CARDIAC FUNCTION RESPONSES TO EXERCISE TRAINING IN CORONARY ARTERY DISEASE

CARDIAC FUNCTION RESPONSES TO STAIR CLIMBING BASED HIGH INTENSITY INTERVAL TRAINING IN INDIVIDUALS WITH CORONARY ARTERY DISEASE

By SYDNEY ELLA VALENTINO, Hon.B.Sc.Kin

A Thesis Submitted to the School of Graduate Studies in Partial Fulfillment of the Requirements for the Degree Master of Science in Kinesiology

McMaster University MASTER OF SCIENCE (2019)

Hamilton, Ontario (Kinesiology)

TITLE: Cardiac responses to stair climbing based high intensity interval training in individuals with coronary artery disease

AUTHOR: Sydney Ella Valentino, Hon.B.Sc.Kin (McMaster University)

SUPERVISOR: Professor Maureen J. MacDonald

NUMBER OF PAGES: x, 89

LAY ABSTRACT

Cardiac rehabilitation exercise is an important part of recovery after a heart attack, and it has been shown to improve heart function measured using standard ultrasound assessments. Studies have suggested that novel measures of heart function may be more sensitive in comparison to these standard ultrasound measures, yet these novel measures have not been examined in individuals completing stair-climbing based high intensity cardiac rehabilitation exercise training. This work examined the changes in both novel and standard ultrasound measures of heart function after either stair climbing-based high intensity interval training or traditional moderate intensity exercise training in individuals who have heart disease. While this study found that both stair climbing based high intensity interval training and traditional cardiac rehabilitation both resulted in increases in cardiorespiratory fitness after 12 weeks of training, no changes were observed in any of the standard measures of heart function. Supporting the concept that novel measures of heart function might be more sensitive, as some training associated changes were observed in the novel measures of heart function.

ABSTRACT

Cardiac rehabilitation (CR) exercise training, which traditionally involves the prescription of moderate intensity continuous exercise, can slow the progression of heart disease and improve cardiorespiratory fitness (CRF). Cardiac function is typically investigated using calculations of ejection fraction (EF) from echocardiography, yet EF measures do not provide information about the unique twisting motion of the heart. Novel measures of cardiac function, such as LV twist, myocardial performance index (MPI) and global longitudinal strain (GLS), may provide additional information about changes in LV mechanics associated with exercise training for individuals with coronary artery disease (CAD). The aims of this study were to investigate the changes in cardiac function, using both standard and novel measures, at baseline (0 weeks; T1), post-initial training (4 weeks;T2), and post-training (12 weeks; T3) in response to either stair climbing-based high intensity interval training (STAIR) or traditional moderate intensity continuous training (TRAD). We recruited 16 individuals with CAD (61±7years; 1W) and randomized them into TRAD and STAIR groups (n=8/group). Standard (CRF and EF), and novel (LV twist, MPI, GLS), measures of cardiovascular function were assessed at all three timepoints. CRF improved in both groups, after 4 and 12 weeks (STAIR: T1:22.1±4.2, T2:24.7±4.9, T3:25.4±5.2 and TRAD: T1:22.8±2.5, T2:25.2±4.9, T3:26.0±5.0 mL/kg/min; $P<0.005$) of CR exercise. We observed an increase in apical rotation ($P=0.01$) and LV twist ($P=0.03$), but no changes in either traditional (EF $P=0.15$), or novel (MPI $P=0.19$; GLS $P=0.81$) measures of cardiac function over time, in either group. It is possible that the relatively short training period (12 weeks) was not

sufficient to result in significant changes in cardiac function, despite improvements in CRF. Future research should assess both standard and novel indices of cardiac function over longer exercise training periods to determine the ideal indices for tracking changes over time with interventions in this population.

ACKNOWLEDGEMENTS

There has been many mentors, friends, and family that have provided continuous teachings and support and I cannot go without honouring their contribution to this work. First and foremost, thank you to my supervisor, Dr. Maureen MacDonald, for giving me a chance in my 3RP3 practicuum. You gave me a glimpse into the world of scientific investigation, that has given a home to all my passions, with curiosity at the root of it all. You have the qualities of a true leader and I am so fortunate to have found belonging in your lab these past two years and years to come.

To the SCORE study collaborators, Dr. Martin Gibala, Dr. Stuart Phillips, Dr. Eva Lonn, Jonathan Dubberley, Dr. Sara Oikawa, Dr. Chris McGlory, and Dr. Mary Jung, this project wouldn't have been possible without your time and input. Thank you to my committee members, Dr. Jamie Burr and Dr. Martin Gibala, I appreciate all the guidance and patience you have had while working with me through the past two years. I am inspired by each of your research programs and I am thankful for your unique insights to bring my project to fruition.

Thank you to Todd Prior, Glenna Davis, Carol Robinson, and Doris Burns for all your help and countless hours put towards making the Department of Kinesiology run smoothly. To my science mentors and role models, Dr. Eric Stöhr, Dr. Vicky Tolfrey-Goosey, and Dr. Jan van der Scheer. Through talking with you, I have been able to widen my understanding and explore the possibilities of research through a different lens which I am incredibly grateful for.

I cannot go without mentioning the Kin Graduate Body, including my officemates (Sheereen and Laura), current and past lab mates (Jason, Jem, Stacey, Vanessa, Jenny, Kajeetha, and Joey), my biking pals (Joey, Alexis and Madi), and my lifelong friends (Chloe and Meaghan). These friendships have been instrumental to my growth as person leading to this point. In addition, thank you for providing laughs and memories for all the in-between moments.

To Dr. Emily Dunford, who has a place in all of these "categories", I am incredibly lucky to have been part of SCORE with you. Thank you for your openness to mentor, guide and teach the whole way through this project, but most importantly for your friendship. We truly made an awesome team, and I think "unplanned matching outfits" speak for itself.

And lastly, to my amazing family, you have always told me I ask too many questions but continued to great lengths to answer. When it came to research, you have always listened, encouraged and supported me in ways no one else could. Thank you.

TABLE OF CONTENTS

LIST OF APPENDICES

LIST OF TABLES AND FIGURES

TABLES

FIGURES

LIST OF ABBREVIATIONS AND SYMBOLS

A	Isovolumic contraction time and isovolumic relaxation time
B	Ejection time
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CFI	Collateral flow index
CO	Cardiac output
CPET	Cardiopulmonary exercise test
CR	Cardiac rehabilitation
CRF	Cardiorespiratory fitness
CVD	Cardiovascular disease
EDV	End diastolic volume
EF	Ejection fraction
ESV	End systolic volume
GLS	Global longitudinal strain
HIIT	High intensity interval training
LV	Left ventricle
MI	Myocardial infarction
MICT	Moderate intensity continuous training
MPI	Myocardial performance index
PCI	Percutaneous coronary intervention
SV	Stroke volume
TSR	Torsion-to-shortening ratio
VO_2 peak	Peak oxygen uptake

CHAPTER 1
Literature Review

1.1 Introduction

Cardiovascular disease (CVD) is prominent in Canadian society, with one in every twelve Canadians living with heart disease, and CVD often progresses until the consequences are fatal, making it the leading cause of death after age 65 (100). Coronary artery disease (CAD), the most common manifestation of CVD, is characterized by the presence of plaque in the arterial walls of the heart muscle (113). This arterial narrowing typically proceeds undetected until the blood flow is inadequate during times of higher metabolic demand, such as exercise, often causing angina, and in severe cases, progressing to myocardial infarction (MI) (69). With CAD, if myocardial damage occurs, infarcted segments of the heart no longer move properly causing further ventricular wall stress leading to worsened ventricular function (49, 98). Declines in cardiac function after a myocardial event, or with progressive CAD, are traditionally characterized by reduced ejection fraction (EF) and increased left ventricle (LV) volumes (127). Further declines in these indices may be indicative of detrimental changes in cardiac structure, described as LV remodeling. If these adverse functional and structural adaptations worsen, they have the potential to lead to heart failure and death. Once CAD is detected, depending on the severity of stenosis, surgical procedures are considered, including angioplasty, percutaneous coronary intervention (PCI), and coronary artery bypass graft (CABG). In addition to medical intervention, CAD management can be further enhanced through a lifestyle modification program called cardiac rehabilitation (CR). Exercise based CR is a method of secondary prevention for individuals with CAD and reduces the chance of

cardiovascular mortality by 25% (31). As our population ages, it is necessary for clinicians and researchers to develop new approaches to disease identification and treatment, with the goal of improving longevity and quality of life in advanced ages (28).

1.1.2 Risk factors associated with CVD

Early signs of atherosclerosis begin in youth and are influenced by risk factors for clinical coronary heart disease (CHD) (74). A risk factor is a condition or behavior that is thought to be linked to the development of disease, used in the prediction and prevention of disease. Although non-modifiable risk factors (family history, sex, age, race/ethnicity) are challenges individuals cannot control, the effect of modifiable risk factors (physical activity, nutrition, smoking) can be mitigated and alter the progression of disease. In research conducted on left anterior descending coronary arteries, lesions of higher blockage were associated with obesity and hypertension (74). Physical activity is an important mediating factor in the development of disease, as its influence can play a role in the prevention and restoration of cardiovascular health status (52, 83). Most importantly, improvements in physical activity often have impressive impacts as initial behavior change must translate into long-term behavioral maintenance to continue receiving health benefits (84), such as an improvement in angina symptoms and other risk markers. A risk marker is a biological or neuropsychological trait that is not causally related to the development of disease and is frequently a measure of the disease itself or a byproduct of the disease process. Traditional risk markers of cardiovascular disease include angina, coronary plaques, and high cardiac troponin I levels (5). Investigation of

emerging risk markers is required to aid the reclassification of risk for future CAD, as well as secondary prevention for individuals who already have diagnosed CAD (129).

1.2 Standard measures of cardiac function

Echocardiographic measurement of the heart to assess cardiac structure and function is well established (35). Currently, echocardiographic assessment is routinely performed in CAD patients and involves evaluation of a set of standard indices of cardiac function and structure. This point-of-care analyses typically include visual assessment of global and septal left ventricular wall motion and function, and valve function. To assess cardiac systolic function, measurements, such as LV mass, and a single heart cycle calculation of end diastolic volume (EDV) and end systolic volume (ESV) to obtain stroke volume (SV), EF, and cardiac output (CO), may be performed. These indices are performed with the patient in a resting supine position using a two-dimensional ultrasound in the parasternal short axis and apical four-chamber views, then analyzed using manual placement of measurement markers on the ultrasound image. Although there are many other measures of cardiac function, EF is the most used clinically, and in research, due to its feasibility and predictability (13), but it is not without its limitations in image acquisition and lack of sensitivity. EF can be measured using Cube methods, Teichholz (Teich) method, or Simpson's biplane method in the apical 2 chamber and apical 4 chamber views of the left ventricle (10, 91, 101). Minimal differences between methods lead to categorizing patients in different levels of heart failure (6, 91), which suggests those using these techniques should know the inherent assumptions of the

available methods. When echocardiography was first introduced in 1968 as a potential method of cardiac quantification (36), multiple methods were developed using different equations and views of the left ventricle to obtain ejection fraction and one study compared all three methods (101). All studies showed a significant underestimation of LV function using 2D echo compared to invasive angiography and of all the available methods the 2D Simpson's biplane method had the smallest limits of agreement when comparing to radionuclide ventriculography using a Bland-Altman plots (10). Although various techniques are not interchangeable (10), the context for these variables must be interpreted with the same locally available techniques. Recommendations from Lang e*t al.* provide strong guidance and explanation of the nuances of each method for clinical use (61).

1.2.1 Standard measures with aging and cardiovascular disease

Immediately after a myocardial infarction, cardiac function is often impaired and the degree to which it will recover is dependent on both the location and size of the infarct zone. If the myocardial infarction is unresolved, heart function may further decline, through a process of adverse remodeling, and progress to heart failure (51). EF is the most common echocardiographic measure reported post myocardial infarction, due to simple and time-efficient quantification methods that can even be "eyeball" estimated and to well-developed classifications that indicate stages of systolic heart failure (13). According to European Society of Cardiology, an EF of 35% or lower is indicative of heart failure and a poor prognostic outcome (76). An EF of 35-50% is suggestive of slightly reduced systolic heart function and represents an intermediate area between

pathological and healthy heart functioning (76). Changes in LV shape (or morphology) post-myocardial infarction are called LV remodeling and adverse remodeling is classified as a clinically significant increase, greater or equal to 15% increase in ESV (93). In contrast, reverse remodeling, which can occur as a result of factors such as exercise training, surgical procedures, and medications, is the clinically significant reduction in ESV of greater than 15% in ESV, or improvement in EF by 5% (48, 89).

With healthy aging, the changes in LV shape do not occur as rapidly as with myocardial infarction, and an increase in myocardial fibrosis typically occurs at a rate of 1% per 10 years (95). One hallmark of cardiac aging is a reduction in heart rate with age, due to lack of sympathetic activation (37, 111). Decreases in diastolic function, such as reduced EDV and in turn, CO, can also be expected (95). With reductions in loading on the heart, LV mass also decreases, independent of the size of the heart (90).

1.2.2 Standard cardiac measures with exercise training

Exercise training-induced adaptations of the myocardium occur throughout the lifespan. During exercise, heart rate (HR) and preload acutely increase, causing changes in systolic features, such as increases in contractile force of the heart and cardiac output, as well as diastolic features, such as enhanced relaxation and increased suction during shortened diastole (32). These stressors on the heart cause micro-adaptations that can lead to long term changes, dependent on the type of exercise performed and the duration of exercise training. Increases in maximal cardiac output are the most important functional improvement observed with exercise training, and are a product of an enlargement in

cardiac dimensions (EDV, ESV, LV mass), improved contractility (HR), and an increase in blood volume, causing greater filling of the LV and a greater SV (42). Thickening of the myocardial wall is also long term adaptation to exercise training, termed physiological LV hypertrophy or "athlete's heart", and can be measured by increases in cardiac myocyte size in animal models and increases in LV mass in humans (24, 50). An exercise training regime consistent throughout the lifespan with a masters athletes can even cause an increase SV to account for the reduction in HR that occurs with age (103). Exercise training can induce protective effects on the myocardium pre-myocardial infarction; alteration of coronary circulation, elevated myocardial levels of antioxidants, and increased expression of sarcolemmal ATP-sensitive potassium channels coronary arteries and the resiliency of the muscle post-myocardial infarction (99). Although, in extreme cases, such as acutely after an ultra-endurance marathon, healthy endurance trained hearts have been shown to have a brief, reversible reductions in function, measured by a depression in EF and reduced circumferential peak strain (29, 30).

1.3 Novel measures of cardiac function

Clinical echocardiographic assessments of LV function are informative for well-established diagnoses, but these indices are not always proficient in identifying subtle differences in cardiac function. White *et al.* demonstrated the clinical value of assessments of LV remodeling after myocardial infarction, and found that the highest mortality during follow-up was in patients who had significantly larger LV volumes and lower LVEF than survivors (127). Recent findings from Awadalla et. al., reevaluated this

model by including both standard (end diastolic and systolic volumes, EF, enzyme concentrations), and novel (LV twist, segmental wall motion abnormality) measures of cardiac function from assessments conducted immediately post-myocardial infarction and found that higher levels of twist LV twist was the strongest predictor of LV remodeling (8). Investigating novel parameters of LV function could provide new insight into more subtle changes in LV function in response to various pharmacologic and/or exercise interventions.

1.3.1 Background of left ventricular twist

Standard echocardiography is thorough, but not capable of capturing all features of cardiac function, including the twisting motion of cardiac contraction and relaxation dictated by the spiraling myocyte arrangement of the LV. The architecture of the LV is unique from the other cardiac chambers, and is formed by layers of fibres uniquely oriented in a cross-helical pattern (94, 107). The two layers that construct this muscular wall are the inner subendocardial layer, in which the fibres are arranged in a left-handed helical pattern, and the outer layer of epicardium, in which the fibres are arranged in a right-handed helical pattern (94). As a result of this double-layered helical structure at the mid-level of the LV, contraction of the circumferential fibres causes opposing rotation of basal and apical portions of the heart (107, 109). As such, at the end of systole, the base of the heart is rotated maximally in the clockwise direction and the apex is rotated maximally in the counterclockwise direction when viewed from the apex (Figure 1) (94). The outer epicardial layer has a greater radius and therefore a greater moment arm to

influence the summated apical rotation and basal rotation (94). This summation of overall rotation is termed LV twist and is calculated as the instantaneous difference between the apical and basal rotation throughout the heart cycle (22). The LV also undergoes other dimensional changes to its length and diameter during contraction, and therefore it has been suggested to normalize LV twist assessment by comparison of only the peak magnitude of LV twist for different sizes of LV (107). In a healthy individual with a clear image of LV function, the peak LV twist of the heart is in the counterclockwise direction at the end of systole.

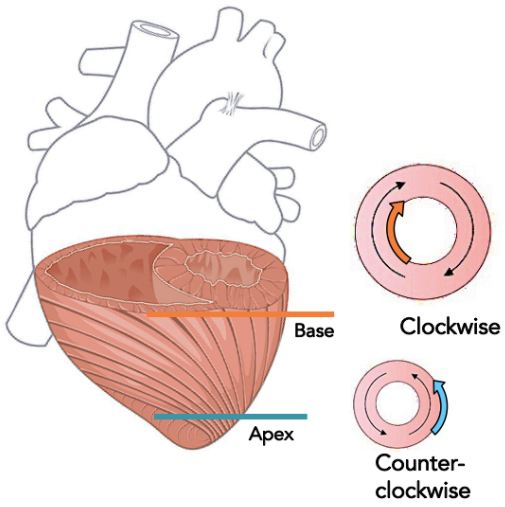


Figure 1. A depiction of the basal and apical regions of the left ventricle and the direction of rotation when viewed from the apex.

Historically, LV twist was investigated exclusively in animal models as the available imaging techniques were fairly invasive, however, in the past three decades, the literature has moved toward measuring LV twist by echocardiography as an accurate and

highly reproducible measure of the dynamic heart mechanics in humans (14, 41, 82). In particular, quantification of LV twist can help identify early abnormalities in systolic and diastolic myocardial function that are not captured by conventional echocardiographic imaging assessments (109). Furthermore, assessments of the twisting motion of the heart provide a key mechanistic link between the systolic and diastolic phases of heart contraction (109).

1.3.1.1 LV twist and aging and cardiovascular disease

With age, the LV stiffens outward, with the stiffening becoming more pronounced in the subendocardium compared to the epicardium (109). In addition to the proportionally greater stiffening, the subendocardium also experiences a relatively greater decrease in contractile function with age (66, 95). It has been speculated that this age associated decrease in contractile function is due to either: 1) subendocardial fibrosis, or 2) prolonged decay time in calcium transients greatest in the epicardium, measured by increases in torsion-to-shortening ratio (TSR) (66, 95). TSR is essentially a method for quantifying the differences between inner and outer myocardial wall contractile myofibre function, which is necessary considering the different changes experienced by the inner and outer layers of the myocardium in healthy human aging. Relative reductions in inner layer rotation, due to both increased stiffening and decreased contractile function, create a situation in which the outer layer (epicardial) rotation is relatively unopposed, resulting in increased peak LV twist magnitude with aging (114). Regardless of sex, LV twist progressively increases from infancy to adulthood (94) and when studied across a wide

age range, there are significant differences in both magnitude and timing such that peak LV twist is increased with age (12, 114). Some normative values have been suggested by Kocabay et. al, from a sample of 247 volunteers, of which 55 participants were between 56-80 years old, and established average values of: basal rotation of -8.2±3.1º, apical rotation of 14.8±7.3º, and LV twist of 23±8.0º (57). Reference values in the younger ages were lower in all three measures (57), consistent with previous research that LV twist increases in healthy aging (114). Increases in LV twist are largely driven by stiffening and reduction in basal rotation, with an increase in apical rotation (114), due to the relative dominance of the epicardial fibres with age (92).

There is conflicting evidence on whether stiffening of the heart with age that the degree of untwisting and the rate of untwisting are reduced and delayed in middle and older age compared to younger adults (12, 56). Alterations in diastolic filling with age are attributed to multiple mechanisms: 1) phosphorylation of titin leading to myocyte stiffness (47), 2) decreased calcium (Ca^{2+}) handling rate leading to decreased active myocardial relaxation (44), and 3) increased state of inflammation causing dysfunctional coronary microcirculation (18). Diastolic dysfunction is known to progress without symptoms until the later stages of heart failure with preserved ejection fraction (65). LV twist and UTR dynamics provide promise as emerging indicators of cardiac conditions, and in particular diastolic dysfunction that are difficult to detect with traditional measures (94).

LV twist also changes with different cardiac conditions; even in cases where the traditional measurement of LV EF is preserved (107). The changes in LV twist with heart

failure follow a timeline in which during the early stages of heart failure with preserved ejection fraction there is an increase in LV twist, followed by normalization and further reductions in LV twist as the level of diastolic dysfunction advances, compared with normal controls (96). The response of LV twist with heart failure in comparison to healthy controls is variable across different cardiac diseases and conditions. LV twist was observed to be reduced in cardiac ischemia with MI driven by a reduction in apical rotation when tested in 30 patients with anterior acute MI for greater than 1 month (115), a reduction that has been associated with LV remodeling (93). LV twist has been described as decreased, delayed, and uncoordinated in dilated cardiomyopathy (120), yet it is increased with type 1 (16) and type 2 diabetes mellitus, and this increase is especially pronounced in individuals that also present with LV hypertrophy (67). In hypertension, with or without LV hypertrophy, LV twist is delayed and decreased in conjunction with the level of LV hypertrophy (92). Although LV twist is altered in various cardiac disease states, the physiological regulation of the LV mechanics in response to different intensities of exercise training in conjunction with cardiac disease is poorly understood.

1.3.1.1 LV twist and exercise training

LV function, measured by LV twist, has emerged as a valuable indicator of cardiac health that is sensitive to myocardial decline in various disease states, manifesting as a reduction in peak LV twist following an MI and in patients with heart failure with preserved EF (86, 115). Similar to what has been observed in the vasculature (58), increases in cardiac stiffening with healthy aging result in an increase in resting peak LV

twist with age, across the age spectrum (87, 114). Despite these discrete changes with age, in first-year university student athletes, LV twist was also increased after a 90-day program of intensive endurance exercise training implemented in a varsity level rowing team (125). There are both augmentations in LV with exercise training and age, therefore these alterations must be further classified into categories of pathological versus beneficial changes in LV function. At this time, research has yet to solidify the directional association of LVT and improvements in cardiac function. Following the assessment after 3 months of training, the young healthy individuals continued a maintenance phase exercise training program for 39 months before an additional assessment and individuals were excluded from the final analysis if they took any breaks greater than 14 days during that time period. Researchers found the acute augmentation in peak LV twist, from baseline to 3 months of intensive varsity exercise training, returned to baseline levels following the chronic maintenance phase of training level 39 months later (125). In other words, peak LVT acutely increased after exercise training and later decreased back to baseline, when exercise training was continued. To date no other longitudinal training studies greater than 6 months in length have been conducted. In a cross-sectional study, examining young, middle-aged, and older-aged males of sedentary (n=75) and endurance-trained backgrounds (n=106), it was found that trained individuals had reduced peak LV twist driven by lower basal rotation, whilst similar apical rotations (71). Alternatively, young recreationally trained men, after 12 weeks of whole body resistance exercise, did not have any alterations in peak LV twist (7) suggesting aerobic exercise, but not resistance exercise, seems to elicit changes in LV twist mechanics. In other research, in a

population with CAD, there was no change in traditional indices of LV function after 10 weeks of involvement in moderate intensity continuous training as part of a CR program, whereas LV twist was shown to decrease, this reduction in LV twist was cited as a potential improvement in LV function and assessing LV twist was highlighted as a sensitive cardiac measure (75). In the past literature cited here, reductions in LV twist have been referenced as both improvements and declines in cardiac function and it is clear that the individual changes in rotation that are associated with changes in twist need to be considered along with other potential cardiac structure and function changes when interpreting LV twist findings. Thus, more comprehensive research will inform the interpretation of LV twist as a individual health measure of cardiac function.

The physiological state of the myocardium (ie. resting, exercise) can impact LV twist measurements, as peak LV twist is independently augmented by increases in preload and contractility of the heart, and attenuated by increases in afterload (9, 109). Another component to consider is the rate of twisting in the systolic phase and the untwisting rate (UTR) in the diastolic phase, as these will determine the filling and loading of the heart. Preload is the amount of blood in the heart at the end of diastole, quantified as EDV, whereas afterload is the amount of blood in the heart at the end of systole, quantified as ESV. In studies with acute saline infusion, LV twist was increased with larger preload due to increased apical rotation, with a respective decrease in UTR, while ESV, HR, and blood pressure remained unchanged (25, 39). Essentially preload alters the loading on the heart, and through the Frank-Starling length-tension relationship, greater loading causes greater degrees of recoil at a slower velocity (126). Alternatively, afterload can be

augmented using hand-grip exercise in young healthy individuals leading to acute reductions in both LV twist and UTR, while keeping EDV, HR, and blood pressure remained unchanged (25, 39, 68). Exercise training can further impact these mechanisms by increasing blood volume and improving venous return (17, 106) and it is important to measure these variables simultaneous to these indicators of systemic hemodynamic function particularly in exercise training programs where these factors may be altered.

In summary, LV twist is an emerging echocardiographic parameter that may have increased sensitivity in comparison to traditional echocardiographic measures, for the identification of more subtle changes in ventricular function that precede larger functional gains in cardiac function. Although resting peak LV twist is altered in cardiovascular disease states and healthy endurance trained individuals, the measurement of LV mechanics with the layered conditions of disease and exercise training have not been thoroughly investigated.

1.3.3 Global longitudinal strain

Recently, global longitudinal strain (GLS) has become a prognostic parameter to assess LV wall dysfunction that has been accepted by clinicians for its high sensitivity in multiple cardiac conditions, high reproducibility, and accuracy (13, 102). Using 2D speckle-tracking echocardiography, in the apical four-chamber view, in GLS, the movement of 6 LV segments is tracked and compiled into a single index to provide an overall peak degree of strain at end-systole. In this context, strain is used to define shortening, thickening, or lengthening as a measurement of regional LV function (108).

Due to the high sensitivity and specificity of GLS (97, 128), it is possible to detect the difference between fibrous and viable myocardium with some meta-analyses suggesting it is more sensitive than EF at predicting mortality when EF is normal or near normal (53). As the heart reaches end-systole, the LV fibres shorten, causing the apex to move closer to the base and eject blood into the aorta. Based on a recent meta-analysis using 28 datasets of GLS, it has been suggested that values of peak strain -12% and above signify impaired function of the myocardium, whereas -20% and below is indicative of normal function (53). These values leave an intermediate region, in which a cut-off has yet to be defined. When assessing adverse remodeling, defined as a 15 to 20% increase in EDV and/or ESV, GLS values range between -12.8% and -10.2% (48). In previous studies GLS provided substantial prognostic value over clinical and standard echocardiographic variables in predicting LV remodelling (130) and global LV function improvement (2) using multivariate analysis. With respect to previously observed changes in GLS with exercise training, although there was no observed change in LV strain at rest for individuals with CAD after 10 and 12 weeks of exercise training (43, 75), higher pre-training VO_2peak was correlated with higher GLS values (43, 59). Strain is adequate for identification of pathological heart function; however, the assessment of GLS does not seem to always improve with exercise training. Some of the main downfalls with using GLS as a comprehensive index of cardiac structure and function, are the load dependency, the image quality requirements, and the inherent assumption of geometric uniformity when obtaining the apical four-chamber and two-chamber views in the 2D plane (53). Although standard echocardiographic measures are sufficient for the

evaluation of overall functioning, measurements, such as GLS, to assess subtle differences LV function provide additional value to cardiac assessment.

1.3.3 Myocardial performance index

In 1995, Tei described a novel method of combining echocardiographic measurements of LV systolic and diastolic heart function (118). The myocardial performance index (MPI) or Tei index was first established in children 20 days to 18 years old and has since been investigated in a wide range of cardiac diseases (60, 118). The measure is easily calculated from standard echocardiographic assessment parameters by using the sum of the isovolumic contraction and relaxation times divided by ejection time (Figure 2), evaluated using the LV outflow and mitral valve inflow velocity profiles. Although a consensus on an abnormality threshold has yet to be established, it has been suggested that normal MPI should be under 0.47 and some sources suggest as low as 0.36 (34, 61, 104). MPI is easily obtained and has been shown to be independent of LV geometry, age, heart rate, and blood pressure.

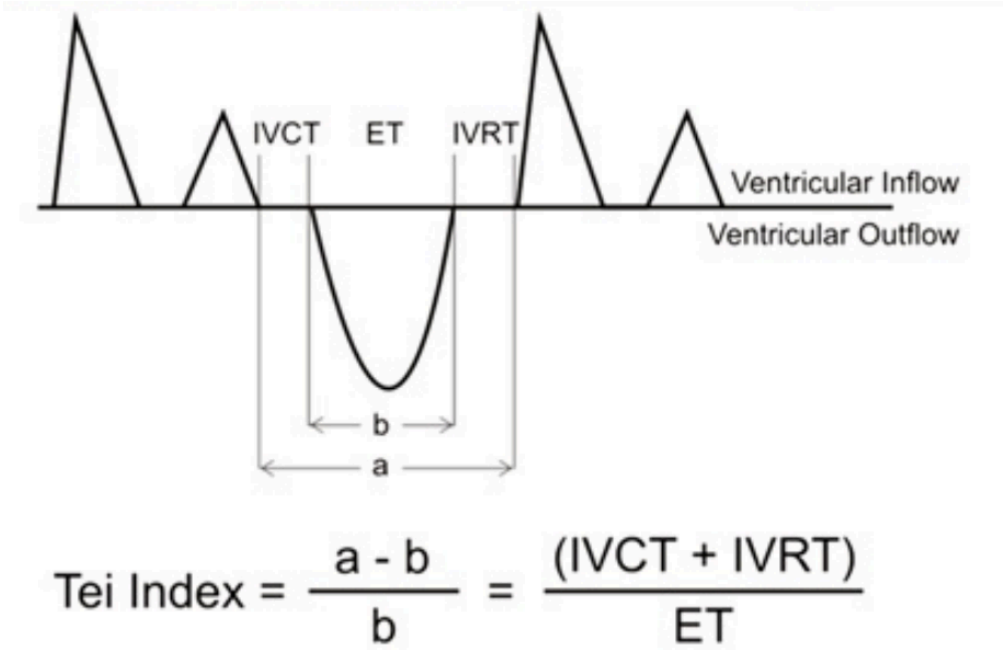


Figure 2. Depiction of simplified ultrasound tracings and time intervals required to calculate myocardial performance index or Tei index adapted from Hu et al**.** (46)

Higher MPI values are associated with more pathological states, such as CAD, heart failure, valvular disease, pulmonary hypertension, cardiac amyloidosis (60). MPI combines LV systolic and diastolic function, and is therefore an effective assessment tool in individuals who have experienced an MI where inferior and anterior regions are affected (54). Individuals with more severe CAD post-MI, as assessed by coronary angiography with 3 or more diseased vessels, had higher MPI in comparison to healthy controls, with values in the range of 0.705 compared to 0.455 respectively (88). With exercise training, healthy individuals seem to be able to reduce their MPI, mainly as a function of increased ejection time and decreased isovolumic contraction time (64, 104,

110). MPI has also been shown to change after six months of standard CR exercise training after acute MI (54, 122) with the most improvement in those with the lowest baseline function while no improvement in EF (121). Furthermore, greater improvement was seen in cardiac patients with lower baseline function (121). Therefore, MPI may be a beneficial tool for the continued evaluation and monitoring of individuals with CAD considering both systolic and diastolic LV function is often affected and may potentially be recovered.

1.4 Cardiac rehabilitation

Treatment post-MI has become exponentially more involved since its original prescription of prolonged bed rest in the 1930s (15). Every decade following these initial prescriptions has been studded with a small increase in the mobility physicians are willing to prescribe, from chair therapy, to small bouts of walking 3 to 5 minutes, to structured early walking through an inpatient CR program (105). By 1985, advancements in CR programming were unrecognizable from the earliest form, including multidisciplinary lifestyle modification programming and exercise approaches (105). Exercise training post-myocardial event, has numerous physiological benefits such as reductions in all-cause mortality risk, decreased re-occurrence of myocardial events, and adaptive LV remodeling (40, 63). Currently, the standard of care in Canada for exercise prescription in CR recommends exercise sessions 5 times per week of 30 minutes of aerobic exercise per session (119). In Canada, cardiopulmonary exercise testing (CPET) is typically conducted in hospital on a stationary bicycle or treadmill to obtain an estimated cardiorespiratory

fitness (CRF), before and after CR programming (77). One of the main benefits of CR exercise training is an improvement in CRF, which is associated with a significantly lower mortality risk (85). In a study investigating CR programming, an increase in CRF as measured by peak oxygen uptake (VO_2peak) by 3.5 ml/kg/min was equivalent to a 10% reduction in cardiovascular mortality (122).

After an MI, all cases are typically pharmaceutically managed with a combination of medications that alter the cardiac response to exercise. CPET is used by kinesiologists to understand individual limitations and to set heart rate targets for their initial exercise prescription. In a randomized control trial, CRF improvements were found in as little as 4 weeks, yet the exercise program length was 8 weeks shorter than the Canadian recommendations (79). In a review by Lavie and Milani, an improvement of 15% in VO_2peak may be expected following 6 months of CR of traditional moderate intensity (62). Although the degree of CRF benefits are dependent on length and intensity, CR exercise is known to improve CRF (20, 70, 77), which is associated with reduction in mortality risk (85).

The effect of CR programming on EF is less clear. Haykowsky *et al.* (2011) found improvements in EF that increased with the duration of the CR exercise training program beyond 3 months, and decreased as the time between MI and initiation of the program lengthened (40). Another observational study found that in patients, early reduced LV twist was associated with patients who developed LV remodeling, defined as 15% or greater increases in LV ESV and lower EF (93). Often improvements in VO_2 peak have been found to parallel indicators of adaptive LV remodeling such as EF (27, 75),

however improvements in VO_2 peak may be found whilst no change in EF is observed (43, 121). These cardiac independent improvements in CRF may also be driven by peripheral changes such as vascular function (21), improvement in anaerobic threshold (62), and muscle strength (112).

In terms of the heart, CR exercise training has been shown to result in an improvement in coordination of heart contractility, revascularization of the heart, and increased blood flow to the infarcted segment(s) (3, 54, 62, 79). In two studies assessing patients entering CR, after 12 weeks of exercise training, improvements were found in myocardial polarization dispersion that may be associated with malignant ventricular arrythmias and sudden cardiac death (3, 54). A well-conducted study measured collateral innervation, using the gold standard, coronary collateral flow index (CFI) and noted improved CFI after 4 weeks of CR exercise training, regardless of exercise intensity, indicating improved collateral innervation of 40% to the diseased vessel and no difference in the control group (79). Most notably, recent evidence by McGregor *et al.* has shown that 10 weeks of 20-40 minutes of moderate intensity continuous exercise training as part of a CR exercise program performed twice per week in a CAD population resulted in reductions in total degrees of LV twist (75). Alternatively, individuals with CAD in non-exercising age-matched control group showed increases in LV twist, which were cited as suggestive of an impairment in LV function (75).

1.4.1 High intensity interval training in cardiac rehabilitation

The physiological and functional improvements associated with CR exercise training are most effective when they become permanent lifestyle modifications maintained beyond the initial period of exercise training (80). HIIT was first used in CR as type of exercise training in 1990 in a research setting but initially elicited safety concerns, which led to limited use (78). In a recent meta-analysis conducted on 17 studies using high intensity interval training (HIIT) and moderate intensity continuous training (MICT) for CR programming, HIIT induced higher CRF improvements than MICT (22). HIIT defined as Additional to intensity, CR programs with durations shorter than 6 weeks found no change in CRF, whereas programs longer than 12 weeks of HIIT did not show larger gains in CRF compared to those between 6 and 12 weeks duration (38). After following up with participants once the CR program ended, adherence was found to be the strongest predictor of survival and was a stronger predictor than fitness level at the beginning of the program onset, exercise intensity, medications, and employment status (116). Cited barriers to exercise participation in this population include time, cost, and access to equipment (23) and some studies show long term adherence to HIIT is better than MICT (1, 80). HIIT has recently been shown to be a superior alternative to MICT in inducing cardiorespiratory improvements, with a considerably lower time commitment, in CAD patients entering a CR exercise program greater than 6 weeks in duration (38, 81, 117). Alternately, when comparing the change in vascular adaptations in CAD patients, HIIT has only shown to be equivalent to MICT in inducing improvements in endothelial function, measured by reductions in flow-mediated dilation (19, 123).

Generally, these HIIT protocols in patients with CVD are completed on a stationary bicycle or on exercise equipment in a hospital setting (1, 19, 26); however, HIIT has recently been translated into stair climbing interventions in non-clinical populations, as a more versatile and easily accessible exercise modality (4, 11, 24, 50, 124). In healthy young sedentary women, stair climbing-based HIIT performed 2-3 times per week for 6 weeks, led to clinically meaningful increases in VO_2peak (7%) (4). Stair climbing exercise training was well-tolerated and enjoyed by individuals with type 2 diabetes, despite no changes in glycemic control (33). Although not yet typically prescribed in a clinical cardiac population, stair climbing challenges both the cardiovascular and musculoskeletal systems and has been shown to improve fitness, cardiovascular health, strength and balance in older persons (24, 124). Resistance training in combination with aerobic training, has been shown to be permissive to greater improvements in VO_2peak in CAD populations (70, 72, 73). Stair-climbing based high intensity interval training is an appealing exercise strategy that combines aerobic and resistance elements, is feasible in terms of equipment, time efficient, and may facilitate long-term exercise adherence for some individuals in a CR population. It is unknown whether stair-climbing HIIT as a modality leads to changes in cardiac structure and function and aerobic capacity in individuals with CAD.

1.5 Purpose and hypotheses

Evidently, there is much to be understood with respect to exercise training in a CAD population. HIIT protocols have been shown to improve CRF, but less research has

examined cardiac function outcomes to comprehensively assess LV remodeling with this form of exercise training. CRF programming in a rehabilitation setting typically lasts 3 months or longer, but it is unknown whether stair climbing-based HIIT is feasible, or if it provides a sufficient physiological exercise load to result in improvements in LV function, in comparison to the traditional CR exercise training programs, over this timescale. Assessments were conducted at baseline and following both the supervised (4 weeks) and unsupervised (12 weeks) phases of either STAIR or TRAD training.

The aims of this study were two-fold:

1) to determine if stair climbing-based, high intensity interval training (STAIR) and traditional CR exercise training (TRAD) are associated with improvements in CRF and cardiac function in a CR population,
2) to compare the response of standard (EF, EDV, ESV, SV) and novel (LV twist, MPI, GLS) indices of cardiac function, to 4 and 12 weeks of STAIR and TRAD CR exercise training in a CR population.

We hypothesized that:

1) CRF, as measured by VO_2peak, would increase in response to 4 and 12 weeks of exercise training in both the STAIR and the TRAD groups,
2) there would be improvements in LV twist and MPI, whereas there would be no improvements in neither GLS, EF nor other standard indices of cardiac structure, after 12 weeks of exercise training in either the STAIR or the TRAD groups.

1.6 References

1. **Aamot I-L**, **Karlsen T**, **Dalen H**, **Støylen A**. Long-term exercise adherence after

high-intensity interval training in cardiac rehabilitation: a randomized study. *Physiother Res Int* 21: 54–64, 2016.

2. **Abate E**, **Hoogslag GE**, **Antoni ML**, **Nucifora G**, **Delgado V**, **Holman ER**, **Schalij MJ**, **Bax JJ**, **Marsan NA**. Value of three-dimensional speckle-tracking longitudinal strain for predicting improvement of left ventricular function after acute myocardial infarction. *Am J Cardiol* 110: 961–967, 2012.
3. **Ali A**, **Mehra MR**, **Malik FS**, **Lavie CJ**, **Bass D**, **Milani R V.** Effects of aerobic exercise training on indices of ventricular repolarization in patients with chronic heart failure. *Chest* 116: 83–87, 1999.
4. **Allison M**, **Baglole J**, **Martin B**, **Macinnis M**, **Gurd B**, **Gibala M**. Brief intense stair climbing improves cardiorespiratory fitness. *Med Sci Sports Exerc* 49: 298–307, 2017.
5. **Antman E**, **Tanasijevic M**, **Thompson B**, **Schactman M**, **McCabe C**, **Cannon C**, **Fischer G**, **Fung A**, **Thompson C**, **Wybenga D**, **Braunwald E**. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med* 335: 1342–1349, 1996.
6. **Arora G**, **Morss AM**, **Piazza G**, **Ryan JW**, **Dinwoodey DL**, **Rofsky NM**, **Manning WJ**, **Chuang ML**. Differences in left ventricular ejection fraction using teichholz formula and volumetric methods by cmr : implications for patient stratification and selection of therapy. *J Cardiovasc Magn Reson* 12: 1–2, 2010.
7. **Au JS**, **Oikawa SY**, **Morton RW**, **Phillips SM**, **MacDonald MJ**, **Stöhr EJ**. Absence of functional left ventricular remodelling with resistance exercise training

– A longitudinal study in men. *Appl Physiol Nutr Metab* 7: 1–7, 2019.

8. **Awadalla H**, **Saleh MA**, **Abdel Kader M**, **Mansour A**. Left ventricular torsion assessed by two-dimensional echocardiography speckle tracking as a predictor of left ventricular remodeling and short-term outcome following primary percutaneous coronary intervention for acute myocardial infarction: A single-cent. *Echocardiography* 34: 1159–1169, 2017.
9. **Balmain B**, **Stewart GM**, **Yamada a.**, **Chan J**, **Haseler LJ**, **Sabapathy S**. The impact of an experimentally induced increase in arterial blood pressure on left ventricular twist mechanics. *Exp Physiol* 101: 124–134, 2016.
10. **Bellenger NG**, **Burgess MI**, **Ray SG**, **Lahiri A**, **Coats AJS**. Comparison of left ventricular ejection fraction and volumes in heart failure by echocardiography , radionuclide ventriculography and cardiovascular magnetic resonance: Are they interchangeable? *Eur Heart J* 21: 1387–1396, 2000.
11. **Boreham CAG**, **Kennedy RA**, **Murphy MH**, **Tully M**, **Wallace WFM**, **Young I**. Training effects of short bouts of stair climbing on cardiorespiratory fitness, blood lipids, and homocysteine in sedentary young women. *Br J Sports Med* 39: 590–593, 2005.
12. **Burns AT**, **La Gerche A**, **MacIsaac AI**, **Prior DL**. Augmentation of left ventricular torsion with exercise is attenuated with age. *J Am Soc Echocardiogr* 21: 315–320, 2008.
13. **Cameli M**, **Mondillo S**, **Solari M**, **Righini FM**, **Andrei V**, **Contaldi C**, **De Marco E**, **Di Mauro M**, **Esposito R**, **Gallina S**, **Montisci R**, **Rossi A**, **Galderisi**

M, **Nistri S**, **Agricola E**, **Mele D**. Echocardiographic assessment of left ventricular systolic function: from ejection fraction to torsion. *Heart Fail Rev* 21: 77–94, 2016.

14. **Catalano M**, **Lamberti-Castronuovo A**, **Catalano A**, **Filocamo D**, **Zimbalatti C**. Two-dimensional speckle-tracking strain imaging in the assessment of mechanical properties of carotid arteries: Feasibility and comparison with conventional markers of subclinical atherosclerosis. *Eur J Echocardiogr* 12: 528–535, 2011.
15. **Certo CM**. History of cardiac rehabilitation. *Phys Ther* 65: 1793–1795, 1985.
16. **Chung J**, **Abraszewski P**, **Yu X**, **Liu W**, **Krainik AJ**, **Ashford M**, **Caruthers SD**, **McGill JB**, **Wickline SA**. Paradoxical increase in ventricular torsion and systolic torsion rate in type 1 diabetic patients under tight glycemic control. *J Am Coll Cardiol* 47: 384–390, 2006.
17. **Convertino VA**. Blood volume response to physical activity and inactivity. *Am J Med Sci* 334: 72–79, 2007.
18. **Csiszar A**, **Ungvari Z**, **Koller A**, **Edwards JG**, **Kaley G**. Proinflammatory phenotype of coronary arteries promotes endothelial apoptosis in aging. *Physiol Genomics* 17: 21–30, 2004.
19. **Currie KD**, **Dubberley JB**, **McKelvie RS**, **Macdonald MJ**. Low-volume, high-intensity interval training in patients with CAD. *Med Sci Sports Exerc* 45: 1436–1442, 2013.
20. **Currie KD**, **Rosen LM**, **Millar PJ**, **McKelvie RS**, **MacDonald MJ**. Heart rate

recovery and heart rate variability are unchanged in patients with coronary artery disease following 12 weeks of high-intensity interval and moderate-intensity endurance exercise training. *Appl Physiol Nutr Metab* 38: 644–650, 2013.

21. **Currie KD**, **West CR**, **Krassioukov A V.** Difference in left ventricular global function and mechanics in paralymic athletes with cervical and thoracic spinal cord injuries. *Front Physiol* 7: 1–8, 2016.
22. **van Dalen BM**, **Soliman OII**, **Vletter WB**, **ten Cate FJ**, **Geleijnse ML**. Age-related changes in the biomechanics of left ventricular twist measured by speckle tracking echocardiography. *Am J Physiol Heart Circ Physiol* 295: H1705-11, 2008.
23. **Daly J**, **Sindone AP**, **Hons B**, **Thompson DR**, **Hancock K**, **Chang E**, **Davidson P**. Barriers to participation in and adgerence to cardiac rehabiltiation programs: a critical literature review. *Prog Cardiovasc Nurs* 17: 8–17, 2002.
24. **Donath L**, **Faude O**, **Roth R**, **Zahner L**. Effects of stair-climbing on balance, gait, strength, resting heart rate, and submaximal endurance in healthy seniors. *Scand J Med Sci Sport* 24: 93–101, 2014.
25. **Dong S-J**, **Hees PS**, **Huang W**, **Buffer SA**, **Weiss JL**, **Shapiro EP**, **James L**, **Shapiro EP**. Independent effects of preload, afterload, and contractility on left ventricular torsion [Online]. *Am J Physiol - Hear Circ Physiol* 277: 1053–1060, 1999. http://ajpheart.physiology.org/content/277/3/H1053.abstract.
26. **Ehsani AA**, **Hagberg JM**, **Hickson RC**. Rapid changes in left ventricular dimensions and mass in response to physical conditioning and deconditioning. *Am J Cardiol* 42: 52–56, 1978.

27. **Ellison GM**, **Waring CD**, **Vicinanza C**, **Torella D**. Physiological cardiac remodelling in response to endurance exercise training: Cellular and molecular mechanisms. *Heart* 98: 5–10, 2012.

28. **Fleg JL**, **Strait J**. Age-associated changes in cardiovascular structure and function: a fertile milieu for future disease. *Heart Fail Rev* 17: 545–54, 2012.

29. **George K**, **Shave R**, **Oxborough D**, **Cable T**, **Dawson E**, **Artis N**, **Gaze D**, **Hew-Butler T**, **Sharwood K**, **Noakes T**. Left ventricular wall segment motion after ultra-endurance exercise in humans assessed by myocardial speckle tracking. *Eur J Echocardiogr* 10: 238–243, 2009.

30. **La Gerche A**, **Burns AT**, **Mooney DJ**, **Inder WJ**, **Taylor AJ**, **Bogaert J**, **MacIsaac AI**, **Heidbüchel H**, **Prior DL**. Exercise-induced right ventricular dysfunction and structural remodelling in endurance athletes. *Eur Heart J* 33: 998–1006, 2012.

31. **Gielen S**, **Laughlin MH**, **O'Conner C**, **Duncker DJ**. Exercise training in patients with heart disease: review of beneficial effects and clinical recommendations. *Prog Cardiovasc Dis* 57: 347–355, 2015.

32. **Gielen S**, **Schuler G**, **Adams V**. Cardiovascular effects of exercise training: molecular mechanisms. *Circulation* 122: 1221–1238, 2010.

33. **Godkin FE**, **Jenkins EM**, **Little JP**, **Nazarali Z**, **Percival ME**, **Gibala MJ**. The effect of brief intermittent stair climbing on glycemic control in people with type 2 diabetes: a pilot study. *Appl Physiol Nutr Metab* 43: 969–972, 2018.

34. **Goroshi M**, **Chand D**. Myocardial performance index (Tei index): A simple tool

to identify cardiac dysfunction in patients with diabetes mellitus. *Indian Heart J* 68: 83–87, 2016.

35. **Gottdiener JS**, **Bednarz J**, **Devereux R**, **Gardin J**, **Klein A**, **Manning WJ**, **Morehead A**, **Kitzman D**, **Oh J**, **Quinones M**, **Schiller NB**, **Stein JH**, **Weissman NJ**. American Society of Echocardiography recommendations for use of echocardiography in clinical trials: A report from the american society of echocardiography's guidelines and standards committee and the task force on echocardiography in clinical trials. *J Am Soc Echocardiogr* 17: 1086–1119, 2004.
36. **Gramiak R**, **Shah P**. Echocardiography of the aortic root. *Invest Radiol* 3: 356–366, 1968.
37. **Hajduczok G**, **Chapleau MW**, **Abboud FM**. Increase in sympathetic activity with age. II. Role of impairment of cardiopulmonary baroreflexes. *Am J Physiol Circ Physiol* 260: H1121–H1127, 2017.
38. **Hannan AL**, **Hing W**, **Simas V**, **Climstein M**, **Coombes JS**, **Jayasinghe R**, **Byrnes J**, **Furness J**. High-intensity interval training versus moderate-intensity continuous training within cardiac rehabilitation: a systematic review and meta-analysis. *Open access J Sport Med* 9: 1–17, 2018.
39. **Hansen DE**, **Daughters GT**, **Alderman EL**, **Ingels NB**, **Stinson EB**, **Miller DC**. Effect of volume loading, pressure loading, and inotropic stimulation on left ventricular torsion in humans. *Circulation* 83: 1315–1326, 1991.
40. **Haykowsky M**, **Scott J**, **Esch B**, **Schopflocher D**, **Myers J**, **Paterson I**, **Warburton D**, **Jones L**, **Clark AM**. A meta-analysis of the effects of exercise

training on left ventricular remodeling following myocardial infarction: start early and go longer for greatest exercise benefits on remodeling. *Trials* 12: 1–8, 2011.

41. **Helle-Valle T**, **Crosby J**, **Edvardsen T**, **Lyseggen E**, **Amundsen BH**, **Smith H-J**, **Smiseth OA**, **Smith H-J**, **Rosen BD**, **Lima JA**, **Torp H**, **Ihlen H**, **Smiseth OA**. New noninvasive method for assessment of left ventricular rotation speckle tracking echocardiography. *Circulation* 112: 3149–3156, 2005.

42. **Hellsten Y**, **Hoier B**. Capillary growth in human skeletal muscle: physiological factors and the balance between pro-angiogenic and angiostatic factors. *Biochem Soc Trans* 42: 1616–1622, 2014.

43. **Van De Heyning CM**, **De Maeyer C**, **Pattyn N**, **Beckers PJ**, **Cornelissen VA**, **Goetschalckx K**, **Possemiers N**, **Van Craenenbroeck EM**, **Voigt JU**, **Vanhees L**, **Shivalkar B**. Impact of aerobic interval training and continuous training on left ventricular geometry and function: a SAINTEX-CAD substudy. *Int J Cardiol* 257: 193–198, 2018.

44. **Hohendanner F**, **Ljubojević S**, **Macquaide N**, **Sacherer M**, **Sedej S**, **Biesmans L**, **Wakula P**, **Platzer D**, **Sokolow S**, **Herchuelz A**, **Antoons G**, **Sipido K**, **Pieske B**, **Heinzel FR**. Intracellular dyssynchrony of diastolic cytosolic [Ca2+] decay in ventricular cardiomyocytes in cardiac remodeling and human heart failure. *Circ Res* 113: 527–538, 2013.

45. **Hongu N**, **Shimada M**, **Miyake R**, **Nakajima Y**, **Nakajima I**, **Yoshitake Y**. Promoting stair climbing as an exercise routine among healthy older adults attending a community-based physical activity program. *Sports* 7: 23, 2019.

46. **Hu K**, **Liu D**, **Niemann M**, **Herrmann S**, **Gaudron PD**, **Ertl G**, **Weidemann F**. Methods for assessment of left ventricular systolic function in technically difficult patients with poor imaging quality. *J Am Soc Echocardiogr* 26: 105–113, 2013.

47. **Hudson B**, **Hidalgo C**, **Saripalli C**, **Granzier H**. Hyper-phosporylation of mouse cardiac titin contributes to transverse aortic constriction induced diastolic dysfunction. *Circ Res* 109: 858–866, 2011.

48. **Huttin O**, **Coiro S**, **Selton-Suty C**, **Juillière Y**, **Donal E**, **Magne J**, **Sadoul N**, **Zannad F**, **Rossignol P**, **Girerd N**. Prediction of left ventricular remodeling after a myocardial infarction: Role of myocardial deformation: A systematic review and meta-analysis. *PLoS One* 11: 1–15, 2016.

49. **Jackson G**, **Gibbs CR**, **Davies MK**, **Lip GYH**. Left ventricular radius to wall thickness ratio. *Am J Cardiol* 43: 1189–1194, 2000.

50. **Jenkins EM**, **Nairn LN**, **Skelly LE**, **Little JP**, **Gibala MJ**. Do stair climbing exercise "snacks" improve cardiorespiratory fitness ? *Appl Physiol Nutr Metab* 684: 681–684, 2019.

51. **Jessup M**, **Brozena S**. Heart Failure. *N Engl J Med* 348: 2007–2018, 2003.

52. **Joyner MJ**, **Green DJ**. Exercise protects the cardiovascular system: Effects beyond traditional risk factors. *J Physiol* 587: 5551–5558, 2009.

53. **Kalam K**, **Otahal P**, **Marwick TH**. Prognostic implications of global LV dysfunction: A systematic review and meta-analysis of global longitudinal strain and ejection fraction. *Heart* 100: 1673–1680, 2014.

54. **Kalapura T**, **Lavie CJ**, **Jaffrani W**, **Chilakamarri V**, **Milani R V.** Effects of

cardiac rehabilitation and exercise training on indexes of dispersion of ventricular repolarization in patients after acute myocardial infarction. *Am J Cardiol* 92: 292–294, 2003.

55. **Kemi OJ**, **Loennechen JP**, **Wisløff U**, **Ellingsen Ø**. Intensity-controlled treadmill running in mice: cardiac and skeletal muscle hypertrophy. *J Appl Physiol* 93: 1301–1309, 2015.

56. **Kim HK**, **Sohn DW**, **Lee SE**, **Choi SY**, **Park JS**, **Kim YJ**, **Oh BH**, **Park YB**, **Choi YS**. Assessment of left ventricular rotation and torsion with two-dimensional speckle tracking echocardiography. *J Am Soc Echocardiogr* 20: 45–53, 2007.

57. **Kocabay G**, **Muraru D**, **Peluso D**, **Cucchini U**, **Mihaila S**, **Padayattil-Jose S**, **Gentian D**, **Iliceto S**, **Vinereanu D**, **Badano LP**. Normal left ventricular mechanics by two-dimensional speckle-tracking echocardiography. Reference values in healthy adults. *Rev Española Cardiol (English Ed* 67: 651–658, 2014.

58. **Kohn JC**, **Lampi MC**, **Reinhart-King CA**, **Wang M**, **Deshpande DA**, **Pintus G**, **Reinhart-King CA**, **Kohn JC**, **Lampi MC**. Age-related vascular stiffening: Causes and consequences. *Front Genet* 6: 1–17, 2015.

59. **Kou S**, **Suzuki K**, **Akashi YJ**, **Mizukoshi K**, **Takai M**, **Izumo M**, **Shimozato T**, **Hayashi A**, **Ohtaki E**, **Osada N**, **Omiya K**, **Nobuoka S**, **Miyake F**. Global longitudinal strain by two-dimensional speckle tracking imaging predicts exercise capacity in patients with chronic heart failure. *J Echocardiogr* 9: 64–72, 2011.

60. **Lakoumentas JA**, **Panou FK**, **Kotseroglou VK**, **Aggeli KI**, **Harbis PK**. The Tei index of myocardial performance: applications in cardiology [Online]. *Hell J*

Cardiol 46: 52–58, 2005. http://www.ncbi.nlm.nih.gov/pubmed/15807396.

61. **Lang RM**, **Badano LP**, **Mor-Avi V**, **Afilalo J**, **Armstrong A**, **Ernande L**, **Flachskampf FA**, **Foster E**, **Goldstein SA**, **Kuznetsova T**, **Lancellotti P**, **Muraru D**, **Picard MH**, **Rietzschel ER**, **Rudski L**, **Spencer KT**, **Tsang W**, **Voigt JU**. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American society of echocardiography and the European association of cardiovascular imaging. *Eur Heart J Cardiovasc Imaging* 16: 233–271, 2015.

62. **Lavie CJ**, **Milani R V.** Cardiac rehabiltiation in exercise training in secondary coronary heart disease prevention. *Prog Cardiovasc Dis* 53: 397–403, 2011.

63. **Lawler PR**, **Filion KB**, **Eisenberg MJ**. Efficacy of exercise-based cardiac rehabilitation post – myocardial infarction : A systematic review and meta-analysis of randomized controlled trials. *Am Heart J* 162: 571–584, 2011.

64. **Libonati JR**, **Ciccolo J**, **Glassberg H**. The Tei index and exercise capacity. *J Sports Med Phys Fitness* 41: 108–113, 2001.

65. **Loffredo FS**, **Nikolova AP**, **Pancoast JR**, **Lee RT**. Heart failure with preserved ejection fraction: Molecular pathways of the aging myocardium. *Circ Res* 115: 97–107, 2014.

66. **Lumens J**, **Delhaas T**, **Arts T**, **Cowan BR**, **Young AA**. Impaired subendocardial contractile myofiber function in asymptomatic aged humans, as detected using MRI. *AJP Hear Circ Physiol* 291: H1573–H1579, 2006.

67. **Ma H**, **Xie M**, **Wang J**, **Lü Q**, **Wang X**, **Lu X**, **Yang Y**, **Hu L**. Ultrasound

speckle tracking imaging contributes to early diagnosis of impaired left ventricular systolic function in patients with type 2 diabetes mellitus. *J Huazhong Univ Sci Technol - Med Sci* 28: 719–723, 2008.

68. **MacGowan GA**, **Burkhoff D**, **Rogers WJ**, **Salvador D**, **Azhari H**, **Hees PS**, **Zweier JL**, **Halperin HR**, **Siu CO**, **Lima JAC**, **Weiss JL**, **Shapiro EP**. Effects of afterload on regional left ventricular torsion. *Cardiovasc Res* 31: 917–925, 1996.

69. **Mallet RT**, **Manukhina EB**, **Ruelas SS**, **Caffrey JL**, **Downey HF**. Cardioprotection by intermittent hypoxia conditioning: evidence, mechanisms, and therapeutic potential. *Am J Physiol Circ Physiol* 315: 216–232, 2018.

70. **Marzolini S**, **oh PI**, **Brooks D**. Effect of combined aerobic and resistance training versus aerobic training alone in individuals with coronary artery disease: A meta-analysis. *Eur J Prev Cardiol* 19: 81–94, 2012.

71. **Maufrais C**, **Schuster I**, **Doucende G**, **Vitiello D**, **Rupp T**, **Dauzat M**, **Obert P**, **Nottin S**. Endurance training minimizes age-related changes of left ventricular twist-untwist mechanics. *J Am Soc Echocardiogr* 27: 1208–1215, 2014.

72. **McCartney N**, **Mckelvie RS**. The role of resistance training in patients with cardiac disease. *Eur J Cardiovasc Prev Rehabil* 3: 160–166, 1996.

73. **McCartney N**, **McKelvie RS**, **Haslam DRS**, **Jones NL**. Usefulness of weightlifting training in improving strength and maximal power output in coronary artery disease. *Am J Cardiol* 67: 939–945, 1991.

74. **Mcgill HC**, **Mcmahan CA**, **Zieske AW**, **Tracy RE**, **Malcom GT**, **Herderick EE**, **Strong JP**. Association of coronary heart disease risk factors with microscopic

qualities of coronary atherosclerosis in youth. *Circulation* 102: 374–379, 2000.

75. **McGregor G**, **Stöhr EJ**, **Oxborough D**, **Kimani P**, **Shave R**. Effect of exercise training on left ventricular mechanics after acute myocardial infarction-an exploratory study. *Ann Phys Rehabil Med* 61: 119–124, 2018.

76. **McMurray JJV**, **Adamopoulos S**, **Anker SD**, **Auricchio A**, **Böhm M**, **Dickstein K**, **Falk V**, **Filippatos G**, **Fonseca C**, **Gomez-Sanchez MA**, **Jaarsma T**, **Kober L**, **Lip GYH**, **Maggioni A Pietro**, **Parkhomenko A**, **Pieske BM**, **Popescu BA**, **Ronnevik PK**, **Rutten FH**, **Schwitter J**, **Seferovic P**, **Stepinska J**, **Trindade PT**, **Voors AA**, **Zannad F**, **Zeiher A**, **Bax JJ**, **Baumgartner H**, **Ceconi C**, **Dean V**, **Deaton C**, **Fagard R**, **Funck-Brentano C**, **Hasdai D**, **Hoes A**, **Kirchhof P**, **Knuuti J**, **Kolh P**, **Mcdonagh T**, **Moulin C**, **Reiner Ž**, **Sechtem U**, **Sirnes PA**, **Tendera M**, **Torbicki A**, **Vahanian A**, **Windecker S**, **Bonet LA**, **Avraamides P**, **Ben Lamin HA**, **Brignole M**, **Coca A**, **Cowburn P**, **Dargie H**, **Elliott P**, **Flachskampf FA**, **Guida GF**, **Hardman S**, **Iung B**, **Merkely B**, **Mueller C**, **Nanas JN**, **Nielsen OW**, **Orn S**, **Parissis JT**, **Ponikowski P**. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. *Eur J Heart Fail* 14: 803–869, 2012.

77. **McPhee PG**, **Winegard KJ**, **MacDonald MJ**, **McKelvie RS**, **Millar PJ**. Importance of early cardiac rehabilitation on changes in exercise capacity: a retrospective pilot study. *Appl Physiol Nutr Metab* 40: 1314–1317, 2015.

78. **Meyer K**, **Lehmann M**, **Sünder G**, **Keul J**, **Weidemann H**. Interval versus continuous exercise training after coronary bypass surgery: A comparison of

training-induced acute reactions with respect to the effectiveness of the exercise methods. *Clin Cardiol* 13: 851–861, 1990.

79. **Möbius-Winkler S**, **Uhlemann M**, **Adams V**, **Sandri M**, **Erbs S**, **Lenk K**, **Mangner N**, **Mueller U**, **Adam J**, **Grunze M**, **Brunner S**, **Hilberg T**, **Mende M**, **Linke AP**, **Schuler G**. Coronary collateral growth induced by physical exercise: results of the impact of intensity exercise training on coronary collateral circulation in patients with stable coronary artery disease (EXCITE) trial. *Circulation* 133: 1438–1448, 2016.

80. **Moholdt T**, **Lise I**, **Granøien I**, **Gjerde L**, **Myklebust G**, **Walderhaug L**, **Hole T**, **Graven T**, **Stølen T**, **Mølmen-hansen HE**, **Støylen A**, **Skogvoll E**, **Arild S**, **Wisløff U**. Long-term follow-up after cardiac rehabilitation A randomized study of usual care exercise training versus aerobic interval training after myocardial infarction. *Int J Cardiol* 152: 388–390, 2011.

81. **Moholdt T**, **Madssen E**, **Rognmo O**, **Aamot I**. The higher the better? Interval training intensity in coronary heart disease. *Kinesitherapie* 15: 30–37, 2014.

82. **Mor-Avi V**, **Lang RM**, **Badano LP**, **Belohlavek M**, **Cardim NM**, **Derumeaux G**, **Galderisi M**, **Marwick T**, **Nagueh SF**, **Sengupta PP**, **Sicari R**, **Smiseth OA**, **Smulevitz B**, **Takeuchi M**, **Thomas JD**, **Vannan M**, **Voigt JU**, **Zamorano JL**. Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese society of echocardiography. *Eur J Echocardiogr* 12: 167–205, 2011.

83. **Mora S**, **Cook N**, **Buring JE**, **Ridker PM**, **Lee I**. Physical activity and reduced risk of cardiovascular events: potential mediating mechanisms. *Circulation* 116: 2110–2118, 2007.

84. **Mozaffarian D**, **Kris-etherton P**, **Horn L Van**, **Lichtenstein AH**, **Kumanyika S**, **Kraus WE**, **Fleg JL**, **Redeker NS**, **Meininger JC**, **Banks J**, **Stuart-shor EM**, **Fletcher BJ**, **Miller TD**, **Hughes S**, **Braun LT**, **Kopin LA**, **Berra K**, **Hayman LL**, **Ewing LJ**, **Ades PA**, **Durstine JL**, **Houston-miller N**, **Burke LE**, **Co-chair SC**, **Heart A**. Interventions to promote physical activity and dietary lifestyle changes for cardiovascular risk factor reduction in adults. *Circulation* 122: 406–441, 2010.

85. **Myers J**, **Prakash M**, **Froelicher V**, **Partington S**, **Atwood J**. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* 346: 793–801, 2002.

86. **Nagueh SF**, **Chang SM**, **Nabi F**, **Shah DJ**, **Estep JD**. Cardiac imaging in patients with heart failure and preserved ejection fraction. *Circ Cardiovasc Imaging* 10: 1–13, 2017.

87. **Nakai H**, **Takeuchi M**, **Nishikage T**, **Kokumai M**, **Otani S**, **Lang RM**. Effect of aging on twist-displacement loop by 2-dimensional speckle tracking imaging. *J Am Soc Echocardiogr* 19: 880–885, 2006.

88. **Nearchou NS**, **Tsakiris AK**, **Stathacopoulos DN**, **Loutsidis KE**, **Skoufas PD**. A new Doppler index combining systolic and diastolic myocardial performance. Behavior and significance during hospitalization of patients with acute myocardial

infarction. *Hell J Cardiol* 40: 486–496, 1999.

89. **Nijland F**, **Kamp O**, **Verheugt FWA**, **Veen G**, **Visser CA**. Long-term implications of reocclusion on left ventricular size and function after successful thrombolysis for first anterior myocardial infarction. *Circulation* 95: 111–117, 1997.

90. **Nio A**, **Stohr E**, **Shave R**. Age-related differences in left ventricular structure and function between healthy men and women. *Climacteric* 20: 476–483, 2017.

91. **Nishikage T**, **Nakai H**, **Mor-avi V**, **Lang RM**, **Salgo IS**, **Settlemier SH**, **Husson S**, **Takeuchi M**. Quantitative assessment of left ventricular volume and ejection fraction using two-dimensional speckle tracking echocardiography. *Eur J Echocardio* 10: 82–88, 2009.

92. **Notomi Y**, **Popovic ZB**, **Yamada H**, **Wallick DW**, **Martin MG**, **Oryszak SJ**, **Shiota T**, **Greenberg NL**, **Thomas JD**, **Yamada H**, **Dw W**, **Mg M**, **Diastole E**. Ventricular untwisting: a temporal link between left ventricular relaxation and suction. *Am J Physiol Hear Circ Physiol* 44195: 505–513, 2008.

93. **Nucifora G**, **Marsan NA**, **Bertini M**, **Delgado V**, **Siebelink HMJ**, **Van Werkhoven JM**, **Scholte AJ**, **Schalij MJ**, **Van Der Wall EE**, **Holman ER**, **Bax JJ**. Reduced left ventricular torsion early after myocardial infarction is related to left ventricular remodeling. *Circ Cardiovasc Imaging* 3: 433–442, 2010.

94. **Omar A**, **Vallabhajosyula S**, **Sengupta P**. Left ventricular twist and torsion: research observations and clinical applications. *Circ Cardiovasc Imaging* 8, 2015.

95. **Parikh JD**, **Hollingsworth KG**, **Wallace D**, **Blamire AM**, **MacGowan GA**.

Normal age-related changes in left ventricular function: Role of afterload and subendocardial dysfunction. *Int J Cardiol* 223: 306–312, 2016.

96. **Park SJ**, **Miyazaki C**, **Bruce CJ**, **Ommen S**, **Miller FA**, **Oh JK**. Left ventricular torsion by two-dimensional speckle tracking echocardiography in patients with diastolic dysfunction and normal ejection fraction. *J Am Soc Echocardiogr* 21: 1129–1137, 2008.

97. **Perk G**, **Tunick PA**, **Kronzon I**. Non-doppler two-dimensional strain imaging by echocardiography-From technical considerations to clinical applications. *J Am Soc Echocardiogr* 20: 234–243, 2007.

98. **Pfeffer MA**, **Braunwald E**. Ventricular remodeling after myocardial infarction: Oberservations and clinical implications. *Circulation* 81: 1161–1172, 1990.

99. **Powers SK**, **Quindry JC**, **Kavazis AN**. Exercise-induced cardioprotection against myocardial ischemia-reperfusion injury. *Free Radic Biol Med* 44: 193–201, 2008.

100. **Public Health Agency of Canada**. 2009 Tracking Heart Disease and Stroke in Canada [Online]. http://www.phac-aspc.gc.ca/publicat/2009/cvd-avc/pdf/cvd-avs-2009-eng.pdf.

101. **Quinones MA**, **Waggoner AD**, **Reduto LA**, **Nelson JG**, **Young JB**, **Winters WL**, **Ribeiro LG**, **Miller RR**. A new, simplified and accurate method for determining ejection fraction with two-dimensional echocardiography. *Circulation* 64: 744–753, 1981.

102. **Reisner SA**, **Lysyansky P**, **Agmon Y**, **Mutlak D**, **Lessick J**, **Friedman Z**. Global longitudinal strain: A novel index of left ventricular systolic function. *J Am Soc*

Echocardiogr 17: 630–633, 2004.

103. **Rodeheffer RJ**, **Gerstenblith G**, **Becker LC**, **Fleg JL**, **Weisfeldt ML**, **Lakatta EG**. Exercise cardiac output is maintained with advancing age in healthy human subjects: Cardiac dilatation and increased stroke volume compensate for a diminished heart rate. *Circulation* 69: 203–213, 1984.

104. **Ruisi M**, **Levine M**, **Finkielstein D**. The assessment and potential implications of the myocardial performance index post exercise in an at risk population. *Cardiol Res* 4: 173–177, 2013.

105. **Sandesara PB**, **Lambert CT**, **Gordon NF**, **Fletcher GF**, **Franklin BA**, **Wenger NK**, **Sperling L**. Cardiac rehabilitation and risk reduction: Time to "rebrand and reinvigorate." *J Am Coll Cardiol* 65: 389–395, 2015.

106. **Sawka M**, **Convertino V**, **Eichner E**, **Schnieder S**, **Young A**. Blood volume: Importance and adaptations to exercise training, environmental stresses, and trauma/sickness [Online]. *Med Sci Sports Exerc* 32: 332–348, 2000. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed5&NEWS=N&AN=2000072995.

107. **Sengupta PP**, **Tajik AJ**, **Chandrasekaran K**, **Khandheria BK**. Twist mechanics of the left ventricle: Principles and application. *JACC Cardiovasc Imaging* 1: 366–376, 2008.

108. **Smiseth OA**, **Torp H**, **Opdahl A**, **Haugaa KH**, **Urheim S**. Myocardial strain imaging: How useful is it in clinical decision making? *Eur Heart J* 37: 1196-1207b, 2016.

109. **Stöhr EJ**, **Shave RE**, **Baggish AL**, **Weiner R.** Left ventricular twist mechanics in the context of normal physiology and cardiovascular disease: a review of studies using speckle tracking echocardiography. *Am J Physiol Hear Circ Physiol* : 633–644, 2016.

110. **Stoylen A**, **Wisløff U**, **Slørdahl S**. Left ventricular mechanics during exercise: A Doppler and tissue Doppler study. *Eur J Echocardiogr* 4: 286–291, 2003.

111. **Stratton JR**, **Levy WC**, **Cerqueira MD**, **Schwartz RS**, **Abrass IB**. Cardiovascular responses to exercise. Effects of aging and exercise training in healthy men. *Circulation* 89: 1648–55, 1994.

112. **Sumide T**, **Shimada K**, **Ohmura H**, **Onishi T**, **Kawakami K**, **Masaki Y**, **Fukao K**, **Nishitani M**, **Kume A**, **Sato H**, **Sunayama S**, **Kawai S**, **Shimada A**, **Yamamoto T**, **Kikuchi K**, **Amano A**, **Daida H**. Relationship between exercise tolerance and muscle strength following cardiac rehabilitation: Comparison of patients after cardiac surgery and patients with myocardial infarction. *J Cardiol* 54: 273–281, 2009.

113. **Sytkowski P**, **Kannel W**, **D'Agostino R**. Changes in risk factors and the decline in mortality from cardiovascular disease: The Framingham heart study. *N Engl J Med* 322: 1635–1641, 1990.

114. **Takeuchi M**, **Nakai H**, **Kokumai M**, **Nishikage T**, **Otani S**, **Lang RM**. Age-related changes in left ventricular twist assessed by two-dimensional speckle-tracking imaging. *J Am Soc Echocardiogr* 19: 1077–1084, 2006.

115. **Takeuchi M**, **Nishikage T**, **Nakai H**. The assessment of left ventricular twist in

anterior wall myocardial infarction using two-dimensional speckle tracking imaging. *J Am Soc Echocardiogr* 20: 36–44, 2006.

116. **Taylor C**, **Tsakirides C**, **Moxon JW**, **Moxon JW**, **Dudfield M**, **Witte K**, **Ingle L**, **Carroll S**. Exercise dose and all-cause mortality within extended cardiac rehabilitation: a cohort study. *Open Hear* 4: e000623, 2017.

117. **Taylor J**, **Keating SE**, **Leveritt MD**, **Holland DJ**, **Gomersall SR**, **Coombes JS**. Study protocol for the FITR Heart Study: Feasibility, safety, adherence, and efficacy of high intensity interval training in a hospital-initiated rehabilitation program for coronary heart disease. *Contemp Clin Trials Commun* 8: 181–191, 2017.

118. **Tei C**, **Ling LH**, **Hodge DO**, **Bailey KR**, **Oh JK**, **Rodeheffer R**, **Tajik AJ**, **Seward JB**. New index of combined systolic and diastolic myocardial performance: A simple and reproduble measure of cardiac function - A study in normals and dilated cardiomyopathy. *J Cardiol* 26: 357–366, 1995.

119. **Thomas RJ**, **King M**, **Lui K**, **Oldridge N**, **Piña IL**, **Spertus J**, **Bonow RO**, **Estes NAM**, **Goff DC**, **Grady KL**, **Hiniker AR**, **Masoudi FA**, **Piña IL**, **Radford MJ**, **Rumsfeld JS**, **Whitman GR**. AACVPR/ACC/AHA 2007 performance measures on cardiac rehabilitation for referral to and delivery of cardiac rehabilitation/secondary prevention services. *J Am Coll Cardiol* 50: 1400–1433, 2007.

120. **Tibayan FA**, **Lai DTM**, **Timek TA**, **Dagum P**, **Liang D**, **Daughters GT**, **Ingels NB**, **Miller DC**. Alterations in left ventricular torsion in tachycardia-induced

dilated cardiomyopathy. *J Thorac Cardiovasc Surg* 124: 43–49, 2002.

121. **Ueshima K**, **Suzuki T**, **Nasu M**, **Saitoh M**, **Kobayashi N**, **Yamazaki T**, **Hiramori K**. Effects of exercise training on left ventricular function evaluated by the Tei index in patients with myocardial infarction. *Circ J* 69: 564–566, 2005.

122. **Vanhees L**, **Fagard R**, **Thijs L**, **Staessen J**, **Amery A**. Prognostic significance of peak exercise capacity in patients with coronary artery disease. *J Am Coll Cardiol* 23: 358–363, 1994.

123. **Vona M**, **Rossi A**, **Capodaglio P**, **Rizzo S**, **Servi P**, **De Marchi M**, **Cobelli F**. Impact of physical training and detraining on endothelium-dependent vasodilation in patients with recent acute myocardial infarction. *Am Heart J* 147: 1039–1046, 2004.

124. **Webb OJ**, **Eves FF**, **Kerr J**. A statistical summary of mall-based stair-climbing interventions. *J Phys Act Heal* 8: 558–565, 2011.

125. **Weiner RB**, **Baggish AL**. Cardiovascular Adaptation and Remodeling to Rigorous Athletic Training. *Clin Sports Med* 34: 405–418, 2015.

126. **Weiner RB**, **Weyman AE**, **Khan AM**, **Reingold JS**, **Chen-Tournoux AA**, **Scherrer-Crosbie M**, **Picard MH**, **Wang TJ**, **Baggish AL**. Preload dependency of left ventricular torsion the impact of normal saline infusion. *Circ Cardiovasc Imaging* 3: 672–678, 2010.

127. **White H**, **Norris R**, **Brown M**, **Brandt P**, **Whitlock R**, **Wild C**. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. *Circulation* 76: 44–51, 1987.

128. **Woo JS**, **Kim WS**, **Yu TK**, **Ha SJ**, **Kim SY**, **Bae JH**, **Kim KS**. Prognostic value of serial global longitudinal strain measured by two-dimensional speckle tracking echocardiography in patients with ST-segment elevation myocardial infarction. *Am J Cardiol* 108: 340–347, 2011.

129. **Yeboah J**, **Mcclelland RL**, **Polonsky TS**, **Burke GL**, **Sibley CT**, **Leary DO**, **Carr JJ**, **Herrington DM**. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. *JAMA* 308: 788–795, 2012.

130. **Zaliaduonyte-Peksiene D**, **Vaskelyte JJ**, **Mizariene V**, **Jurkevicius R**, **Zaliunas R**. Does longitudinal strain predict left ventricular remodeling after myocardial infarction? *Echocardiography* 29: 419–427, 2012.

CHAPTER TWO: MANUSCRIPT – Cardiac function responses to stair-climbing based high intensity interval training in individuals with coronary artery disease

S.E. Valentino, E.C. Dunford, J. Dubberley, E. Lonn, M.J. Gibala, S.M. Phillips, and M.J. MacDonald.

Declaration of Academic Achievement

S.E. Valentino assisted with the study conceptualization and design, and led cardiac data collection, data analysis, and data interpretation. E.C. Dunford led study conceptualization and design, data collection, data analysis, and data interpretation. M.J. MacDonald assisted with the study conceptualization and design, data interpretation, and provided the funding for the study. S.M. Phillips and J. Dubberley assisted with data collection, the study conceptualization and design, and data interpretation. M.J. Gibala and E.M. Lonn assisted with the study conceptualization and design, and data interpretation.

2.1 Abstract

Coronary artery plaques, which may progress to a myocardial infarction, are a hallmark of coronary artery disease (CAD) and can go undetected until times of higher myocardial demand. The lasting cardiac effects of a myocardial event due to CAD can be quantified using standard echocardiographic measures, such as ejection fraction (EF). More novel measures of cardiac function, such as left ventricular (LV) twist, myocardial performance index (MPI), and global longitudinal strain (GLS) can provide additional information and may be more sensitive to change after interventions such as cardiac rehabilitation (CR) exercise training. The aim of this study was to investigate cardiac function in response to 12 weeks of traditional (TRAD) and stair climbing-based high intensity interval (STAIR) CR exercise training using both standard and novel echocardiographic measures. Cardiorespiratory fitness (CRF) and both standard and novel indexes of cardiac function were measured at baseline (0 weeks, T1), post-initial training (4 weeks, T2), and post-training (12 weeks, T3). CRF improved in both groups, after 4 and 12 weeks (TRAD: T1:22.8±2.5, T2:25.2±4.9, T3:26.0±5.0 mL/kg/min; STAIR: T1:22.1±4.2, T2: 24.7±4.9, T3: 25.4±5.2 mL/kg/min; $P<0.05$) of CR exercise training. There was a training associated increase in cardiac apical rotation in both groups with a main effect of time (TRAD: T1: 6.3±2.9,T2:8.9±3.1, T3:6.9±5.0° and STAIR: T1:4.7±3.7, T2:7.9±3.9, T3: 8.2±2.7°; $P=0.01$) and in LV twist in both groups with a main effect of time (TRAD: T1: 13.1±4.0,T2:15.4±3.8, T3:13.2±6.4° and STAIR: T1:10.2±2.6, T2:15.7±6.0, T3: 16.3±7.1°; $P=0.03$), but there were no additional changes in any of the traditional or novel measures of cardiac function assessed. This small increase in apical rotation and LV twist may be an indication of early exercise training associated changes in cardiac function. The similar responses in all measures across both groups indicate that STAIR exercise training may be a comparable alternative to traditional modes of

CR exercise training, however the lack of cardiac function changes may indicate that increases in the training program frequency, intensity or duration may be needed to induce significant cardiac function improvements. Future research should continue to assess both standard and novel indices of cardiac function to provide comprehensive assessments and determine the time course of changes.

Keywords

Cardiac rehabilitation, coronary artery disease, left ventricular twist, longitudinal strain, left ventricular remodeling, speckle-tracking echocardiography, cardiac function, stair climbing-based HIIT, exercise training

2.2 Introduction

The prevalence of coronary heart disease (CHD) increases ~10% per decade in adults over 50 years old, and the number of acute myocardial infarctions are steadily increasing over time (16). The presence of arterial lesions is evident in youth and progresses with aging (35). Coronary artery narrowing generally causes the most severe blockages and can go undetected until times of high myocardial demand, such as during exercise, when oxygen delivery to the heart muscle can be limited (31). Once moderate to severe coronary artery disease (CAD) is detected, surgical procedures to improve the coronary blood flow, such as percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG), are typically performed. After a myocardial event, such as myocardial infarction, the cardiac muscle can undergo adverse remodeling of the left ventricle (LV) to accommodate changes in heart function due to the presence of necrotic tissue (44). The extent of LV remodeling and the associated functional

changes that occur are dependent on both the location and severity of the CAD and the infarct (44). Clinical echocardiographic measures such as ejection fraction (EF), LV mass, stroke volume (SV), end diastolic volume (EDV) and end systolic volume (ESV) are commonly assessed to provide an indication of cardiac structure and function (8, 13, 19). Novel echocardiographic parameters such as LV twist, myocardial performance index (MPI), and global longitudinal strain (GLS) can provide additional information about cardiac function and may be able to facilitate detection of more subtle changes in cardiac function after interventions such as cardiac rehabilitation (CR) (3, 28). Exercise training is often prescribed as part of CR programming and has been demonstrated to result in improved blood flow to the myocardium and mitigation of further progression of CAD (30, 37). In the last four decades, the focus of most CR exercise programs has been on moderate intensity continuous exercise training as the accepted exercise training method to improve cardiac function (10). Generally, this exercise prescription includes, 30 minutes per day of moderate intensity aerobic exercise, performed 5 days per week (49). It has been shown that adherence to the training program is more important than exercise type and intensity for prediction of survival, and importantly, the physiological benefits of exercise training are not sustained if exercise habits are not adhered to (48). Recent research has suggested that high intensity interval training (HIIT), might be an alternative exercise prescription for individuals with CAD (38, 39). HIIT training has been found to be equivalent to moderate intensity continuous exercise training at inducing cardiorespiratory fitness improvements as part of a CR program in populations with CAD (6, 11, 18, 39, 53, 58). Despite concerns related to the safety of implementing HIIT in CR populations, it has been shown that HIIT presents a relatively low risk for inducing myocardial events in CR (56). Although HIIT is currently not recommended for individuals with atrial fibrillation,

musculoskeletal restrictions, uncontrolled angina and hypertension, it may serve as a time and physiologically effective alternative for those CR participants who find time is the limiting factor for incorporating exercise into their schedule (7). Other barriers to exercise participation for CR include access to services and financial cost (7). Stair climbing training has been used in many populations as an interval-based exercise (2, 17, 21, 23, 45, 46, 54). Stair climbing-based HIIT may present a feasible alternative that addresses many of the previously identified barriers to CR exercise and has been successfully used as an exercise modality in young healthy populations (2, 4, 23), and in clinical populations such as individuals with diabetes and pre-diabetes (12, 14, 21, 45, 46). Additional to an aerobic challenge, stair climbing presents a resistance exercise challenge. Specifically to climb the stairs, requires a resistive component to complete concentric contractions of leg muscles to repeatedly lift body weight, as well as eccentric contractions performed during the descending phase the stairs. Stair climbing has been previously shown to improve muscle strength in healthy older adults (22). Stair climbing-based HIIT has yet to be examined for CAD populations entering CR and novel measures of cardiac function, such as LV twist and MPI, may provide additional information in the application of stair climbing-based HIIT in comparison to usual care exercise prescription over the course of CR programming.

As such, we investigated the changes in CRF and cardiac function using both standard and novel echocardiographic measures before and after either traditional CR exercise programming (TRAD) or stair climbing-based HIIT (STAIR). The purposes of this study were to assess CRF and both standard and novel indices of cardiac function, in response to 4 and 12 weeks of either TRAD, or STAIR, CR exercise training post-myocardial event. Echocardiographic and CRF assessments were conducted at baseline and following both the supervised (initial 4 weeks) and unsupervised (additional 8 weeks) phases of either STAIR or

TRAD exercise training. Guided by recent evidence examining traditional CR exercise training compared to a non-exercise control (28), we hypothesized that CRF, LV twist and MPI would improve, as measured by increases in peak oxygen uptake (VO_2peak), reductions in overall degrees of rotation for LV twist and a reduction in MPI, after 12 weeks of exercise training in both the STAIR and the TRAD groups. Additionally, in alignment with the previously observed time course for changes in traditional measures of cardiac function (8, 13, 19) we hypothesized there would be no improvements in neither GLS, EF nor other standard indices of cardiac function, despite improvements in LVT and MPI following this intervention.

2.3 Methods

2.3.1 Participants

Sixteen participants (61 ± 7 years old) were recruited from the Cardiac Health and Rehabilitation Centre (CHRC) at the Hamilton General Hospital. Inclusion and exclusion criteria are indicated in Table 1. From January 31st, 2018 until April 18th, 2019, 761 medical charts were screened, and all 273 eligible participants were provided with a study information sheet during their primary cardiologist appointment at the CHRC. If they indicated interest in the study, participants were directed to meet with the study investigators, for further explanation and provision of contact information. From 40 patients interested in the study, 20 completed the cardiopulmonary exercise stress test (CPET) to confirm eligibility. A cardiologist subsequently reviewed the CPET and checked for electrocardiogram (ECG) abnormalities that might prevent participation, prior to participant enrollment in the study. At this time, 18 participants were enrolled, and 16 participants have completed the study and have been included in the current analysis.

2.3.2 Study design and protocol

To mimic the current timeline of CR programming at the CHRC in Hamilton, our study included two phases: the initial phase involved supervised exercise training for approximately 4 weeks or 6 individual, supervised exercise sessions, and an integration phase of unsupervised exercise performed at the participants' choice of location, either at-home or a community-based facility for an additional 8 weeks, in which they were encouraged to continue exercise training at a frequency of 3 times per week. All supervised sessions had at least one study investigator and a CHRC Registered Kinesiologist present. All cardiac echocardiography assessments were conducted at McMaster University. Each participant was randomized into one of two treatment groups (n=8/group), either TRAD or STAIR. See Figure 1 for a schematic of the study timeline. At the end of 4 weeks of supervised CR exercise programming, another CPET and cardiovascular assessment were performed to assess any potential changes in physiological function over the initial phase of training. At the end of the 12-week rehabilitation period, a final CPET, and cardiovascular assessment were once again performed. The study protocols were approved by the Hamilton Integrated Research Ethics Board (HIREB #3301) and conform to the *Declaration of Helsinki* concerning the use of human subjects as research participants. Written and verbal informed consent were obtained from all subjects.

Table 1. Inclusion and exclusion criteria.

Inclusion Criteria
• Men and (post-menopausal) women • Registered to participate in the CHRC at the Hamilton General Hospital • History of previous myocardial infarction, CABG and/or PCI • Non-smoker (within 3-months) • Local resident with transportation to the CHRC at the Hamilton Health Sciences General Division.

- Ability to understand written and verbal instructions and provide written informed consent
- Stable medical therapy

Exclusion Criteria

- Non-cardiac surgical procedure within two months
- Myocardial infarction within two months; coronary artery bypass graft surgery within two months; percutaneous coronary intervention within one month
- Baseline work capacity < 25 watts
- New York Heart Association (NYHA) class II-IV symptoms of heart failure
- Documented significant valve stenosis
- Positive exercise stress test (i.e. typical symptoms of chest discomfort and ECG changes or positive nuclear scan)
- Symptomatic peripheral arterial disease that limits exercise capacity
- Uncontrolled supraventricular or ventricular dysrhythmia
- Unstable angina
- Uncontrolled hypertension (blood pressure >160/90 mmHg)
- Documented chronic obstructive pulmonary disease - classified as those with a forced expiration volume (FEV1) of less than 60% and/or a forced vital capacity (FVC) less than 60%
- Any musculoskeletal abnormality that would limit exercise participation

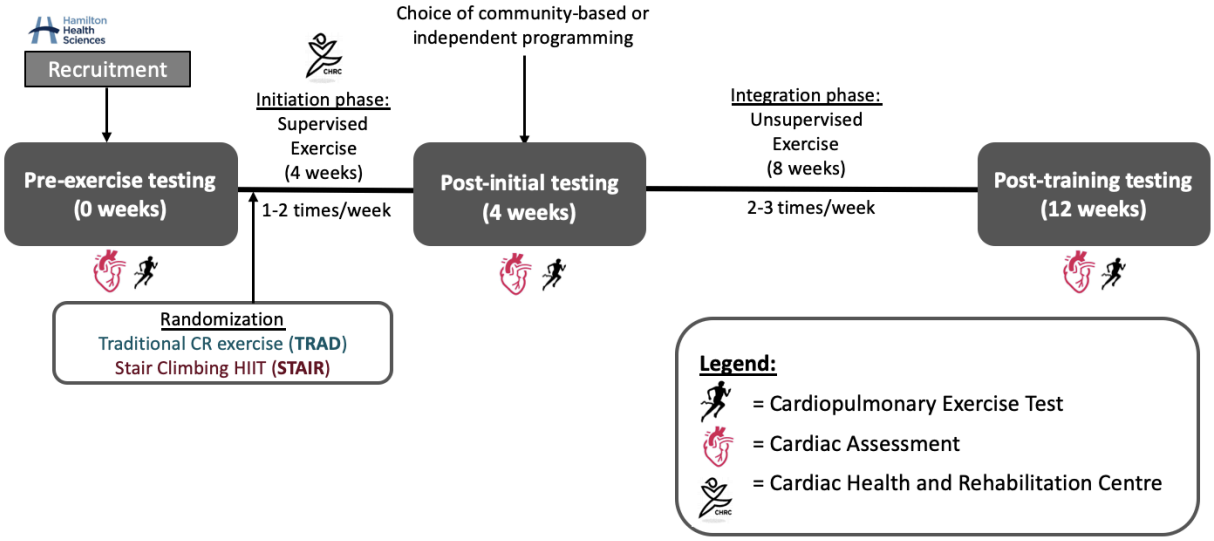


Figure 3: Study protocol mimicking the timeline of cardiac rehabilitation program that is currently performed at Hamilton General Hospital CHRC. All cardiac assessments were

completed at McMaster University and all CPETs were conducted at the Hamilton General Hospital Medical Diagnostic Unit.

2.2.3 Cardiorespiratory fitness

CRF was assessed under medical supervision, at the Hamilton General Hospital, using a CPET. Participants were continuously monitored using 12-lead electrocardiogram, heart rate, and blood pressure. They were fitted with a mask to directly measure peak oxygen uptake (VO_2peak) determined by analysis of expired gases using a metabolic cart (SensorMedics Vmax 229; California, USA). Participants completed the test on either a stationary bicycle or treadmill using a ramped protocol. The cycle workload was increased by 100 KPM per minute. Treadmill workload begins at 2.0 mph and 0% grade and after the first minute the speed increases to 3.0mph. Thereafter the incline increases by 2.5% per minute. Once the grade reaches 20% the speed is increased by 0.5 mph each minute. The exercise modality was consistent within each participant.

2.2.4 Interventions

Following assignment to an exercise group, all participants were provided with a receiver (watch) and a corresponding heart rate sensor chest strap (Model A300, Polar H7 heart rate sensor, Polar Electro Oy, Finland). The data from each completed exercise session was subsequently downloaded using software available online (MacOS FlowSync 2.6.4, Polar Electro 2018).

2.2.4.1 Traditional moderate intensity continuous training (TRAD)

During each exercise training session, the TRAD group performed an accumulation of 30 minutes of moderate intensity exercise using a rotation of different exercise machines, including a treadmill, recumbent bicycle, and arm cycle ergometer, with a 10-minute warm up and 5-minute cooldown, for a total exercise time of 45 minutes. Each exercise session, regardless of modalities involved, was performed a workload of 60-80% of the individual VO_2 reserve determined from the pre-training CPET and with an intensity goal of 11-13 on Borg's Rate of Perceived Exertion (RPE) scale.

2.2.4.2 Stair climbing-based high intensity interval training (STAIR)

During each training session, the STAIR group completed a HIIT exercise session consisting of 3 bouts of exercise, with each bout comprised of climbing a single flight of stairs 6 times at a vigorous pace with brief periods of active recovery (walking on flat ground) between each bout. The participants were instructed to "ascend a flight of 12 steps at a pace that you find challenging and descend at a pace you find comfortable" with each bout consisting of a total of 72 steps. While the work period was based on the amount of time it took each person to climb 72 stairs, the active recovery period was double the active period, with a work to rest ratio for each bout of exercise versus active recovery at a 1:2 ratio. This protocol was based on the volume of stairs completed in the stair climbing-based HIIT exercise training study previously described by Allison *et al.* (2). During each supervised session the time duration of the recovery period was determined by the duration of the first stair climbing bout and maintained consistent throughout the session.

2.2.4.3 Integration phase

During the integration phase of exercise training, participants were instructed to continue their respective exercise training program without supervision in either in a community-based facility or through home-based exercise programming. Participants were recommended to complete 3 sessions per week of their respective exercise training program.

2.2.5 Experimental measures

For each experimental testing session, participants visited the Vascular Dynamics Laboratory at McMaster University in a >2 hours fasted state. Each testing session visit began with recording of anthropometric measurements (height and weight). Prior to any assessments, participants rested in the supine position for a 10-minute period to ensure a steady-state baseline was achieved for cardiovascular parameters. First, resting supine upper arm blood pressure was obtained (Dinamap V100; GE Healthcare). All cardiac measures were then assessed via non-invasive ultrasound imaging of the heart. The ultrasound operator conducted the ultrasound measures at the left side of the participants thoracic cage with the ultrasound probe placed between the ribs for the sharpest acoustic window. Short video segments of at least five heart cycles were recorded at an approximate depth of 13 cm at a frame rate of 30-50 fps, using a 1.5-3.6 MHz sector phased-array probe connected to a commercial ultrasound unit (Vivid q; GE Medical Systems, Horten, Norway). The views obtained included the parasternal short axis (PSAX) view at the base of the left ventricle obtained at the level of both the mitral valve (MV) and the apex (AP), a parasternal long axis (PLAX) view, an apical 4-chamber (A4C) view in 2D and pulse wave (PW) mode, and an apical 5-chamber (A5C) view in PW mode. Data was stored offline and later analyzed using commercially available software for subsequent analysis

(EchoPAC 110.0.2; GE Medical Systems, Horten, Norway). All measurements were conducted in triplicate, using the clearest three consecutive heart cycles of each ultrasound cineloop when possible, then averaged. All cardiac analysis was performed using a research randomization scheme, in which the analysis order of the three study timepoints (baseline (T1), end of initial phase training (T2) and end of exercise training (T3)) within a participant were randomized using an online randomization tool (52).

2.2.5.1 Left ventricular twist

As the primary outcome measure, LV twist was analyzed via two-dimensional speckle tracking echocardiography (Q-analysis, Echo-PAC PC, Version 110.0.2; GE Medical Systems, Horten, Norway). The inner myocardial wall borders were manually traced for three heart cycles of both the PSAX-MV and PSAX-AP views. Subsequently, using the standard analysis package associated with this measure (Q-analysis), an automated quality analysis of the ability to track the 6 different wall segments across the heart cycles was performed. If the speckle-tracking was not accurate for 85% of the heart cycle, an alternate speckle location was chosen and often an alternate heart cycle was chosen until the best option was determined and then the final traces were reviewed for quality. After this image analysis quality check was complete, drift compensation was applied to bring the traces through the x-axis by assuming constant estimation error over the cardiac cycle to reduce erroneous baseline shift. These practices were performed by the same rater according to standard practice in our lab, and in accordance with current guidelines (40). The circumferential and radial parameters generated from this analysis were then exported to excel files for further trace analysis with the 2D Strain Analysis Tool (Stuttgart,

Germany), which uses cubic spline interpolation for all the traces to 1200 points and calculates peak values for statistical analysis.

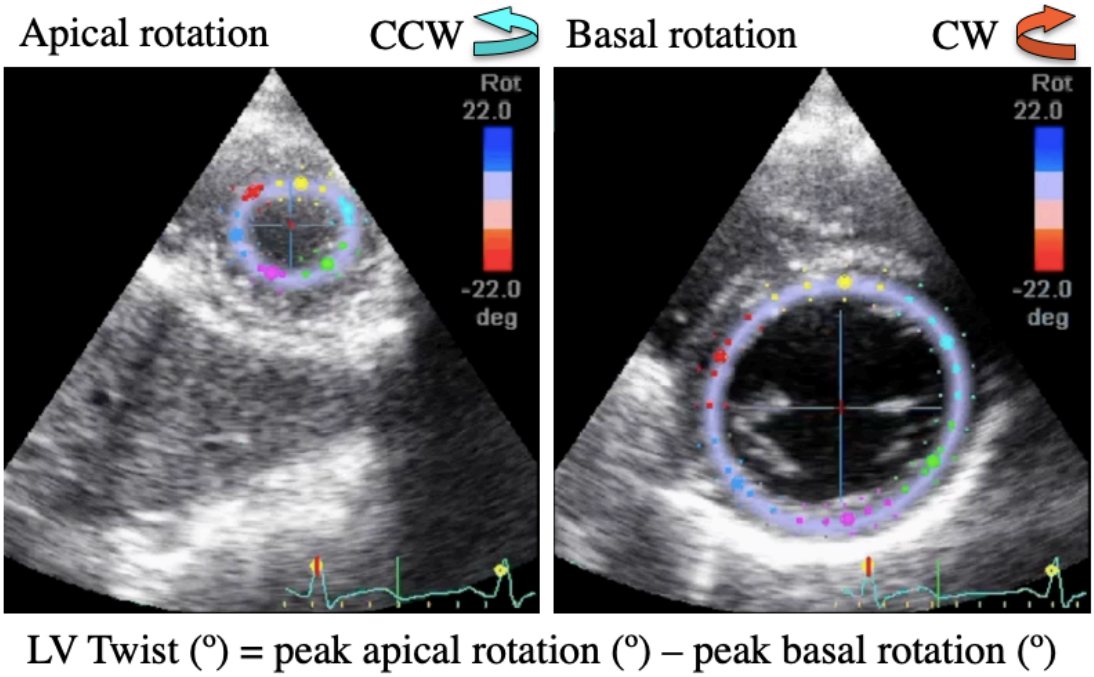


Figure 2: Speckle-tracking echocardiography analysis of PSAX-AP and PSAX-MV images and the subsequent calculation required to obtain LV twist.

2.2.5.2 Myocardial performance index (MPI)

We evaluated MPI from an average of three cardiac cycles using Doppler time intervals that were obtained from the LV outflow (A5C-PW mode) and the LV inflow (A4C-PW mode) measurements, as represented in Figure 3. The sum of isovolumic contraction time (ICT) and isovolumic relaxation time (IRT) was obtained by subtracting ejection time (ET) (Fig 3, b) from the time interval between two mitral adjacent inflow periods (Fig 3, a). MPI then was determined as [(a-b)/b], where *a* is the time interval between two mitral inflow periods and *b* is ejection time (47).

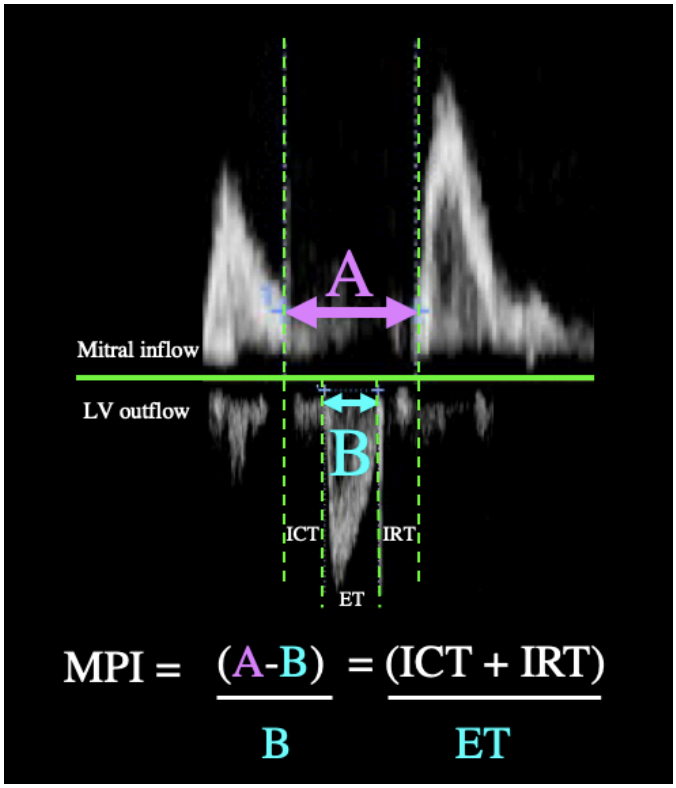


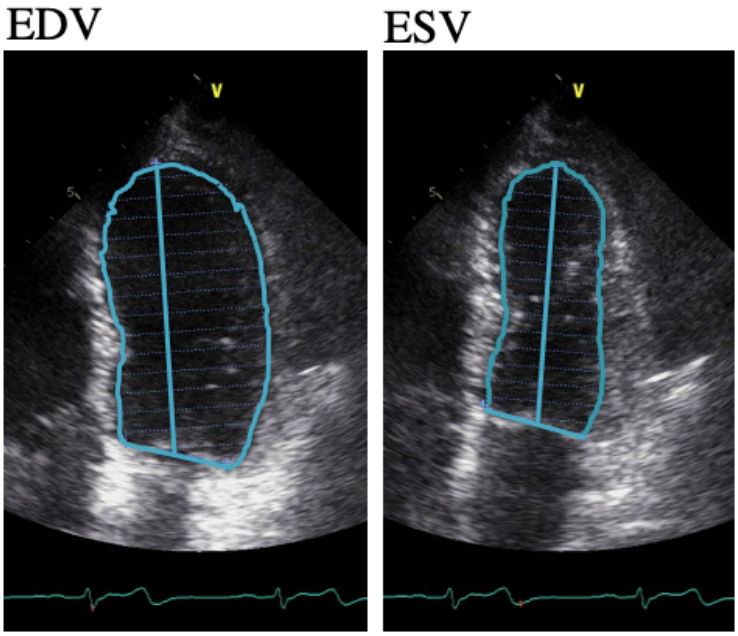
Figure 3: Representative image of MPI analysis from Doppler tracings of mitral inflow and LV outflow. A = time between filling periods; B = ejection time (ET). The sum of is isovolumic contraction time (ICT) and isovolumic relaxation time (IRT) can be obtained by the subtraction of B from A. Image is not to scale for the purpose of depicting the analysis.

2.2.5.3 Global longitudinal strain

GLS was obtained using the A4C view and tracing the LV endocardium at the tissue-blood interface, without including the trabeculae. Using Q-analysis, 6 segments of the LV were tracked including basal septal, mid septal, apical septal, apical lateral, mid lateral, and basal lateral segments. All tracking quality of all six segments were passed through an automatic checking system identical to that described above for LV twist measures. Further processing was completed using the 2DStrain tool, as described above.

2.2.5.4 Other cardiac measures

Standard measures of cardiac structure and function and were obtained from various echocardiographic views as follows: cardiac output (CO) was measured using the LV outflow tract velocity time integral to obtain SV, which was measured just below the aortic valve, and the ECG tracing to obtain HR, calculated as: (HRxSV). EDV and ESV and were determined using the Simpson's monoplane method (29), and from these, stroke volume was determined by subtracting is associated with increases in LV twist or a reduction in LV untwisting rate (UTR;



$$EF(\%) = \frac{EDV - ESV}{EDV}$$

27, 47). While LV twist is related to the systolic function of the heart, LV UTR is related to the diastolic function of the heart and is linked to the filling of the LV (27). It is known ESV from EDV. EF was calculated as: [(EDV-ESV)/EDV]

Figure 4: A sample analysis tracing of myocardium in end diastole (left) and end systole (right) as used to calculate EF using the Simpson's monoplane method. EF = ejection fraction; EDV = end diastolic volume; ESV = end systolic volume.

To measure diastolic filling of the LV, measurements were completed using the LV inflow from the A4C-PW mode velocity tracing with the PW sample volume positioned at the tips of the mitral leaflets. The peaks of both the early active filling (E-wave) and late passive filling (A-wave) velocity waves were assessed and the ratio was calculated (E/A ratio). LV mass is commonly represented as the thickness of the inner and outer LV wall in diastole, measured using the PLAX view, and was calculated using the linear method shown in equation 1, where 1.04 is the specific gravity of the myocardium (g/cm^3), LVEDD is left ventricular end diastolic dimension (mm), IVS_d is intraventricular septal thickness at end-diastole (mm), PWT_d is posterior wall thickness at end-diastole (mm) (29):

(1) $$\boxed{LV\ Mass\ (g) = \ 0.8\ \{1.04[([LVEDD + IVS_d + \ PWT_d]^3 - LVEDD^3)]\} + 0.6}$$

2.2.6 Statistical Analysis

A sample size calculation was computed for the primary outcome variable of peak LV twist using G*Power for Macintosh OSX (9)(version 3.1.9.2; MacOS) using data from the study of McGregor *et al.* as a reference, which reported the effects of moderate intensity continuous training on LV twist in a CR population (36). Assuming a standard deviation of the change in LV twist from baseline to follow-up of 5.3° in each group, we estimated that, to detect a difference of -3.95° in the change of LV twist between exercise groups, a minimum of 19 participants would be required in each group. A significance level of 5% and a statistical power of 80% was defined. Due to timeline and resource restrictions, for the purpose of this thesis, only 8 participants were included in each group for this analysis.

The final dataset was missing 1.38% of the full dataset and a missing values analysis was performed. Additionally, there was 1 CPET test that was not completed due to lack of follow-up.

A Missing Values Analysis indicated that Little's (1988) test of Missing Completely at Random (MCAR) was not significant, χ 2 16.744, DF = 29, p = .97. When significant, this test suggests that the hypothesis that the data are MCAR can be rejected. Therefore, there was no evidence to suggest that the data were not MCAR. Expectation maximization was therefore performed using all timepoints for CRF, basal rotation, apical rotation, and LV twist to impute missing values and complete the dataset.

Statistical analyses were performed using IBM SPSS Statistics for Macintosh OSX (version 20.0.0; IBM Comp., Armonk, N.Y., USA). Participant characteristics were summarised as mean ± standard deviation (SD), with independent t-tests used to compare group means at baseline. To compare all cardiac measures across the 3 timepoints, a 2x3 mixed measures analysis-of-variance (ANOVA) model was used that included assessments of main effects of group (TRAD and STAIR) and time (T1, T2 and T3) and interactions of group by time. We used a 95% confidence interval and statistical significance was considered as $P < 0.05$. Pairwise comparisons post-hoc analysis was conducted for significant interactions or main effects using Bonferroni adjustment for multiple comparisons.

2.3 Results

2.3.1 Recruitment

Of the 16 participants completed, there was missing echocardiographic data due to an inability to acquire clear ultrasound images and insufficient ultrasound image quality for 2 participants at 2 timepoints for apical rotation and 1 timepoint for basal rotation, which affected the calculations of LV twist for those timepoints. All participant characteristics at baseline are outlined in Table 1. The randomly assigned groups were evenly matched for all variables with the exception of the

presence of hypertension (more in TRAD), type 2 diabetes mellitus (more in TRAD), and previous cardiac event (more in STAIR). Despite the group differences in the diagnosis of hypertension, there were no group differences in any resting measure of blood pressure.

Table 1. Participant Characteristics at baseline

	Baseline		
	Stair (n=8)	Trad (n=8)	*P*
Sex (M/F)	(8/0)	(7/1)	
Age (yrs)	61 ± 6	62 ± 7	0.67
Height (cm)	175 ± 6	169 ± 13	0.45
Body mass (kg)	203.3 ± 25.5	209.8 ± 42.6	0.31
BMI (kg/m^2)	29.8 ± 3.5	29.7 ± 4.4	0.96
Resting SBP (mmHg)	121 ± 10	126 ± 23	0.60
Resting DBP (mmHg)	75 ± 7	73 ± 11	0.77
Resting HR (bpm)	54 ± 5	58 ± 11	0.40
Clinical			
STEMI (*n*,%)	2 (25)	1 (12.5)	
NSTEMI (*n*,%)	4 (50)	5 (62.5)	
Angina (*n*,%)	2 (25)	2 (25)	
PCI (*n*,%)	6 (75)	5 (62.5)	
CABG (*n*,%)	2 (25)	3 (37.5)	
Time since event (weeks)	8.1 ± 5.3	7.2 ± 4.3	0.87
Medications			
Beta-blockers (*n*,%)	7 (87.5)	7 (87.5)	
ACE inhibitors (*n*,%)	7 (62.5)	5 (62.5)	
ASA (*n*,%)	8 (100)	8 (100)	
Lipid lowering (*n*,%)	8 (100)	8 (100)	
Metformin (*n*,%)	1 (12.5)	2 (25)	
CV disease risk factors			
Previous smoking history (*n*,%)	2 (25)	3 (37.5)	0.33
T2DM (*n*,%)	1 (12.5)	3 (37.5)	0.03*
Hypertension (*n*,%)	5 (62.5)	7 (87.5)	0.03*
Previous cardiac event (*n*,%)	5 (62.5)	0 (0)	0.00*
Dyslipidemia (*n*,%)	6 (75)	7 (87.5)	0.23

All values are expressed in mean ± SD. BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; STEMI = ST elevated myocardial infarction; NSTEMI = non-ST elevated myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; ACE inhibitors = Angiotensin converting enzyme inhibitor; ASA = Acetylsalicylic Acid; T2DM = Diabetes mellitus; * = independent t-test, $P \leq 0.05$.

2.3.2 Effect of exercise interventions

Exercise adherence for the first 6 sessions during the initial phase was 100% for both groups. All standard measures of CR are displayed in **Table 2.** CRF, as measured by VO_2peak, was increased with training (main effect of time). Post-hoc analysis revealed a difference between T1 and T2 (P=0.001), T1 and T3 (P=0.004), and no difference between T2 and T3. There were no observations of main effects of group or time or interactions for any of the standard cardiac variables with the exception of stroke volume where there was a significant group by time interaction. Post-hoc analysis revealed the SV increased in the STAIR group with training, whereas there was no difference in the TRAD group across time. All novel measures of cardiac function are displayed in **Table 3**. LVT increased with training (main effect of time) and post-hoc analysis revealed a p-value trending towards a difference between T1 and T2 (P=0.06) and no difference between any other timepoints. Apical rotation increased with training (main effect of time) and post-hoc analysis revealed a difference between T1 and T2 (P=0.03). There were no other differences observed for any other novel cardiac variables.

Table 2. Standard measures of cardiac rehabilitation at baseline, post-initial training, and post-training.

	Baseline (0 weeks)		Post-initial training (4 weeks)		Post-training (12 weeks)				
N = 8/group	Stair	Trad	Stair	Trad	Stair	Trad	*P* (time)	*P* (group)	*P* (group x time)
VO_2peak (mL/kg/min)	22.1±4.2	22.8±2.5	24.7±4.9	25.2±4.4	25.4±5.2	26.0±5.0	0.00*	0.77	0.99
BMI (kg/m^2)	29.8±3.5	29.7±4.4	29.3±3.3	29.4±3.9	29.1±2.8	29.0±4.1	0.03*	0.99	0.88
SBP (mmHg)	121±10	126±23	116±10	126±30	121±8	122±25	0.73	0.58	0.26
DBP (mmHg)	75±7	73±11	71±8	73±12	74±5	69±8	0.31	0.70	0.23
HR (bpm)	54±5	58±11	60±12	59±15	62±15	56±9	0.22	0.78	0.09
LV mass (g)	239±78	266±118	263±65	266±115	242±48	282±137	0.73	0.61	0.26
LVM/BSA (g/m^2)	113±38	128±52	125±31	128±48	116±23	136±58	0.76	0.53	0.61
EDV (mL)	149.8±39.9	153.2±46.1	150.7±27.0	161.3±68.7	143.9±27.8	167.3±61.6	0.78	0.59	0.36
ESV (mL)	75.2±35.2	86.3±32.9	81.5±23.7	92.5±46.2	78.8±26.7	101.4±45.1	0.19	0.40	0.43
SV (mL)	65.5±12.5	75.2±13.8	77.7±13.2	73.8±22.8	82.8±14.4	72.0±18.7	0.21	0.81	0.05*
CO (L/min)	4.43±.80	3.57±.84	4.09±.61	4.16±1.33	4.34±.73	4.00±.86	0.84	0.58	0.08
EF (%)	52±14	45±7	47±9	44±7	47±10	40±10	0.15	0.20	0.55
E/A ratio	1.23±.25	.99±.33	1.17±.36	1.05±.41	1.28±.30	1.13±.55	0.50	0.31	0.73

All values are expressed in mean ± SD. VO_2peak = peak oxygen uptake; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; LV mass = left ventricular mass; LVM/BSA = left ventricular mass/body surface area; EDV = end-diastolic volume; ESV = end systolic volume; SV = stroke volume; CO = cardiac

output; EF biplane = ejection fraction using Simpson's monoplane method; E/A ratio = ratio of early passive filling to late active filling of the left ventricle; † = independent t-test, $P < 0.05$; * = significant, $P < 0.05$.

Table 3. Novel measures of cardiac function at baseline, post-initial training, and post-training.

	Baseline (0 weeks)		Post-initial training (4 weeks)		Post-training (12 weeks)				
N = 8/group	Stair	Trad	Stair	Trad	Stair	Trad	*P* (time)	*P* (group)	*P* (group x time)
LV $twist_{peak}$ (º)	10.2±2.6	13.1±4.0	15.7±6.0	15.4±3.8	16.3±7.1	13.2±6.4	0.03*	0.95	0.14
$BRot_{peak}$ (º)	-4.7±5.0	-7.1±3.0	-8.5±3.3	-6.7±3.3	-8.9±5.6	-7.2±1.9	0.27	0.76	0.24
$ApRot_{peak}$ (º)	4.7±3.7	6.3±2.9	7.9±3.9	8.9±3.1	8.2±2.7	6.9±5.0	0.01*	0.79	0.25
GLS (%)	-11.6±3.5	-11.7±3.3	-12.6±2.4	-11.3±2.3	-11.9±2.6	-12.2±3.4	0.88	0.81	0.48
MPI	.49±.13	.35±.04	.47±.14	.46±.12	.44±.14	.43±.16	0.64	0.19	0.25

All values are expressed in mean ± SD. LV $twist_{peak}$ = peak left ventricular twist; $BRot_{peak}$ = peak basal rotation; $ApRot_{peak}$ = peak apical rotation; GLS = global longitudinal strain, MPI = myocardial performance index; * = significant main effect of time, $P \leq 0.05$.

2.4 Discussion

In the current study, we sought to determine the LV function and CRF responses to 12 weeks of TRAD or STAIR exercise training in individuals with CAD. The main findings of this study are three-fold: 1) apical rotation and LV twist increased in the initial phase of both TRAD and STAIR exercise training, 2) there were no other substantial changes in any other standard or novel measures of cardiac function over time with either training program, 3) both training programs were associated with increases in CRF following the initial training (T2) that was maintained after the integration phase (T3) of training.

Following a myocardial event, cardiac function is expected to decline as adverse LV remodeling takes place (42). After surgical interventions repair the blockage with the coronary arteries, changes continue to take place in terms of in cardiac structure and function (42). Increases in EDV of 5-10%, increases in ESV, and decreases in EF 1-5% can typically be expected within the early months following a cardiac event, and in some cases, can progress to further decline and heart failure (42). Previous research indicates novel measures of cardiac function can demonstrate further declines without interventions such as CR exercise training, documented as increased apical rotation, basal rotation, and LV twist after 12 weeks in the non-exercise control group, compared to a group completing traditional moderate intensity continuous training who demonstrated reductions in the same measures (36). In the current study, measures of cardiac function, standard and novel, did not change over the course of the 12 weeks of either TRAD or STAIR exercise training. In the context of previous studies, prevention of further declines in cardiac function can be considered positive, although the current study did not contain a non-exercising group for comparison.

Our data demonstrate that both traditional and stair climbing-based HIIT training resulted in increased degrees of apical rotation and LV twist after the initial phase of training, and no changes in any other measures of cardiac function. Similarly, other research has found that apical rotation may be more sensitive to driving changes in LV twist with CAD and other cardiac conditions (27, 33, 50). Although there are few previous exercise training studies in CAD populations that include measures of LV twist, one previous study in individuals with CAD indicates that exercise training-associated reductions in LV twist may be considered advantageous (36). In contrast, there is evidence to suggest that exercise training in young healthy individuals results in increases in LV twist within 3 months of embarking on an intensive exercise program (55). In the same group of young healthy individuals, cardiac assessments at long term follow-up (39 months) suggest that when exercise training is continued there are further adaptations, resulting in reductions in LV twist compared to both the 3 month post-training timepoint and the pre-training baseline (55). Clearly, more research is required to determine the time course and direction of exercise training associated changes in LV twist in different populations.

Regardless of exercise program, we observed exercise training associated improvements in CRF. CRF was found to increase an average of 3.3mL/kg/min in both groups from baseline (T1) to post-training (T3). One aim of CR programming is secondary prevention through risk reduction, and this can be achieved through increases in CRF. This study was designed to align with the current CR program offered at the Hamilton General Hospital and therefore our 12-week CR program involved an initial phase of exercise initiation for 4 weeks, followed by an integration phase of self-motivated, unsupervised exercise for 8 weeks. Despite the challenges associated with prescribing unsupervised exercise training, our participants were able to maintain

their CRF as evidenced by differences in CRF between T1 and T3. Previous longitudinal research has found it is not the intensity of, but the adherence to, exercise that is most important to the reduction in mortality risk (48). During the 8 weeks of self-motivated exercise programming, only 2 of our participants purchased a community gym membership. The study investigators did not contact the participants throughout the 8 weeks of the integration phase and the current results address the feasibility of participants demonstrating physiologic changes with unsupervised exercise programs in a "real-world" setting.

Previous research has demonstrated exercise training associated increases in standard measures of cardiac function following 12 weeks or longer periods of exercise training and that these changes are indicative of long-term heart function (3, 57). This relatively long time-course for exercise training associated improvements in LV function contrasts with the more rapid adverse LV remodeling observed within 14 days of a myocardial event (37). The earliest documented exercise training associated myocardial function improvements have been found at 2 weeks in young healthy males completing HIIT exercise, and these improvements were measured as increases in apical rotation and LV twist in parallel with increase in CRF (43). In our CAD population, both cardiac function and CRF at baseline were impaired compared to previous cited work in young healthy participants. These differences in clinical and healthy populations seems to produce differential responses in measures of cardiac function. Prior to exercise training we found evidence of elevated cardiac function, indicated by a higher EF, in the STAIR group despite this group having more documented previous myocardial events (Table 1). After 12 weeks of exercise training, although CRF improved, this was not paralleled by cardiac adaptations with the exception of the observed increase in apical rotation over time.

By including multiple echocardiographic measures, our study was able to provide a comprehensive assessment of cardiac function in our participants. MPI is a cardiac function measure that combines systolic and diastolic function together, where an MPI of less than 0.36 is considered a hallmark of reduced LV function (15). Although we did predict an improvement in MPI with exercise training, our study cohort did include some individuals that had reduced diastolic function at baseline, according to accepted cut-off values for MPI, and we would expect that those with reduced function at baseline would have the greatest capacity for improvements with training (41). Individual data inspection allowed us to observe that the one individual in our cohort who had the most severe myocardial infarction also had the lowest MPI and demonstrated what appeared to be increases in MPI with training. One previous study documented that individuals with CAD demonstrate improved MPI values after exercise training prescribed at 90% of documented anaerobic threshold 2-3 times per week for 6 months, in the face of no change in EF (51). Another study involving two groups of home and hospital-based exercise training in patients with heart failure found no difference in MPI, reported as Tei index, after 8 weeks of training, in line with the current study results (25). The differences in length of exercise training programs may have led to these differential findings between studies, where longer training periods are associated with greater observed changes in MPI. Despite these differences, training studies in this population are uncommon, and the data presented here provides value to the currently limited literature.

In line with our hypothesis, GLS did not change with exercise training throughout our study. These results are similar to previous work that documented no change in GLS between groups of aerobic interval training and aerobic continuous training (20, 40). Other training studies using traditional moderate intensity continuous training in individuals with CAD, found

GLS also does not change with CR exercise (20, 34). While GLS does not seem to be affected by exercise, this measure has been found to provide better prognostic value, compared to EF, at documenting improvements in LV function (1). According to current suggestions from Kalam *et al.* (24), strain values lower than -20% are considered normal, and higher than -12% are considered impaired. Throughout the study, our documented average values of GLS were close to this value of -12%, (ranging from -11.3 to -12.6%), suggesting the LV function of our study population was limited. This was an unexpected finding, considering none of our participants had documented heart failure to our knowledge. Previous findings have suggested that higher CRF is associated with better GLS values in individuals with CAD (20, 27), after individual data inspection of VO_2peak and GLS values at baseline, those who had the highest VO_2peak did not correspond with those who had higher GLS values. Although GLS has been documented to better predict patient outcomes than EF, the present study findings do not show greater sensitivity between these measures. Alternatively, our study found the earliest training-associated changes occurred in CRF, without changes in cardiac function.

Individuals were randomly assigned to their respective exercise training groups in our study and we found that there was an even distribution of risk factors between groups, except for a higher number of previous CAD events in the STAIR group. There was similar medication prescription between groups and no medication changes took place during the study period. Although recruitment of female participants was challenging, we believe these results are generalizable to the broader CAD population (5, 26). Of the medical charts screened, 20% were female which suggests Hamilton General Hospital already has a lack of women interested in participating CR in comparison to the available literature values (32). There are many non-medical barriers to female participation in cardiac rehabilitation, such as lack of interest, family

and/or work obligations, lack of support (32), but we did not find there were discernable differences to incorporating our one female participant in the TRAD group. Females continue to be understudied in CR, despite similar rates of CAD especially in older age. We encourage more studies to consider supporting women to be part of research studies by decreasing time enrollment, providing alternative delivery models, and supporting the use of technologies to facilitate participation (30). Some of these commonly cited barriers to CR participation have the potential to be addressed by stair climbing-based HIIT and in the future, this form of exercise may provide an alternative to CR exercise programming that could increase the participation of women in CR overall.

2.5 Limitations and Future Directions

Our study had several limitations including the fact that we did not reach the sample size calculated to be required to detect differences in LV twist due to time and resource limitations. The top three medical reasons for ineligibility were smoking within the past 3 months (27%), valve replacement (21%), and atrial and/or ventricular fibrillation (8%). The two reasons most frequently provided by participants as barriers to participation in the study were proximity to McMaster University or the Hamilton General Hospital and lack of time. Despite this, the sample that was recruited is comparable to the general CAD population as it includes individuals with comorbidities that did not require specific exercise prescription or limit their ability to participate in stair climbing-based HIIT (26). Future studies should consider addressing these barriers by supporting communities and providing short duration, home-based options for CR programming.

The control group used in this study completed CR exercise according to the traditional CR exercise prescription. A lack of non-exercising control group limits that ability to apply our

findings in the context of individuals who elect to not participate in CR exercise training. However, we do believe it is unethical to withhold exercise from a group of individuals with CAD who have elected to participate in CR exercise. Further, previous research has already demonstrated declines in our primary outcome variables in a non-exercise control group of individuals with similar CAD characteristics (36). Future studies may find it beneficial to allow individuals who self-select to not join CR exercise training programs to participate in physiological assessments, and therefore act as a non-exercise control group.

There were circumstances where we were unable to collect ultrasound and CPET data, which resulted in 11 cases of missing data (1.38%) in our whole dataset. Ultrasound image acquisition is unpredictable in individuals due to challenging anatomy, especially for older individuals in which the cardiac windows are more difficult to landmark in comparison to young healthy participants. Some of the missing data in our study was in our primary outcome variables and therefore we were able to impute the data as an alternative to excluding these participants and further reducing our observation numbers. Other studies should attempt to screen or recruit additional participants when possible to account for challenging cardiac ultrasound imaging.

2.6 Conclusion

We investigated the changes in cardiac function in response to 12 weeks of either stair climbing-based HIIT or traditional CR exercise. Over time, we observed improvements in CRF, an increase in apical rotation and LVT, while no change in other standard and novel measures of cardiac function with either TRAD or STAIR exercise training in our group of individuals with CAD. Our study findings provide support for a feasible CR training model that incorporates 8 weeks of unsupervised exercise training following an initial period of supervised exercise

sessions. Future research should continue to incorporate novel metrics of cardiac function assessment to gain a comprehensive understanding of cardiac function in response to exercise interventions in individuals with CAD.

2.8 References

1. **Abate E**, **Hoogslag GE**, **Antoni ML**, **Nucifora G**, **Delgado V**, **Holman ER**, **Schalij MJ**, **Bax JJ**, **Marsan NA**. Value of three-dimensional speckle-tracking longitudinal strain for predicting improvement of left ventricular function after acute myocardial infarction. *Am J Cardiol* 110: 961–967, 2012.
2. **Allison M**, **Baglole J**, **Martin B**, **Macinnis M**, **Gurd B**, **Gibala M**. Brief intense stair climbing improves cardiorespiratory fitness. *Med Sci Sports Exerc* 49: 298–307, 2017.
3. **Awadalla H**, **Saleh MA**, **Abdel Kader M**, **Mansour A**. Left ventricular torsion assessed by two-dimensional echocardiography speckle tracking as a predictor of left ventricular remodeling and short-term outcome following primary percutaneous coronary intervention for acute myocardial infarction: A single-cent. *Echocardiography* 34: 1159–1169, 2017.
4. **Boreham CAG**, **Kennedy RA**, **Murphy MH**, **Tully M**, **Wallace WFM**, **Young I**. Training effects of short bouts of stair climbing on cardiorespiratory fitness, blood lipids, and homocysteine in sedentary young women. *Br J Sports Med* 39: 590–593, 2005.
5. **Colbert JD**, **Martin B**, **Haykowsky MJ**, **Hauer TL**, **Austford LD**, **Arena RA**, **Knudtson ML**, **Meldrum DAN**, **Aggarwal SG**, **Stone JA**. Cardiac rehabilitation referral, attendance and mortality in women. *Eur J Prev Cardiol* 22: 979–986, 2015.
6. **Currie KD**, **Dubberley JB**, **McKelvie RS**, **Macdonald MJ**. Low-volume, high-intensity interval training in patients with CAD. *Med Sci Sports Exerc* 45: 1436–1442, 2013.

7. **Daly J**, **Sindone AP**, **Hons B**, **Thompson DR**, **Hancock K**, **Chang E**, **Davidson P**. Barriers to participation in and adgerence to cardiac rehabiltiation programs: a critical literature review. *Prog Cardiovasc Nurs* 17: 8–17, 2002.

8. **Ehsani AA**, **Hagberg JM**, **Hickson RC**. Rapid changes in left ventricular dimensions and mass in response to physical conditioning and deconditioning. *Am J Cardiol* 42: 52–56, 1978.

9. **Faul F**, **Erdfelder E**, **Lang A-G**, **Buchner A**. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods* 39: 175–191, 2007.

10. **Fletcher GF**, **Ades PA**, **Kligfield P**, **Arena R**, **Balady GJ**, **Bittner VA**, **Coke LA**, **Fleg JL**, **Forman DE**, **Gerber TC**, **Gulati M**, **Madan K**, **Rhodes J**, **Thompson PD**, **Williams MA**. Exercise standards for testing and training: a scientific statement from the American Heart Association. *Circulation* 128: 873–934, 2013.

11. **Freyssin C**, **Verkindt C**, **Prieur F**, **Benaich P**, **Maunier S**, **Blanc P**. Cardiac rehabilitation in chronic heart failure: Effect of an 8-week, high-intensity interval training versus continuous training. *Arch Phys Med Rehabil* 93: 1359–1364, 2012.

12. **Gay JL**, **Buchner DM**, **Erickson ML**, **Lauture A**. Effect of short bouts of high intensity activity on glucose among adults with prediabetes: A pilot randomized crossover study. *Diabetes Res Clin Pract* 141: 168–174, 2018.

13. **Giannuzzi P**, **Temporelli PL**, **Corrà U**, **Tavazzi L**. Antiremodeling effect of long-term exercise training in patients with stable chronic heart failure: Results of the exercise in left ventricular dysfunction and chronic heart failure (ELVD-CHF) trial. *Circulation* 108: 554–559, 2003.

14. **Godkin FE**, **Jenkins EM**, **Little JP**, **Nazarali Z**, **Percival ME**, **Gibala MJ**. The effect of brief intermittent stair climbing on glycemic control in people with type 2 diabetes: a pilot study. *Appl Physiol Nutr Metab* 43: 969–972, 2018.

15. **Goroshi M**, **Chand D**. Myocardial performance index (Tei index): A simple tool to identify cardiac dysfunction in patients with diabetes mellitus. *Indian Heart J* 68: 83–87, 2016.

16. **Government of Canada**. Heart disease in Canada: highlights from the Canadian chronic disease surveillance system. .

17. **Halsey LG**, **Watkins DAR**, **Duggan BM**. The Energy Expenditure of Stair Climbing One Step and Two Steps at a Time: Estimations from Measures of Heart Rate. *PLoS One* 7, 2012.

18. **Hannan A**, **Hing W**, **Simas V**, **Climstein M**, **Coombes J**, **Jayasinghe R**, **Byrnes J**, **Furness J**. High-intensity interval training versus moderate-intensity continuous training within cardiac rehabilitation: a systematic review and meta-analysis. *Open Access J Sport Med* Volume 9: 1–17, 2018.

19. **Haykowsky MJ**, **Liang Y**, **Pechter D**, **Jones LW**, **McAlister FA**, **Clark AM**. A meta-analysis of the effect of exercise training on left ventricular remodeling in heart failure patients. *J Am Coll Cardiol* 49: 2329–2336, 2007.

20. **Van De Heyning CM**, **De Maeyer C**, **Pattyn N**, **Beckers PJ**, **Cornelissen VA**, **Goetschalckx K**, **Possemiers N**, **Van Craenenbroeck EM**, **Voigt JU**, **Vanhees L**, **Shivalkar B**. Impact of aerobic interval training and continuous training on left ventricular geometry and function: a SAINTEX-CAD substudy. *Int J Cardiol* 257: 193–198, 2018.

21. **Honda H**, **Igaki M**, **Hatanaka Y**, **Komatsu M**, **Tanaka SI**, **Miki T**, **Suzuki T**, **Takaishi T**, **Hayashi T**. Stair climbing/descending exercise for a short time decreases blood glucose levels after a meal in participants with type 2 diabetes. *BMJ Open Diabetes Res Care* 4: 2–6, 2016.

22. **Hongu N**, **Shimada M**, **Miyake R**, **Nakajima Y**, **Nakajima I**, **Yoshitake Y**. Promoting stair climbing as an exercise routine among healthy older adults attending a community-based physical activity program. *Sports* 7: 23, 2019.

23. **Jenkins EM**, **Nairn LN**, **Skelly LE**, **Little JP**, **Gibala MJ**. Do stair climbing exercise "snacks" improve cardiorespiratory fitness? *Appl Physiol Nutr Metab* 44: 681–684, 2019.

24. **Kalam K**, **Otahal P**, **Marwick TH**. Prognostic implications of global LV dysfunction: A systematic review and meta-analysis of global longitudinal strain and ejection fraction. *Heart* 100: 1673–1680, 2014.

25. **Karapolat H**, **Demir E**, **Bozkaya YT**, **Eyigor S**, **Nalbantgil S**, **Durmaz B**, **Zoghi M**. Comparison of hospital-based versus home-based exercise training in patients with heart failure: Effects on functional capacity, quality of life, psychological symptoms, and hemodynamic parameters. *Clin Res Cardiol* 98: 635–642, 2009.

26. **Kendir C**, **van den Akker M**, **Vos R**, **Metsemakers J**. Cardiovascular disease patients have increased risk for comorbidity: A cross-sectional study in the Netherlands. *Eur J Gen Pract* 24: 45–50, 2018.

27. **Kim HK**, **Sohn DW**, **Lee SE**, **Choi SY**, **Park JS**, **Kim YJ**, **Oh BH**, **Park YB**, **Choi YS**. Assessment of left ventricular rotation and torsion with two-dimensional speckle tracking echocardiography. *J Am Soc Echocardiogr* 20: 45–53, 2007.

28. **Kou S**, **Suzuki K**, **Akashi YJ**, **Mizukoshi K**, **Takai M**, **Izumo M**, **Shimozato T**,

Hayashi A, **Ohtaki E**, **Osada N**, **Omiya K**, **Nobuoka S**, **Miyake F**. Global longitudinal strain by two-dimensional speckle tracking imaging predicts exercise capacity in patients with chronic heart failure. *J Echocardiogr* 9: 64–72, 2011.

29. **Lang RM**, **Badano LP**, **Mor-Avi V**, **Afilalo J**, **Armstrong A**, **Ernande L**, **Flachskampf FA**, **Foster E**, **Goldstein SA**, **Kuznetsova T**, **Lancellotti P**, **Muraru D**, **Picard MH**, **Rietzschel ER**, **Rudski L**, **Spencer KT**, **Tsang W**, **Voigt JU**. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American society of echocardiography and the European association of cardiovascular imaging. *Eur Heart J Cardiovasc Imaging* 16: 233–271, 2015.
30. **Lavie CJ**, **Bennett A**. Enhancing cardiac rehabilitation in women. *J Women's Heal* 26: 817–819, 2017.
31. **Lavie CJ**, **Milani R V.** Cardiac rehabiltiation in exercise training in secondary coronary heart disease prevention. *Prog Cardiovasc Dis* 53: 397–403, 2011.
32. **Marzolini S**, **Brooks D**, **oh PI**. Sex differences in completion of a 12-month cardiac rehabilitation programme: An analysis of 5922 women and men. *Eur J Prev Cardiol* 15: 698–703, 2008.
33. **Marzolini S**, **Oh PI**, **Brooks D**. Effect of combined aerobic and resistance training versus aerobic training alone in individuals with coronary artery disease: A meta-analysis. *Eur J Prev Cardiol* 19: 81–94, 2012.
34. **Maufrais C**, **Schuster I**, **Doucende G**, **Vitiello D**, **Rupp T**, **Dauzat M**, **Obert P**, **Nottin S**. Endurance training minimizes age-related changes of left ventricular twist-untwist mechanics. *J Am Soc Echocardiogr* 27: 1208–1215, 2014.
35. **McGill HC**, **Mcmahan CA**, **Zieske AW**, **Tracy RE**, **Malcom GT**, **Herderick EE**,

Strong JP. Association of coronary heart disease risk factors with microscopic qualities of coronary atherosclerosis in youth. *Circulation* 102: 374–379, 2000.

36. **McGregor G**, **Stöhr EJ**, **Oxborough D**, **Kimani P**, **Shave R**. Effect of exercise training on left ventricular mechanics after acute myocardial infarction-an exploratory study. *Ann Phys Rehabil Med* 61: 119–124, 2018.

37. **McKay R**, **Pfeffer M**, **Pasternak R**, **Markis J**, **Come P**, **Nakao S**, **Alderman J**, **Ferguson J**, **Safian R**, **Grossman W**. Left ventricular remodeling after myocardial infarction: a corollary to infarct expansion. *Circulation* 74: 693–702, 1986.

38. **Möbius-Winkler S**, **Uhlemann M**, **Adams V**, **Sandri M**, **Erbs S**, **Lenk K**, **Mangner N**, **Mueller U**, **Adam J**, **Grunze M**, **Brunner S**, **Hilberg T**, **Mende M**, **Linke AP**, **Schuler G**. Coronary collateral growth induced by physical exercise: results of the impact of intensity exercise training on coronary collateral circulation in patients with stable coronary artery disease (EXCITE) trial. *Circulation* 133: 1438–1448, 2016.

39. **Moholdt T**, **Madssen E**, **Rognmo O**, **Aamot I**. The high the better? Interval training intensity in coronary heart disease. *J Sci Med Sport* 15: 30–37, 2014.

40. **Moholdt TT**, **Amundsen BH**, **Rustad LA**, **Wahba A**, **Løvø KT**, **Gullikstad LR**, **Bye A**, **Skogvoll E**, **Wisløff U**, **Slørdahl SA**. Aerobic interval training versus continuous moderate exercise after coronary artery bypass surgery: A randomized study of cardiovascular effects and quality of life. *Am Heart J* 158: 1031–1037, 2009.

41. **Nearchou NS**, **Tsakiris AK**, **Stathacopoulos DN**, **Loutsidis KE**, **Skoufas PD**. A new Doppler index combining systolic and diastolic myocardial performance. Behavior and significance during hospitalization of patients with acute myocardial infarction. *Hell J Cardiol* 40: 486–496, 1999.

42. **Nucifora G**, **Marsan NA**, **Bertini M**, **Delgado V**, **Siebelink HMJ**, **Van Werkhoven JM**, **Scholte AJ**, **Schalij MJ**, **Van Der Wall EE**, **Holman ER**, **Bax JJ**. Reduced left ventricular torsion early after myocardial infarction is related to left ventricular remodeling. *Circ Cardiovasc Imaging* 3: 433–442, 2010.

43. **O'Driscoll J**, **Wright S**, **Taylor K**, **Coleman D**, **Sharma R**, **Wiles J**. Cardiac autonomic and left ventricular mechanics following high intensity interval training: a randomised cross-over controlled study. *J Appl Physiol* 125: 1030–1040, 2018.

44. **Pfeffer MA**, **Braunwald E**. Ventricular remodeling after myocardial infarction: Oberservations and clinical implications. *Circulation* 81: 1161–1172, 1990.

45. **Takaishi T**, **Hayashi T**. Stair ascending–descending exercise accelerates the decrease in postprandial hyperglycemia more efficiently than bicycle exercise. *BMJ Open Diabetes Res Care* 5: 1–8, 2017.

46. **Takaishi T**, **Imaeda K**, **Tanaka T**, **Moritani T**, **Hayashi T**. A short bout of stair climbing–descending exercise attenuates postprandial hyperglycemia in middle-aged males with impaired glucose tolerance. *Appl Physiol Nutr Metab* 37: 193–196, 2012.

47. **Takeuchi M**, **Nakai H**, **Kokumai M**, **Nishikage T**, **Otani S**, **Lang RM**. Age-related changes in left ventricular twist assessed by two-dimensional speckle-tracking imaging. *J Am Soc Echocardiogr* 19: 1077–1084, 2006.

48. **Taylor C**, **Tsakirides C**, **Moxon J**, **Moxon JW**, **Dudfield M**, **Witte K**, **Ingle L**, **Carroll S**. Exercise dose and all-cause mortality within extended cardiac rehabilitation: a cohort study. *Open Hear* 4: e000623, 2017.

49. **Thomas RJ**, **King M**, **Lui K**, **Oldridge N**, **Piña IL**, **Spertus J**, **Bonow RO**, **Estes NAM**, **Goff DC**, **Grady KL**, **Hiniker AR**, **Masoudi FA**, **Piña IL**, **Radford MJ**, **Rumsfeld JS**,

Whitman GR. AACVPR/ACC/AHA 2007 performance measures on cardiac rehabilitation for referral to and delivery of cardiac rehabilitation/secondary prevention services. *J Am Coll Cardiol* 50: 1400–1433, 2007.

50. **Toumanidis ST**, **Kaladaridou A**, **Bramos D**, **Skaltsiotes E**, **Agrios JN**, **Vasiladiotis N**, **Pamboucas C**, **Kottis G**, **Moulopoulos SD**. Apical rotation as an early indicator of left ventricular systolic dysfunction in acute anterior myocardial infarction: experimental study [Online]. *Hell J C4ardiology* 54: 264–272, 2013. http://www.ncbi.nlm.nih.gov/pubmed/23912918.

51. **Ueshima K**, **Suzuki T**, **Nasu M**, **Saitoh M**, **Kobayashi N**, **Yamazaki T**, **Hiramori K**. Effects of exercise training on left ventricular function evaluated by the Tei index in patients with myocardial infarction. *Circ J* 69: 564–566, 2005.

52. **Urbaniak G**, **Plous S**. Research Randomizer (Version 4.0) [Computer Software]. *http://www.randomizer.org/*: 2013.

53. **Villelabeitia Jaureguizar K**, **Vicente-Campos D**, **Ruiz Bautista L**, **De La Peña CH**, **Arriaza Gómez MJ**, **Calero Rueda MJ**, **Fernández Mahillo I**. Effect of high-intensity interval versus continuous exercise training on functional capacity and quality of life in patients with coronary artery disease. *J Cardiopulm Rehabil Prev* 36: 96–105, 2016.

54. **Webb OJ**, **Eves FF**, **Kerr J**. A statistical summary of mall-based stair-climbing interventions. *J Phys Act Heal* 8: 558–565, 2011.

55. **Weiner RB**, **Baggish AL**. Cardiovascular adaptation and remodeling to rigorous athletic training. *Clin Sports Med* 34: 405–418, 2015.

56. **Wewege MA**, **Ahn D**, **Yu J**, **Liou K**, **Keech A**. High-intensity interval training for patients with cardiovascular disease-is it safe? A systematic review. *J Am Heart Assoc* 7:

1–19, 2018.

57. **White H**, **Norris R**, **Brown M**, **Brandt P**, **Whitlock R**, **Wild C**. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. *Circulation* 76: 44–51, 1987.

58. **Wisløff U**, **Støylen A**, **Loennechen JP**, **Bruvold M**, **Rognmo Ø**, **Haram PM**, **Tjønna AE**, **Helgerud J**, **Slørdahl SA**, **Lee SJ**, **Videm V**, **Bye A**, **Smith GL**, **Najjar SM**, **Ellingsen Ø**, **Skjærpe T**. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. *Circulation* 115: 3086–3094, 2007.

APPENDIX A – Raw Data

Table A1. Individual data standard cardiac measures

T1 - Individual averages											
Name/Date	**EDV (mL)**	**ESV (mL)**	**EF (%)**	**SV (mL)**	**LV Mass (Linear)**	**LVOT Diam**	**CO (L/min)**	**LVEDV A4C**	**LVESV A4C**	**LVEF A4C**	**SV A4C**
SCORE01	68.7	31.7	53.0	37.0	144.0	2.2	2.3	118.0	63.7	45.3	54.0
SCORE02	95.7	48.3	47.7	47.0	223.0	2.0	2.5	173.3	120.7	30.3	52.3
SCORE03	98.3	33.0	64.3	69.0	147.8	1.8	3.1	150.7	81.7	45.7	69.0
SCORE04	106.0	35.3	67.0	68.0	224.0	2.0	3.7	78.3	25.7	67.7	52.7
SCORE05	83.3	30.3	63.7	52.7	204.0	2.0	3.9	111.7	44.7	60.0	66.7
SCORE06	106.7	40.7	62.3	65.7	265.6	1.9	3.8	175.0	61.4	61.0	75.0
SCORE07	62.3	21.7	65.0	41.0	115.8	2.4	2.7	137.3	46.0	66.3	91.0
SCORE08	98.0	50.7	48.3	47.7	199.3	2.0	2.9	121.0	65.7	45.3	55.0
SCORE09	140.0	79.0	43.7	58.3	321.1	2.2	3.2	206.7	113.3	45.0	93.3
SCORE10	82.3	29.0	64.7	53.7	338.8	2.1	2.8	114.0	47.0	59.0	67.0
SCORE11	128.7	44.0	65.3	84.7	272.2	2.0	5.1	172.3	116.3	33.0	56.0
SCORE12	107.7	62.3	41.3	45.3	398.5	2.4	3.2	190.7	112.3	40.7	78.0
SCORE13	114.3	48.0	58.0	66.7	478.2	2.3	2.9	226.7	143.3	36.3	83.0
SCORE14	78.3	28.3	63.7	50.0	156.5	1.9	2.6	123.3	71.0	42.7	52.3
SCORE16	66.0	26.0	63.3	40.0	272.0	2.0	2.6	120.0	74.7	37.7	45.0
SCORE17	90.7	23.0	74.7	67.3	273.2	2.1	3.5	204.7	112.7	45.0	92.3
AVERAGE	95.4	39.5	59.1	55.9	249.2	2.1	3.2	149.9	79.5	48.5	67.5
SD	21.9	15.5	9.5	13.3	104.6	0.2	0.7	42.1	35.6	12.2	14.6
T2 - Individual averages											
Name/Date	**EDV (mL)**	**ESV (mL)**	**EF (%)**	**SV (mL)**	**LV Mass (Linear)**	**LVOT Diam**	**CO (L/min)**	**LVEDV A4C**	**LVESV A4C**	**LVEF A4C**	**SV A4C**
SCORE01	70.2	28.2	59.3	42.0	137.7	2.2	2.3	124.3	65.2	47.1	59.0
SCORE02	97.2	50.4	45.9	46.7	219.3	2.0	2.5	178.8	128.2	28.1	50.4
SCORE03	101.1	33.0	64.8	69.7	149.6	1.8	3.1	150.9	81.2	45.9	69.7
SCORE04	104.7	36.4	65.7	68.3	235.1	2.0	3.7	77.1	25.6	67.2	51.6
SCORE05	84.8	31.8	62.6	52.6	204.4	2.0	3.9	112.2	46.2	58.7	65.6
SCORE06	101.9	36.2	64.8	65.2	246.9	1.9	3.8	176.7	48.2	67.7	76.7
SCORE07	59.1	22.9	61.7	36.7	112.4	2.4	2.7	137.1	43.3	68.1	93.3
SCORE08	99.3	50.2	49.4	49.2	196.5	2.0	2.9	123.0	66.9	45.1	55.7
SCORE09	140.3	78.7	43.9	58.4	318.1	2.2	3.2	205.9	110.8	46.0	95.1
SCORE10	84.4	28.7	65.9	50.2	345.8	2.1	2.8	112.3	44.0	61.0	68.7
SCORE11	124.9	44.3	64.1	80.6	291.2	2.0	5.1	171.8	122.8	29.3	49.0
SCORE12	112.2	69.8	35.8	42.4	418.8	2.3	3.2	195.6	111.1	42.9	84.3

SCORE13	113.8	48.7	57.3	65.6	484.3	2.3	2.8	224.6	149.1	33.1	75.3
SCORE14	74.4	27.4	62.9	47.0	155.2	1.9	2.6	122.8	70.0	43.2	52.8
SCORE15											
SCORE16	65.0	25.0	65.1	40.0	260.2	2.0	2.6	122.3	76.2	37.6	45.7
SCORE17	91.2	22.7	75.2	68.4	261.8	2.1	3.5	202.2	113.2	44.0	89.4
AVERAGE	95.3	40.4	59.0	56.1	251.1	2.1	3.2	150.9	79.5	48.8	67.7
SD	22.0	16.8	10.5	13.0	109.4	0.2	0.7	42.3	38.3	13.8	15.7
T3 - Individual averages											
Name/Date	**EDV (mL)**	**ESV (mL)**	**EF (%)**	**SV (mL)**	**LV Mass (Linear)**	**LVOT Diam**	**CO (L/min)**	**LVEDV A4C**	**LVESV A4C**	**LVEF A4C**	**SV A4C**
SCORE01	68.6	27.6	59.1	41.0	137.0	2.2	2.3	122.4	65.0	46.5	57.3
SCORE02	89.6	49.9	42.2	39.6	210.9	2.0	2.5	182.0	126.3	30.5	55.6
SCORE03	98.5	32.7	65.4	68.6	150.1	1.8	3.1	149.5	81.0	45.5	68.6
SCORE04	103.2	31.9	69.6	68.1	227.7	2.0	3.7	77.8	26.1	67.0	51.7
SCORE05	83.7	30.4	63.7	52.7	205.5	2.0	3.9	112.3	45.6	59.2	66.4
SCORE06	103.2	38.3	63.4	64.6	263.9	1.9	3.8	176.2	61.6	62.2	84.6
SCORE07	59.1	22.2	62.6	37.2	117.9	2.4	2.7	139.8	42.8	69.1	96.4
SCORE08	97.4	48.0	50.6	49.6	200.6	2.0	2.9	124.0	66.2	46.1	57.6
SCORE09	140.1	77.2	44.9	56.3	323.2	2.2	3.2	206.2	112.4	45.3	93.8
SCORE10	83.3	30.2	63.5	50.3	347.6	2.1	2.8	112.8	46.0	59.3	66.9
SCORE11	128.5	43.1	66.1	85.4	274.4	2.0	5.1	174.4	133.7	24.1	40.7
SCORE12	119.6	68.7	41.4	50.9	420.3	2.4	3.2	198.4	112.5	42.9	85.8
SCORE13	114.0	48.9	57.1	65.7	485.3	2.2	2.8	224.1	143.5	35.5	80.4
SCORE14	73.6	28.6	60.9	45.0	150.0	1.9	2.6	122.7	69.0	44.0	53.7
SCORE16	63.0	24.0	66.8	39.3	259.6	2.0	2.6	122.1	75.0	38.4	46.6
SCORE17	93.0	23.2	75.3	69.6	263.4	2.1	3.5	201.6	111.0	45.0	90.9
AVERAGE	96.7	39.8	59.6	56.2	251.0	2.1	3.2	151.6	80.8	48.4	68.5
SD	22.8	16.4	10.3	13.8	109.8	0.2	0.7	42.6	37.9	13.5	17.1

Table A2. Individual data MPI, E/A ratio, stroke volume, cardiac output.

T1 - Individual Average						
Name/Date	**a**	**b**	**MPI**	**E/A**	**LVSV Dopp**	**LVCO Dopp**
SCORE01	426.666667	304.333333	0.40197152	1.23333333	85.3333333	4.91333333
SCORE02	415.333333	298	0.39373602	1.01666667	80.6666667	4.43
SCORE03	489	329	0.48632219	1.18666667	43	2.32333333
SCORE04	512	346	0.47976879	1.07666667	61.5	2.89
SCORE05	467	341.333333	0.36816406	1.14333333	60.3333333	4.18666667

SCORE06	367	290.666667	0.26261468	1.13	64	3.57333333
SCORE07	486.666667	326	0.49284254	1.54333333	79.3333333	4.93
SCORE08	470.666667	341	0.38025415	1.02	63.6666667	4.62333333
SCORE09	550.333333	325	0.69333333	1.70666667	61	3.11333333
SCORE10	491.333333	327.333333	0.50101833	1.19666667	75	3.91666667
SCORE11	490.333333	297.666667	0.64725644	1.05666667	59.6666667	3.43666667
SCORE12	486.666667	374	0.30124777	0.59333333	84	5.82333333
SCORE13	410.333333	310.666667	0.32081545	0.57	82.3333333	3.69333333
SCORE14	461.666667	350.666667	0.31653992	1.01666667	67	3.62333333
SCORE16	412.333333	308.666667	0.33585313	0.81666667	61.3333333	3.61666667
SCORE17	466.333333	329	0.41742655	1.54333333	97.3333333	4.98333333
AVERAGE	462.729167	324.958333	0.4249478	1.10642857	69.0595238	3.96261905
SD	45.9055744	22.5332265	0.12044044	0.29893962	12.29231	0.92753158
T2 - Individual Average						
Name/Date	**a**	**b**	**MPI**	**E/A**	**LVSV Dopp**	**LVCO Dopp**
SCORE01	467.333333	318	0.46960168	1.9	75.3333333	3.55
SCORE02	415	314	0.32165605	1.00666667	73.3333333	3.98
SCORE03	452.666667	329.666667	0.37310415	1.97333333	78.6666667	4.21
SCORE04	412.666667	249	0.65729585	1.27666667	63.6666667	3.07333333
SCORE05	438.666667	325	0.34974359	1.11333333	79	5.79666667
SCORE06	394.666667	297.333333	0.32735426	0.95666667	81	4.38
SCORE07	475.333333	341.333333	0.39257813	1.3	77.6666667	4.52666667
SCORE08	457	350.666667	0.30323194	0.82333333	37	2.26
SCORE09	488.666667	295.666667	0.65276212	0.87333333	57.6666667	3.28666667
SCORE10	501	336.666667	0.48811881	1.09333333	94	4.46333333
SCORE11	506	327.333333	0.54582485	0.88333333	95.6666667	4.77333333
SCORE12	639.333333	379.666667	0.68393327	0.63	85	5.4
SCORE13	509.666667	367	0.38873751	0.90333333	70	3.13
SCORE14	440.666667	295	0.49378531	0.78666667	62	3.98666667
SCORE16	473.666667	318	0.48951782	0.89	64.3333333	3.39666667
SCORE17	487.666667	332	0.4688755	1.38666667	117.333333	5.74
AVERAGE	472.5	323.520833	0.46288255	1.10857143	75.7291667	4.12208333
SD	56.2213878	30.9582679	0.12303873	0.3956488	18.1251692	0.99916252
T3 - Individual Average						
Name/Date	**a**	**b**	**MPI**	**E/A**	**LVSV Dopp**	**LVCO Dopp**
SCORE01	452	320	0.4125	2.04	89.6666667	4.27333333
SCORE02	426.666667	308.666667	0.38228942	1.20333333	76.6666667	4.04
SCORE03	473.666667	320	0.48020833	1.58333333	80.3333333	4.41

SCORE04	405.666667	316.666667	0.28105263	1.11666667	103.333333	5.33
SCORE05	404.333333	320	0.26354167	1.24333333	57.3333333	3.68333333
SCORE06	475.666667	308.666667	0.54103672	1.33	68.6666667	3.31
SCORE07	452	336.666667	0.34257426	1.49333333	88.6666667	4.53
SCORE08	482.333333	322.666667	0.49483471	1.00666667	67.6666667	4.24
SCORE09	447.666667	274.666667	0.62985437	0.8	60	3.53
SCORE10	438	339	0.2920354	1.68333333	87	4.25333333
SCORE11	513.666667	325	0.58051282	0.99333333	97.3333333	5.30333333
SCORE12	521.333333	404.333333	0.28936521	0.58333333	67	4.04333333
SCORE13	585.666667	332	0.76405622	0.57333333	74	3.1
SCORE14	482.666667	360	0.34074074	0.97333333	49.3333333	2.85
SCORE16	431.333333	308.666667	0.39740821	0.79333333	63.3333333	3.86333333
SCORE17	488.666667	339	0.44149459	1.85	108	5.68666667
AVERAGE	467.583333	327.25	0.43334408	1.18738095	77.3958333	4.15291667
SD	46.5677523	27.6870072	0.14169393	0.41696334	17.0620735	0.79731668

Table A3. Individual data VO_2peak, BMI, and novel measures of cardiac function.

ID	Time (1/2/3)	VO2peak	BMI	BaseRot	ApRot	LVT	EF	GLS
SC01	1	26.1	28.3	-5.3	10.9	16.1	48.0	-15.9
SC02	1	19.1	36.0	-8.4	1.9	10.2	34.3	-7.4
SC03	1	23.0	27.3	3.9	9.1	5.6	45.7	-14.8
SC04	1	15.8	31.5	-0.3	3.0	10.1	67.7	-13.1
SC05	1	21.3	28.7	-6.6	3.4	9.8	60.0	-12.3
SC06	1	28.5	25.4	-1.1	11.9	12.4	61.0	-10.5
SC07	1	21.5	29.9	-6.9	2.9	11.6	66.3	-18.2
SC08	1	24.0	32.6	-9.6	5.7	15.3	45.3	-10.5
SC09	1	25.2	26.8	-6.7	1.9	7.4	45.0	-9.3
SC10	1	25.2	28.8	-10.7	2.8	13.4	59.0	-10.3
SC11	1	18.6	32.7	-7.1	4.3	10.8	33.0	-9.2
SC12	1	26.1	27.5	-1.6	6.8	8.0	40.7	-14.5
SC13	1	19.6	33.3	-8.0	9.7	17.6	36.3	-5.0
SC14	1	23.8	26.7	-11.2	6.4	17.4	42.7	-12.3
SC16	1	20.6	23.3	-5.8	2.7	8.4	37.7	-12.8
SC17	1	21.2	37.2	-8.5	4.7	12.4	45.0	-10.6
SC01	2	33.4	27.4	-8.0	12.4	20.2	54.0	-12.5
SC02	2	22.9	35.2	-7.7	5.9	12.9	36.7	-10.3
SC03	2	24.7	26.6	-16.0	12.6	25.3	51.0	-14.8

SC04	2	16.7	31.0	-6.1	9.1	14.1	56.7	-16.1
SC05	2	22.0	29.5	-1.7	14.0	15.6	50.3	-9.3
SC06	2	33.8	25.1	-9.9	13.8	23.7	48.7	-13.1
SC07	2	25.7	29.8	-6.9	2.3	9.4	45.7	-12.1
SC08	2	25.4	32.4	-3.0	5.2	8.1	42.7	-10.5
SC09	2	24.9	26.3	-5.3	4.4	9.1	36.3	-11.2
SC10	2	27.5	29.0	-8.5	7.8	16.2	58.7	-14.0
SC11	2	21.6	31.8	-7.4	7.7	14.6	39.3	-9.1
SC12	2	30.2	28.0	-5.7	6.5	12.1	32.3	-11.3
SC13	2	22.0	32.7	-7.7	9.7	17.1	38.7	-8.0
SC14	2	25.4	26.7	-6.4	9.5	15.6	50.7	-14.8
SC16	2	21.3	23.2	-8.9	7.3	16.2	43.0	-13.8
SC17	2	22.2	35.2	-12.1	6.5	18.6	41.0	-10.0
SC01	3	34.0	25.9	-5.9	11.5	16.8	37.0	-15.9
SC02	3	22.0	35.6	-7.8	8.1	15.3	49.7	-9.3
SC03	3	23.8	26.5	-16.3	6.7	21.4	56.0	-12.1
SC04	3	16.3	30.6	-10.5	11.2	21.7	58.7	-11.8
SC05	3	22.5	28.2	-6.6	3.4	6.6	52.7	-11.5
SC06	3	34.3	24.7	-10.8	13.0	23.7	55.3	-12.5
SC07	3	27.5	29.6	-2.6	4.6	5.7	39.0	-15.0
SC08	3	23.0	33.3	-4.6	0.2	4.3	38.3	-16.4
SC09	3	26.2	24.4	-2.3	8.5	9.4	37.3	-8.4
SC10	3	27.9	28.6	-16.1	7.1	23.2	45.7	-16.0
SC11	3	25.0	32.4	-4.6	6.6	10.4	32.0	-10.2
SC12	3	28.4	28.2	-5.7	6.8	11.2	26.3	-11.3
SC13	3	23.4	33.3	-7.9	12.8	20.7	27.3	-6.1
SC14	3	24.7	26.6	-10.2	11.6	21.7	43.7	-13.8
SC16	3	21.1	22.9	-7.1	8.0	15.0	39.7	-9.7
SC17	3	31.0	34.0	-9.4	0.7	9.7	53.0	-12.8

Table A4. Individual data LV mass index, resting systolic BP, diastolic BP, and heart rate.

ID	Time (1/2/3)	LVMI	SBPrest	DBPrest	HRrest
SC01	1	72.6	101	63	53
SC02	1	93.9	104	65	54
SC03	1	71.5	127	77	50
SC04	1	113.5	128	79	53
SC05	1	101.4	123	72	80
SC06	1	140.6	114	69	47
SC07	1	51.7	115	70	62

SC08	1	96.2	139	83	63
SC09	1	150.2	126	83	60
SC10	1	157.7	117	71	50
SC11	1	126.6	135	83	56
SC12	1	190.3	117	64	63
SC13	1	214.9	173	95	44
SC14	1	79.8	109	62	51
SC16	1	148.7	108	70	59
SC17	1	118.4	136	76	49
T2					
SC01	2	112.0	93	61	46
SC02	2	102.6	119	68	64
SC03	2	85.0	114	69	57
SC04	2	122.6	129	80	51
SC05	2	96.6	145	81	73
SC06	2	140.8	105	64	46
SC07	2	92.4	118	75	62
SC08	2	93.6	118	70	57
SC09	2	126.7	129	84	67
SC10	2	162.1	105	62	53
SC11	2	171.1	107	69	83
SC12	2	196.0	113	71	87
SC13	2	171.4	186	99	43
SC14	2	63.6	105	57	57
SC16	2	106.6	108	70	60
SC17	2	181.7	142	72	49
T3					
SC01	3	117.1	93	60	46
SC02	3	109.8	126	79	60
SC03	3	82.9	119	72	58
SC04	3	103.8	135	81	56
SC05	3	75.9	109	66	69
SC06	3	136.1	110	66	46
SC07	3	135.1	116	68	66
SC08	3	96.7	115	71	63
SC09	3	152.5	127	78	70
SC10	3	102.8	116	71	50
SC11	3	104.4	121	75	93
SC12	3	161.7	116	65	60
SC13	3	204.9	175	86	41
SC14	3	69.5	113	66	56

SC16	3	134.8	112	67	59
SC17	3	226.1	143	72	52

Table A5. Individual characteristics.

ID	Age	Group	Weight	CADevent	TSI	PrevCAD	CAD_culprit	CAD_surg	Prev_smoker	T2D	HTN	Dyslip
SC01	47	0	182.3	1	2	1	1	1	0	0	1	1
SC02	54	1	251	2	3.5	1	2	1	1	0	1	0
SC03	64	1	190.1	1	5	1	1	1	0	0	0	0
SC04	65	0	187.6	2	20	1	3	1	0	1	1	1
SC05	63	1	286.5	2	15	1	1	2	0	1	1	0
SC06	61	1	164.75	1	4	1	1	1	0	0	0	1
SC07	59	1	218.5	3	8.5	1	1	2	0	0	1	1
SC08	59	0	218.5	2	2	2	4	2	1	0	1	1
SC09	52	1	197.75	3	8	1	1	1	1	0	1	1
SC10	61	1	203.75	2	5.5	1	1	1	0	0	0	1
SC11	69	0	213	2	10	1	1	2	0	0	1	1
SC12	67	0	194	3	9	2	5	1	0	1	1	1
SC13	64	0	224	2	8	2	2	2	1	0	1	1
SC14	73	0	176	2	6	2	1	1	1	0	0	1
SC16	60	1	153.22	3	10	1	1	1	0	1	1	1
SC17	64	1	244.25	2	5.5	2	2	1	0	0	1	1

CAD event: 1=STEMI, 2=NSTEMI, 3=Angina; CAD_surg: 1=PCI, 2=CABG; PrevCAD: 1= First event, 2=second or third event; CAD_culprit: 1= Left anterior descending/Left main, 2=Right coronary arter, 3 = Ramus, 4 = Circumflex, 5 = combination or unknown