decline
- disability
- increased mortality
- obesity
- high blood pressure
- high cholesterol
- diabetes
- depression
- osteoporosis
- increased risk of cardiac and vascular disease
- increased risk of hip fracture
- increased risk of breast cancer

Benefits of regular activity:
- better health
- increased fitness
- better posture and balance
- better coordination
- reduced muscle aches and injuries
- higher immune system
- relaxation and mental wellness
- reduced dependence on medication
- better functioning of the heart

Range needed to stay healthy

Get Active Your Way, Every Day—For Life!

Gorilla’s say accumulate 30 minutes of physical activity every day to stay healthy or improve your health. As you progress, you may decide to fit more physical activity into your daily routine. Use the chart on the next page to build up your physical activity in periods of at least 10 minutes each. Start slowly... and build up.

Time needed depends on effect

- Very Light Effort
- Light Effort
- Moderate Effort
- Vigorous Effort

- Walking
- Stair climbing
- Swimming
- Skating
- Running
- Cross-country skiing
- Jogging
- Biking
- Rock climbing
- Football

Range needed to stay healthy

Health Canada, Ottawa, 1998

Fitness and Health Professionals May Be Interested in the Information Below:

The following companion forms are available for doctors’ use by contacting the Canadian Society for Exercise Physiology (address below):

The Physical Activity Readiness Medical Examination (PARmed-X) is to be used by doctors with patients who answer YES to one or more questions on the PAR-Q.

The Physical Activity Readiness Medical Examination for Pregnancy (PARmed-X for Pregnancy) is to be used by doctors with pregnant patients who wish to become more active.

References:


For more information, please contact:

Canadian Society for Exercise Physiology
202-185 Somerset Street West
Ottawa, ON K2P 0Z
Tel.: 1-877-651-3755 • Fax: (613) 234-1565
Online: www.cscep.ca

The original PAR-Q was developed by the British Columbia Ministry of Health. It has been revised by an Expert Advisory Committee of the Canadian Society for Exercise Physiology chaired by Dr. N. Gaddill (2002).

Disponible en français sous le titre «Questionnaire sur l’aptitude à l’activité physique - Q-AAP» (revised 2002).
Appendix 4. Data Collection Sheets

DATA COLLECTION SHEET 1: VO2MAX TESTING PROTOCOL

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<td>Age:</td>
<td>Barometric Pressure:</td>
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<tr>
<td>Weight (kg):</td>
<td>Temperature:</td>
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<td>Height (cm):</td>
<td>Relative Humidity:</td>
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HIGHLIGHT STAGE WHERE TEST TERMINATED

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<tr>
<th>Time (min)</th>
<th>Resistance (W)</th>
<th>Heart Rate</th>
<th>RPE</th>
<th>Notes</th>
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<tr>
<td>2-min Warm up</td>
<td>25</td>
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DATA COLLECTION SHEET 2: EXERCISE CAPACITY AND ECHOCARDIOGRAPHIC DATA (CARDIOVASCULAR REGULATION LAB/MOUNT SINAI HOSPITAL VISITS)

Participant Code: ________________
Date/Time: ________________
Age: ________________
DOB (MM/DD/YY): ________________
Weight (kg): ________________
Height (cm): ________________

VO2peak Data:

VO2peak (ml/kg/min): ________________
HR@peak: ________________
Predicted HRmax: ________________
Plateau (Y/N): ________________
Max. Resistance: ________________
Max. Power Output: ________________
Filename: ________________

Echocardiographic Data:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Heart Rate (bpm)</th>
<th>Blood Pressure (mmHg)</th>
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<tbody>
<tr>
<td>Rest</td>
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<tr>
<td>Submaximal Exercise</td>
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Average Heart Rate:
Blood Pressure:
DATA COLLECTION SHEET 3: SHORT-TERM ENDURANCE TRAINING

Participant Code:                        Date:

Training Protocol:                      Session:

Room Temperature (°C):

Weight (kg) Pre-exercise: Post-exercise:

Hematocrit (%) Pre-exercise: Post-exercise:

<table>
<thead>
<tr>
<th>Time/Interval</th>
<th>HR (bpm)</th>
<th>Fluid Intake (ml)</th>
<th>Borg Scale</th>
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Total Training Time:

Training Notes: ___________________________________________________
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